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

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

BASIL-2

TRIAL PROTOCOL: Version 7.0

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
Professor Andrew Bradbury

Sampson Gamgee Professor of Vascular Surgery
University of Birmingham

Co-Applicants

Southmead, Bristol: Professor Hinchliffe

Imperial College, London: Professor Davies

Oxford: Mr Perkins; Dr Uberoi

Birmingham: Mr Claridge; Dr Ganeshan

Leicester: Dr Adair

Hull: Professor Chetter; Professor Ettles

Leeds: Professor Scott; Dr Patel

Sheffield: Dr Cleveland

Newcastle: Professor Stansby

Birmingham Clinical Trials Unit

Methodologist: Natalie Rowland

Lead Statistician: Catherine Moakes
Director of Operations: Margaret Grant
Trials Management Team Leader: Gemma Slinn
Trial Manager: Suzanne Lockyer

Health Economist: Zainab Abdali
Lead Research Nurse: Gareth Bate

Trial Steering Committee

Chair: Professor Jonathan Michaels	Honorary Professor of Clinical Decision Science, Health Economics and Decision Science, ScHARR, University of Sheffield
Mr James Griffin	Medical Statistician, University of Warwick
Professor Jon Moss	Consultant Vascular Interventional Radiologist, Southern General Hospital
Mr Andrew Beech	Chief Vascular Scientist, Nottingham University Hospitals
Professor Frances Game	Consultant Diabetologist, University Hospitals of Derby and Burton NHS Foundation Trust

Martin Fox	Vascular Specialist Podiatrist, Huddersfield
Mr Peter Maufe	PAD patient, Patient Representative
Mr Barry Attwood	PAD patient, Patient Representative
Dr Nick Latimer	Senior Research Fellow in Decision Science, ScHARR, University of Sheffield
Data Monitoring Committee	
Chair: Professor Charles McCollum	Professor of Surgery, Division of Cardiovascular Sciences, University of Manchester
Dr Richard Jackson	Acting Director of Statistics, Liverpool Cancer Research UK, Liverpool Cancer Trials Unit
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 8444
Fax: 0121 415 9135
Email: basil-2@trials.bham.ac.uk
Website: www.birmingham.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 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 Statement

By Signing the IRAS form for this trial, the University of Birmingham, acting as sponsor, confirm approval of this protocol.

Sponsor Contact Details

Birgit Whitman
Head of Research Governance & Integrity
Finance Office
University of Birmingham
c\o Room 106 Aston Webb, B Block
Edgbaston
Birmingham, B15 2TT
Email: b.whitman@bham.ac.uk

Principal Investigator:

As Principal Investigator, I confirm that the following protocol has been agreed and accepted, and that I will conduct the trial in compliance with the approved protocol where this does not compromise participant safety.

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

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

1 Trial Summary 12

2 Introduction 15

2.1 The problem of SLI 15

2.2 VB and BET for SLI 15

2.3 BASIL-2 and NICE 16

2.4 BASIL-2 and the HTA ..... **Error! Bookmark not defined.**

2.5 Assessment and Management of Risk 17

3 Trial Design 17

3.1 Trial Objective 17

3.2 Primary Outcome Measure 17

3.3 Secondary Outcome Measures: 17

3.4 Selection of Participants 18

3.5 Inclusion Criteria 19

3.6 Exclusion Criteria 20

4 Trial Procedures and Schedule of Assessments 20

4.1 Informed Consent Procedure 21

4.1.1 Time to consent 22

4.1.2 Consent for long-term follow-up (up to 96 months post-treatment) 22

4.1.3 Withdrawal 23

4.2 Baseline Assessments 23

4.3 Randomisation Procedures and Minimisation 24

4.4 Timing of Intervention 25

4.5 Best Endovascular Treatment 25

4.6 Vein Bypass 26

4.7 Amputation 26

4.8 In-patient Follow-up 26

4.9 Follow-up Visit 27

4.10 Assessment Schedule 27

4.11 Trial Duration ..... **Error! Bookmark not defined.**

5 Recording and Reporting of Adverse Events 28

5.1 Definitions 28
5.2 Adverse Event General Recording Requirements 30
5.3 Adverse Events (AEs) Reporting Requirements 30
5.4 Serious Adverse Events (SAEs) Reporting Requirements 30
5.4.1 Expected SAEs 31
5.4.2 SAEs for Expedited Notification to the Trial Office 32
5.4.3 Provision of Follow-up Information 34
5.5 Reporting Serious Adverse Events to third Parties 34
5.5.1 Related and Unexpected SAEs 34
5.6 Summary of Safety Reporting Procedure for BASIL-2 35
5.7 Annual Progress Reports 35
5.8 Reporting Urgent Safety Measures 35
5.9 Notification of Serious Breaches of GCP and/or the Protocol 35
6 Data Management and Quality Assurance 36
6.1 Source Data 36
6.2 Confidentiality 36
6.3 Data Collection ..... **Error! Bookmark not defined.**
7 Archiving 37
8 Statistical Considerations 38
8.1 Outcome Measures 38
These have been described above at Sections 3.2 and 3.3. 38
8.2 Sample Size and Recruitment 38
8.2.1 Original Sample Size 38
8.3 Statistical Analysis 38
8.3.1 Primary Outcome Analysis 38
8.3.2 Secondary Outcome Analysis 39
8.3.3 Repeat and Cross-over Interventions 39
8.3.4 Planned Sub-group Analysis 40
8.3.5 Pilot Phase 41
8.3.6 Interim Analysis 41
8.3.7 Final Analysis 41
9 Health Economic Analysis 41

9.1 Within Study Analysis 42
9.1.1 Resource Use and Costs 42
9.1.2 Outcomes 43
9.1.3 Analysis 43
9.2 Model Based Analysis 44
10 End of Trial 44
11 Direct Access to Source Data 45
12 Ethics 45
13 Monitoring Requirement for the Trial 45
14 Oversight Committees 45
14.1 TMG 45
14.2 TSC 46
14.3 DMC 46
15 Finance 46
16 Indemnity 47
17 Dissemination and Publication 47
18 Statement of Compliance 47
19 References 48

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
BMS	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
RGT	Research Governance Team
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
TIA	Transient Ischemic Attack
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:** AFS, defined as the time to major limb (above the ankle) amputation of the index (trial) limb or death from any cause. **Secondary end-points:** • OS • In-hospital and 30-day morbidity and mortality • MALE defined as major amputation (above the ankle), or any major vascular re-intervention (thrombectomy, thrombolysis, BA, stenting or surgical bypass surgery) to, the trial leg • MACE defined as SLI and/or major amputation (above the ankle) affecting the contralateral limb, MI, TIA or stroke • Relief of ischaemic rest / night 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 revascularisation intervention rates • Healing of tissue loss (ulcers, gangrene) of arterial aetiology as assessed by the PEDIS and WIfI instruments • 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, Denmark, and Sweden
Participants	The BASIL-2 sample size is based on an event-based approach. The number of randomised patients required to observe 247 events is dependent on the pattern of recruitment over time, the length of follow-up and the event rates over time. These parameters are routinely modelled to predict the number of patients needed to reach this target with two years minimum follow-up.
Main inclusion and exclusion criteria	**Inclusion criteria:** - Have provided written informed consent; - Have SLI due to IP +/- inflow (more proximal) disease; - Have had no previous vascular intervention to the target IP artery within the previous 12 months (vascular interventions to the non-target IP arteries are permitted); - Be judged by the responsible clinicians to require early IP +/- inflow revascularisation (in addition to BMT, analgesia, foot and wound care); - Have 'inflow' adequate to support both trial revascularisation strategies; - Be judged by two consultants to be suitable and medically fit for both VB and BET; - Have an anticipated life expectancy > 6 months; - Are able to understand sufficient English,or there are suitable translation services available at the relevant hospitals, to ensure informed consent; - Are able and willing to complete the HRQoL and health economic questionnaires, with help if required. **Exclusion criteria:** - 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.

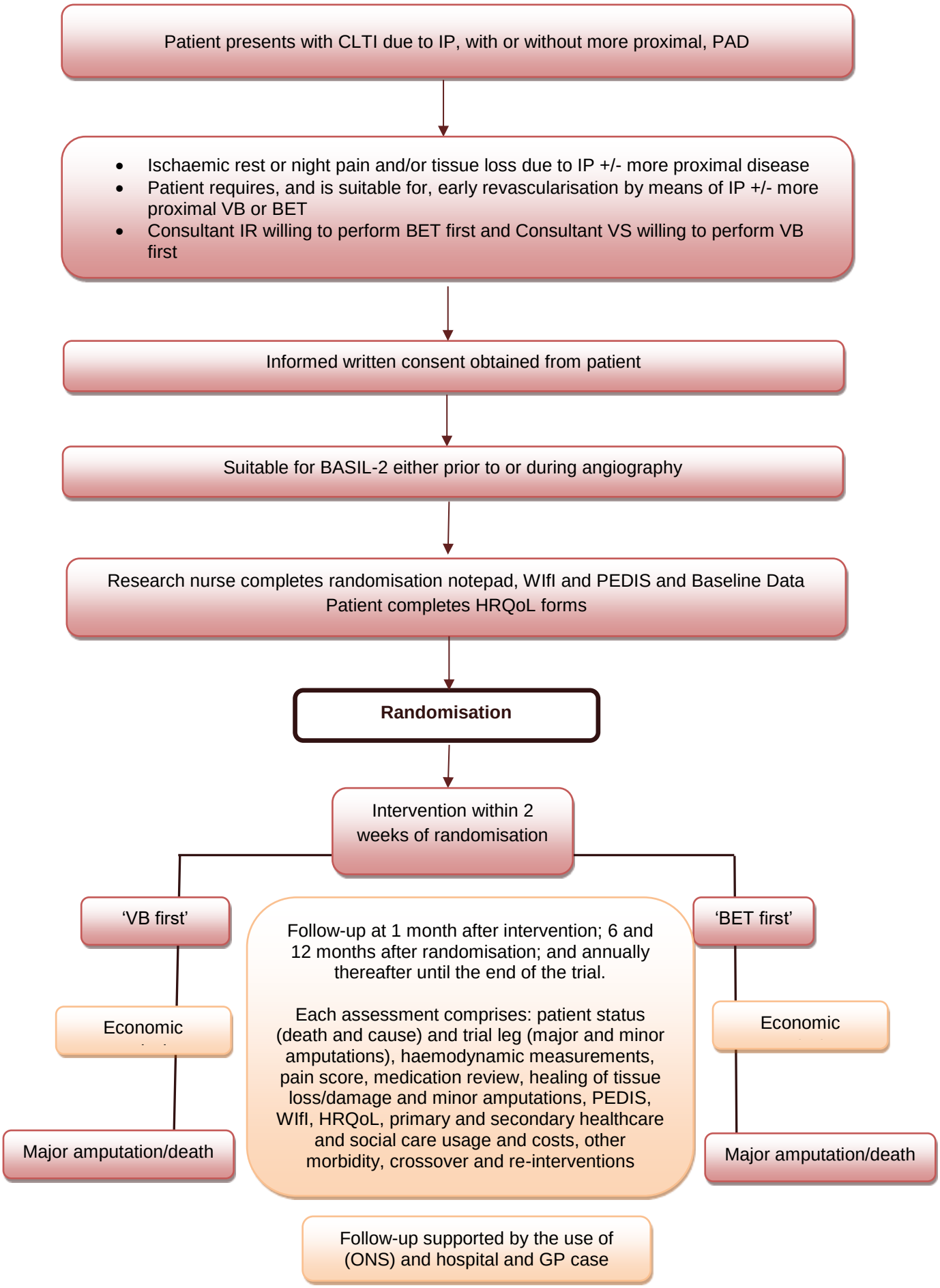


Figure 1. Trial Schema

2 Introduction

2.1 The problem of SLI

As a result of a combination of smoking, DM, high BP, high cholesterol levels, CKD and the ageing process, some patients 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 patient's legs and feet. In the early stages, PAD often causes pain in the leg only when walking, a condition termed IC. However, as PAD progresses, the blood supply to the leg can become so poor that patients get severe pain (often requiring morphine) all the time (ischaemic rest pain), often 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 tissue loss such as ulceration, even gangrene. The presence of rest / night pain, tissue loss, or both, presumed to be caused by PAD is now termed chronic limb threatening ischaemia (CLTI). The condition was formally (at the time of the BASIL-2 grant application) termed critical limb ischaemia (CLI) or severe limb ischaemia (1). The globally accepted term CLTI will now be used throughout.

Although good quality, current epidemiological data are not available, it has been estimated that one in every 1000-2000 people in the UK will be diagnosed with CLTI each year. The incidence of CLTI is rising principally as a result of our ageing population, the increasing numbers of patients with DM, and continuing high rates of smoking. Unless the blood supply to the leg and foot is improved, many patients affected by CLTI will lose their limb and/or die within 12 months. CLTI 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 thought to be for CLTI. Patients with DM are 15 times more likely to need an amputation for CLTI than the general population. As well as causing great suffering, CLTI places a large economic burden upon the NHS and social care services. CLTI is a growing global healthcare problem affecting every country in the world.

2.2 VB and BET for CLTI

The two main treatments currently available for CLTI are:

1. VB, where the patient's own vein is used to bypass the blockage
2. BET, which involves opening up the diseased arteries with balloons (PBA, BA using DCB) and sometimes the use of small metal tubes called stents (BMS, DES)

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 the 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 clear evidence that they are more clinically and/or cost-effective (3).

The purpose of BASIL-2 is to determine which treatment is best at preventing major (above the ankle) amputation and death (from any cause), getting tissue loss and minor (ankle and foot) amputations to heal, relieving ischaemic rest/night pain, and improving HRQoL in patients with CLTI due to IP (PTA, ATA, DPA) and PerA with or without more proximal, PAD. We will invite patients with CLTI due to IP +/- more proximal disease, and who are suitable for both VB and BET, to be randomly allocated, at the point of clinical 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. CLTI 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. CLTI 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 is most cost effective for the NHS and social care services.

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 CLTI due to IP PAD, 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 patients with CLI caused by IP PAD?
2. What is the clinical and cost effectiveness of selective stent placement compared with angioplasty plus primary stent placement for treating patients with CLI caused by IP PAD?

BASIL-2 directly addresses the first of these questions. If BASIL-2 supports BET as a clinically and cost-effective *first* revascularisation strategy for CLTI due to IP PAD then future trials comparing different forms of BET will be able to address the second question.

2.4 Assessment and Management of Risk

All patients randomised in BASIL-2 would have been offered either VB or BET as their first revascularisation procedure in any event and both form part of current UK "standard of care" for CLTI. 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 CLTI due to IP +/- more proximal PAD, 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.

CLTI 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 two years. 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 videoconference/ 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 CLTI due to IP +/- more proximal PAD.

3.2 Primary Outcome Measure

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

3.3 Secondary Outcome Measures:

- Time to death from any case (OS).

- Time to first major (above the ankle) amputation of the trial leg.
- In-hospital and 30-day (from date of first revascularisation of trial leg) morbidity and mortality.
- MALE defined as major (above the ankle) amputation , or any major revascularisation (thrombectomy, thrombolysis, endovascular therapy, or surgical bypass surgery) to the trial leg (time to first MALE will also be included).
- MACE defined as CLTI and/or major amputation affecting the contralateral leg, MI, TIA or stroke (time to first MACE will also be included).
- Relief of ischaemic rest/night pain (VAS, medication usage).
- HRQoL using generic (EQ-5D-5L, SF-12v2, ICECAP-O) and disease specific (VascuQoL) tools.
- Re- and cross-over revascularisation intervention rates.
- Healing of tissue loss (ulcers, gangrene) at or below the ankle presumed to be caused by PAD as assessed by the PEDIS (4) and the WIfI (5).
- Haemodynamic measurements; absolute ankle and toe pressures, ABPI, TBPI[1].

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.

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 VB and one of whom is competent to perform IP BET. 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 written consent for trial entry is

[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, ABPI, TBPI. However, since these are secondary outcomes, inability to collect these haemodynamic data should not prevent randomisation.*

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 written informed consent has been given, and baseline HRQoL 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 of the BASIL-2 Informed Consent Form;
- Has CLTI due to IP +/- more proximal PAD;
- Has had no previous vascular intervention to the target IP artery within the previous 12

months[2];

- Is judged by a minimum of two consultants, at least one of whom is competent to do IP VB, and one of whom is competent to perform IP BET, to require early IP +/- more proximal revascularisation[3];
- Has, or will have adequate AI and FP arterial 'inflow' to support both trial IP revascularisation strategies[4];
- Is judged by a minimum of two consultants, at least one of whom is competent to do IP VB, and one of whom is competent to perform IP BET, to be suitable 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 HRQoL 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 not to be primarily due to PAD.

4 Trial Procedures and Schedule of Assessments

Bilateral CLTI

Some patients may present with CLTI 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 CLTI will not, therefore, be a contra-indication to recruitment and the 'worst' leg (as

[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 AI and FP 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 VB and one of whom is competent to perform IP BET.*

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 a minimum of two consultants, at least one of whom is competent to do IP VB and at least one of whom is competent to perform IP BET.

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 requested 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 within 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. 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 written 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. 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 Consent for long-term follow-up (up to 96 months post-treatment)

Participants are followed-up for up to 96 months after randomisation. As part of a previous amendment, the following sentence was added to the BASIL-2 HRQoL Booklet:

'By completing this questionnaire and sending it to the BASIL-2 trial office, I agree to the data contained herein to be stored and used in the context of the BASIL-2 trial.'

It is acknowledged that there is a small group of participants who consented to take part in the trial prior to the 96-month follow-up being implemented. However, given the age of and health status of the participant population and the ongoing impact of the COVID-19 pandemic, we would like to keep administrative burden for them to a minimum. Therefore, where the participant completes and returns the BASIL-2 HRQol Booklet, we infer that they are happy to continue to be followed-up and for their data to be included in the BASIL-2 trial analysis. Given the length of time between follow-up data collection points, a clinical member of the BASIL-2 team may contact the participant, by telephone to remind them that there is a questionnaire to complete. If the participant does not return the BASIL-2 HRQoL Booklet, or indicates during a telephone call that they are unwilling to complete the BASIL-2 HRQoL Booklet, the participant will be considered partially withdrawn. Any data collected prior to this point will still be included in the BASIL-2 trial analysis. The patient will also be asked to allow electronic follow up of local and national records to continue.

4.1.3 Withdrawal

Participants should be aware at the beginning that they can freely withdraw (discontinue participation) from the trial at any time. Participants can withdraw from all or part of the BASIL-2 trial procedures as below:

- Trial intervention: The participant would no longer like to receive the trial intervention.
- Clinical follow-up: The participant 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).
- HRQOL: The participant no longer wishes to complete HRQOL booklets.
- NHS data: The participant is no longer 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).

4.2 Baseline Assessments

Baseline assessment forms are completed prior to randomisation and trial number allocation and 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 either legs
    - Previous amputations (major and minor)
    - 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, ABPI, TBPI (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 due to PAD)
- Assessment of ischaemic night/rest pain

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

A pseudoanonymised (patient trial number and date of birth) copy of the diagnostic imaging study, along with the contemporaneous report of that study, on which the decision to randomise was based should be forwarded as soon as practically possible, on an encrypted storage device, to the BASIL-2 Trial Office for subsequent angiographic scoring by suitable persons (VS, IR) blind to the treatment allocation. (7).

PEDIS and WIfI scores will be completed for those patients who have tissue loss due to their PAD.

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, written informed consent has been obtained, minimisation variables have been determined, and the baseline HRQoL 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 (ischaemic rest / night pain only, tissue lossonly, or both))
- 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 log in 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 allocated.

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

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

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 presentation and anatomical pattern of disease. The potential options include PBA +/- 'bail-out' BMS, PBA +/- 'bail-out' DES, DCB +/- 'bail-out' BMS, DCB +/- '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 or failure will be determined by the VS or IR undertaking the procedure based on one or more of the following: completion imaging (angiography, US), clinical examination including palpation of foot pulses and haemodynamic measurements.

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
- Success of the intervention in the opinion of the operator as described above

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, where possible, 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. VB success or failure will be determined by the VS undertaking the procedure based on one or more of the following: completion imaging (angiography, US), clinical examination including palpation of foot pulses and haemodynamic measurements.

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
- Success of the intervention in the opinion of the operator as described above

4.7 Amputation

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

4.8 In-patient Follow-up

An **In-patient Form** will be completed every time a patient is admitted to hospital for any reason, whether it is trial or non-trial related. The **In-patient Form** provides a summary of the admissions, captures data on any complications, and records if a trial intervention has been performed. Where an intervention has been performed an Intervention Form will also be

completed

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, video conference and post. Clinical information may also be obtained from the patient's GP, practice nurse, district nurse or podiatrist etc. if necessary.

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

- Interventions since last follow-up assessment *(Inpatient Form only)*
- Hospitalisations since last follow-up assessment *(Inpatient Form only)*
- Other health problems requiring medical intervention in secondary care *(Inpatient Form only)*
- Clinical status of trial leg and contra-lateral leg
- Haemodynamic status of trial leg, where possible[6]
- Mobility status
- Patient HRQoL 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 Examination	Case notes		☑			☑
Imaging	Case notes		☑			☑
Wound Assessment	Case notes		☑			☑
Ischaemic Pain (VAS)	Patient		☑			☑
WIfI	Case notes		☑			☑
PEDIS	Case notes		☑			☑

	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
EQ-5D-5L	Patient		☑			☑
ICECAP-O	Patient		☑			☑
VascuQoL	Patient		☑			☑
Haemodynamic indices	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				☑	☑

5 Recording and Reporting of AE

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 AE		An AE which resulted from the administration of any of the research procedures.
Serious Adverse Event	SAE	An AE that: • Results in death • Is life-threatening*

Event	Acronym	Definition
		• Requires hospitalisation** or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Or is otherwise considered medically significant by the Investigator**
Unexpected and Related AE		An AE which meets the definition of both an Unexpected Event and Related AE
Unexpected Event		The type of adverse event that is not listed in the protocol as an expected occurrence.
Expected (S)AE		(S)AEs that are 'expected' in the sense that they are recognised and accepted complications / consequences of CLTI, VB and BET.

***** *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. NB: Planned hospitalisations that clearly are not related to the condition under investigation or hospitalisations / prolongation of hospitalisation due to social reasons should be documented in the patient's notes but do not need to be reported to the BASIL-2 Trial Office.*

Hospitalisations that are brought forward due to worsening symptoms of CLTI or in which patients are admitted for clinical observation of their CLTI are reportable SAEs.

Hospitalisations for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition should be documented in the patient's notes but do not need to be reported to the BASIL-2 Trial Office.

******* *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 AFS and, as such, neither major amputation nor revascularisation surgery or BET-related deaths require reporting as expected SAE, the data will be collected via the appropriate CRF.

5.2 AE General Recording Requirements

The collection and reporting of AE and SAE will be concordant with the principles of GCP as defined in 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 AE in the patient's medical notes. It is also recommended that this includes an assessment of severity whether it is caused by (related to) the trial intervention

Safety monitoring will occur throughout the trial and has been delegated by the Sponsor (University of Birmingham) to the BCTU. As there are no IMPs being used in BASIL-2, and all of the surgical techniques being tested in this trial are part of current UK 'standard of care', few (S)AEs are anticipated as a unique consequence of participation in BASIL-2.

5.3 AE Reporting Requirements

As BASIL-2 patients are likely to have significant co-morbidities the frequency of AE and SAE is likely to be high. However, it is anticipated that most AEs and SAEs occurring in BASIL-2 will be 'expected' in the sense that they are recognised and accepted complications / consequences of CLTI, VB and BET.

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 SAE Reporting Requirements

SAE occurring **more than 30 days after the trial intervention**, for any given patient, **do NOT require routine notification using an SAE form**, since they are likely to be due to the underlying PAD (CLTI), other pre-existing and new co-morbidities unrelated to the trial interventions (VB, BET). However, a PI can still choose to notify events occurring more than 30 days after the trial intervention should they believe that they are due to the trial interventions.

On receipt of an SAE form, the BASIL-2 Trials Office will allocate each SAE a unique reference number (to be used on all subsequent correspondence regarding the SAE) and send this t the trial site within one working day.

If the site has not received confirmation of receipt of the SAE, and a unique reference number, from the BASIL-2 Trials Office within 1 working day, the site should contact the Trials Office.

5.4.1 Expected SAE

As noted above. there are many well-recognised SAE (**expected SAE**) associated with CLTI, VB and BET which do **NOT** require **expedited notification** (within 24 hours of the site becoming aware of the SAE; Table 3.

E**xpected SAE** only require parts A, B and D of the SAE form to be completed. Expected SAE forms should be sent to the BASIL-2 Trial Office within 2 weeks. PI should also notify their own institutions of SAE in accordance with their institutional policies.

SAE should be recorded in the medical records. Expected SAE will be collated at the BASIL-2 Trial Office, but will not require evaluation by the CI. All SAE 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 Unexpected SAE for Expedited Notification to the BASIL-2 Trial Office

Unexpected SAE (those not listed in Table 3) occurring **within 30 days of the trial intervention** must be notified to the BASIL-2 Trial Office **within 24 hours** of the PI becoming aware of the event. Unexpected SAE require all parts of the SAE form to be completed so that relatedness and expectedness can be assessed.

Unexpected 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

Unexpected SAEs will immediately be referred to the CI or delegated deputy 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 unexpected SAE 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 unexpected SAE in accordance with their institutional policies.

Assessment of Relatedness

When completing the SAE form, the PI will be asked to categorise the causality (relatedness) and the severity of the **unexpected SAE** (Table 4)**.** When categorising causality the PI should consider if any concomitant events or medications may have contributed to the SAE 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 SAE.

On receipt of an unexpected SAE form the BASIL-2 Trial Office will forward it, with the unique reference number, to the CI (or delegate), who will independently review the causality of the unexpected SAE. An unexpected 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. The PI's category of causality will not be downgraded by the CI (or delegate). If the CI (or delegate) disagrees with the PI's category of causality, the categories of both parties will be documented.

Table 4. Categories and definitions of causality of an unexpected SAE.

Category	**Definition**	**Causality**
(1) Unrelated	There is no evidence of any causal relationship.	

(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).	Unrelated
(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 unexpected SAE for expectedness

Table 5).

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	SAE is consistent with known information about the trial related procedures.
(2) Unexpected	SAE is not consistent with known information about the trial related procedures.

5.4.3 Provision of Follow-up Information

Following submission of a SAE Form, the participant should be followed up until resolution or stabilisation. Once the SAE has been resolved or stabilised, all follow-up information has been received, and the paperwork is complete, the final version of the SAE Form completed at site must be returned to the BASIL-2 Trial Office and a copy kept in the Site File.

5.5 Reporting SAE to third Parties

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

BCTU will report all Unexpected and Related SAE to the REC and the UoB Research Governance Team (RGT) within 15 days.

The 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.

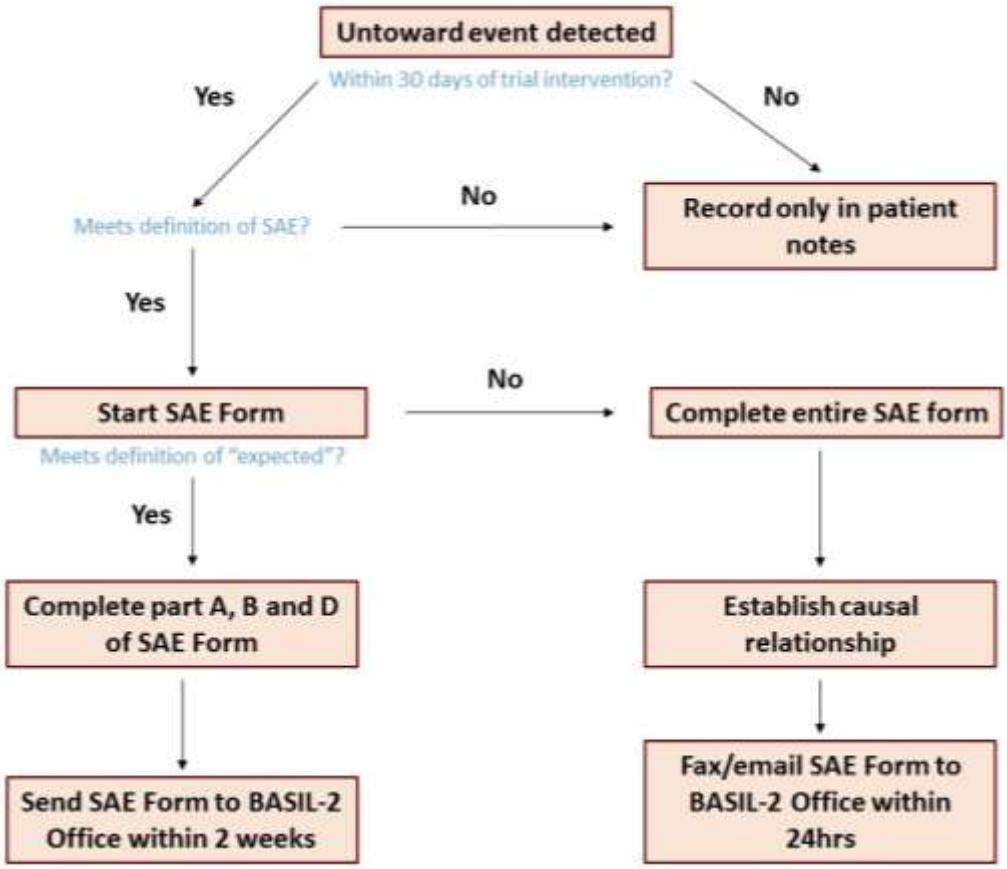
5.5.1 Related and Unexpected SAE

SAE categorised by a PI or the CI as both related and unexpected will be expeditiously 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 DMC will be provided with details of all SAEs.

5.6 Summary of Safety Reporting Procedures for BASIL-2



5.7 Annual Progress Reports

A progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and then 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 and RGT 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 sponsor 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 are defined as all of the information contained within the original records and certified copies of original records. Source data will be accessible and maintained.

Source data are 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.

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 CRF

The BASIL-2 patient population is likely, in the main, to be both elderly and infirm. Thus, where possible, 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 Table 6.

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

Table 6. Form Table

Form Name	Schedule for Submission
Randomisation Form	Collected at point of randomisation
Patient Contact Details	Collected at randomisation
Baseline Medical Status Form	Collected at randomisation
Baseline Clinical Assessment Form	Collected at randomisation
In-patient Day case 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 Forms	As soon as possible after each follow-up assessment point
HRQoL Booklets	As soon as possible after each assessment point
SAE Form	If “unexpected”; faxed within 24hrs of research staff becoming aware of event If “expected”, as defined in the protocol, page 1 only, sent within 2 weeks.

Outcomes will be collected by RNs and entered onto paper CRF. 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 CRF 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 Calculation

The sample size calculation for this trial was based on a time-to-event analysis to be undertaken two-years after completion of recruitment. It was anticipated that recruitment would 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 were based on the original BASIL-1 trial.

Based on the above, and allowing for 10% dropout for the primary outcome (the lost to follow-up rate in BASIL-1 was around 1%) a trial of 600 patients would 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.

8.2.2 Revised Sample Size

The initial assumptions made in BASIL-2 concerning recruitment rates were not achieved. The BASIL-2 sample size changed to an event-based approach. The number of randomised patients required to observe 247 events was dependent on the pattern of recruitment over time, the length of follow-up and the event rates over time. These parameters were routinely modelled to predict the number of patients needed to reach this target with two years minimum follow-up.

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 outcome will be compared between treatment arms using survival analysis methods. Kaplan-Meier survival curves will be constructed for visual presentation of time-to-event comparisons. A Cox proportional hazards model will be fitted to obtain a hazard ratio, 95% confidence interval (CI) and corresponding p-value, adjusting for the minimisation variables as listed in section 4.3. The primary analysis will be based on the intention to treat (ITT) principle.

Further analysis of the primary outcome will involve fitting a flexible parametric survival model to model the underlying differences in hazard, and to allow for non-proportional hazards.

8.3.2 Secondary Outcome Analysis

Secondary outcome measures that are time to event outcomes (e.g. OS, MALE and MACE) will be presented and analysed as per the primary analysis for AFS.

Outcome measures that are based on a continuous scale (pain VAS, EQ-5D-5L, etc.) will be reported using means and standard deviations at each time point. Longitudinal plots of the mean scores over time by treatment group will be produced for visual inspection of the data. Adjusted mean differences at the primary time points (1, 12 and 24 months) will be estimated through the use of mixed effect repeated measures models.

Binary outcome measures (MALE, MACE etc.) will be summarised using frequencies and percentages. A log-binomial model will be used to generate adjusted risk ratios and risk differences (using an identity link function).

Other binary outcome measures which are measured at multiple assessment times (medication usage etc.) will be will be summarised using frequencies and percentages at each assessment. Adjusted odds ratios at the primary time points (1, 12 and 24 months) will be estimated through the use of mixed effect repeated measures.

All estimates of differences between groups will be presented with 95%, two-sided CIs, and will be adjusted for the minimisation variables where possible. All analyses will be based on the ITT principle.

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

The original aim was to have 11 regional vascular centres and randomise 600 patients over 3 years. Each centre received funding for a dedicated BASIL-2 RN. At the end of the first year, recruitment was assessed against several pre-specified “stop” criteria; specifically, were fewer than:

- 2/3 of centres recruiting
- 60 patients randomised
- 80% of patients receiving their allocated treatment
- 2/3rds of centres recruiting 2 patients per month from month 4 onwards

Although at the end of the pilot phase the first three pre-specified criteria had been exceeded, regional vascular centres were not able to recruit at 2 patients per month. In agreement with the funder and Sponsor the trial was opened to all UK vascular centres. Centres in Kolding, Denmark and Stockholm, Sweden, were also opened. The funding was also changed to a per patient payment model.

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

The end of trial will be six months after the date of last data capture (to include resolution of missing data and data queries). The BASIL 2 Trial Office will notify the REC that the trial has ended within 90 days of the end of trial. Where the trial has terminated early, the BASIL 2 Trial Office will inform the REC within 15 days of the end of trial. The BASIL 2 Trial Office will provide them with a summary of the clinical trial report within 12 months of the end of trial.

A copy of the end of trial notification as well as the summary report will also be sent to the Sponsor at the time of sending these to the REC.

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 (this includes relevant imaging and radiology).

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 the trial protocol, the principles of Good Clinical Practice (GCP) as defined by the UK Policy Framework for Health and Social Care Research 2017 and the Data Protection Act 2018.

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.