Multi-centre randomised controlled trial of clinical and cost-effectiveness of drug coated balloons, drug eluting stents and plain balloon angioplasty with bail-out bare metal stent revascularisation strategies for severe limb ischaemia due to femoro-popliteal disease

BAlloon vs Stenting in Severe Ischaemia of the Leg-3

TRIAL PROTOCOL: Version 4.0 06 Aug 2019

Sponsor:	**University of Birmingham**
Chief Investigator:	**Professor Andrew Bradbury**
Coordinating Centre:	**Birmingham Clinical Trials Unit**
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NIHR | National Institute for Health Research

UNIVERSITY OF BIRMINGHAM | BCTU Birmingham Clinical Trials Unit

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Safety Reporting

Safety reporting is described in Section 6

Fax SAE Forms to: 0121 415 9136

Chief Investigator and Sponsor Signatures

The Chief Investigator and Sponsor have discussed and agree to abide by this this protocol and to conduct the trial in compliance with GCP, the General Data Protection Regulation and the Data Protection Act (2018) the Trust Information Governance Policy (or other local equivalent) and the Research Governance Framework (2005 2nd Edition; as amended).

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

1 Protocol Amendments

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

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
1	*22 Jan 2016*	*2.0*	*Substantial*	*Revision of inclusion and exclusion criteria, Revision of randomisation minimisation variables*
3	*22 Jun 2016*	*2.0*	*Non-substantial (category C)*	*Escalation of patient-completed booklet to V1.1*
11	*22 Jun 2017*	*3.0*	*Substantial*	*Provision to seek written informed consent in less than 24 hours of initial approach* *Changed definition regarding the composition of the MDTOther confirmatory and grammatical changes*
18	*17 JUL 2019*	*4.0*	*Substantial*	*Re-open to recruitment following a pause relating to an urgent safety measure* *Changed definitions of types of withdrawal* *Changed SAE report form process* *Extended follow-up period of patients* *Other confirmatory and grammatical changes*

Please note that those amendments not listed above are both non-substantial and category B. They have therefore been communicated to the clinical centre(s) which they directly concern.

Principal Investigator Signature Page

Principal Investigator:

I have read and agree 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 Main Research Ethics Committee (MREC).

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-3 Trial Office

Table of Contents

2 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
EAG	Expert Advisory Group
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
JAHA	Journal of the American Heart Association
LA	Local Anaesthetic
MACE	Major Adverse Cardiovascular Event
MALE	Major Adverse Limb Event
MDA	Medical Device Alert
MDT	Multi-disciplinary Team
MHRA	Medicines and Healthcare products Regulation Agency
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

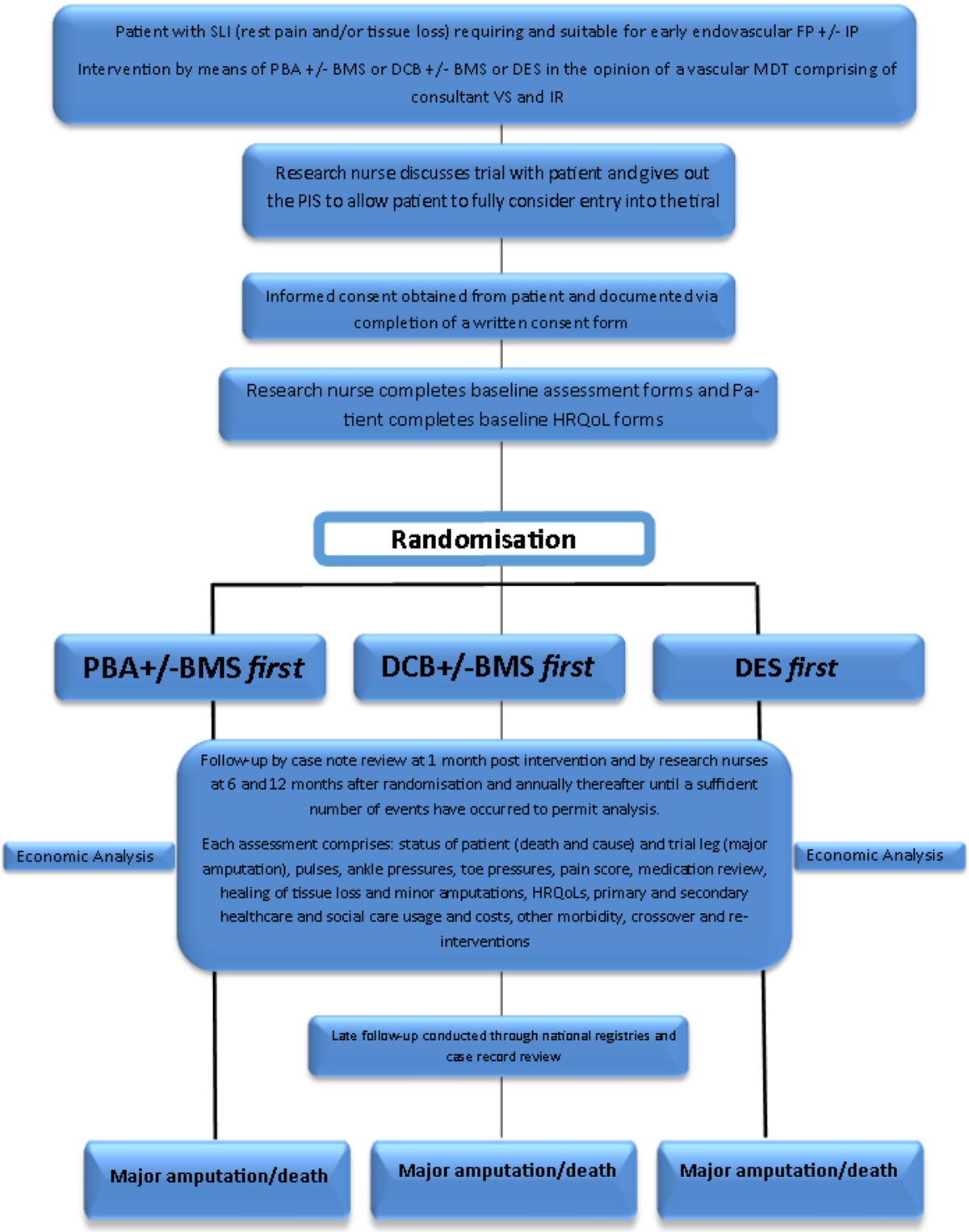
VS	Vascular Surgeon
WIFI	Wound, Ischaemia and Foot Infection
+ / -	With or Without

3 Trial Summary

Title	Multi-centre RCT of clinical and cost-effectiveness of DCBs, DESs and PBA with bail-out BMS revascularisation strategies for SLI due to atherosclerotic FP, +/- IP, PAD
Short title/Acronym	**BA**lloon vs. Stenting in **S**evere **I**schaemia of the **L**eg-3 Trial: **BASIL-3 Trial**
Type of trial	A pragmatic individually randomised multi-centre three-arm open trial comparing DCB +/- "bail-out" BMS, DES, and PBA+/-BMS *first* revascularisation strategies for SLI due to atherosclerotic FP +/- IP PAD; incorporating an internal pilot phase and within-trial health economic analysis.
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 • Amputation • Re- and cross-over intervention rates • MALE, defined as amputation (transtibial or above) or any major vascular re-intervention (thrombectomy, thrombolysis, BA, stenting or surgery) • In-hospital and 30-day morbidity and mortality • MACE (SLI and amputation affecting the contralateral limb, ACS, stroke) • Relief of ischaemic pain (VAS, medication usage) • Psychological morbidity using HADS • HRQL using generic (EQ-5D-5L, ICECAP-0, SF-12) and disease specific (VascuQoL) tools • Healing of tissue loss (ulcers, gangrene) using the PEDIS and WiFi instruments • Extent and healing of minor (toe and forefoot) amputations • Haemodynamic changes; absolute ankle and toe pressures ABPI, TBPI
Trial design	Superiority RCT

Trial duration per participant	Minimum of 24 months
Estimated total trial duration	Approximately 85 months
Planned trial sites	Multicentre, UK
Participants	Patient recruitment will be terminated once 291 events (primary end point) are achieved
Main inclusion and exclusion criteria	**Inclusion criteria:** - SLI due to atherosclerotic FP +/- IP PAD - Judged by the responsible clinicians (at least two Consultants (Vascular Surgeons and /or Interventional Radiologists)) working as part of a MDT to require early endovascular FP +/- IP revascularisation in addition to BMT, foot and wound care - Has adequate 'inflow' to support all trial revascularisation strategies or intervention is planned to restore inflow (either during serial interventions or "hybrid" revascularisation)Judged suitable for all three trial revascularisation strategies following diagnostic imaging and a formal (documented) discussion by the MDT meeting **Exclusion criteria:** - Life expectancy ≤6 months - Is, in the opinion of the clinician, unable to provide informed consent - Non-English speaker where translation facilities are insufficient to guarantee informed consent - Judged unsuitable for any of the revascularisation strategies being evaluated - Previous intervention to the target vessel within the past 12 months - Unable or unwilling to complete the QoL and health economic booklet

3.1 Trial Schema (Figure 1)



This protocol describes the BASIL-3 trial only. The trial will be conducted in accordance with the protocol and GCP. 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

4 Introduction

4.1.1 The problem of SLI

As a result of diabetes, smoking, high blood pressure, high cholesterol and kidney failure, some people develop atherosclerosis (aka 'hardening of the arteries') of the arteries in their legs. This atherosclerosis blocks their arteries so reducing the blood supply to their legs and feet. In the early stages, such disease often causes pain in the leg only on walking but as the disease progresses the blood supply to the leg can become so poor that people get severe pain (requiring morphine) all the time, especially at night. 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.

Unless the blood supply to the leg and foot is improved, many affected people will lose the limb and/or die within 12 months as a result of this so-called SLI. One in every 1000-2000 people in the UK will be diagnosed with SLI each year; and this rate is rising as a result of the ageing population, increases in diabetes, and continuing high rates of smoking. Without treatment, up to one in four patients will die within 12 months and a further one in three will require major limb amputation.

Recovery time from SLI treatment is often prolonged and caring for patients with SLI is extremely costly (NHS and social care). 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 costly adaptations to their houses.

As a result of data from the HTA-funded BASIL-1 trial, most SLI patients with more limited disease in the femoro-popliteal arteries are treated by endovascular means, rather than bypass surgery, in the first instance because, in general, it is less risky and expensive; and seems to work as well as bypass in the short term (2-3 years).

For many years the 'standard of care' endovascular treatment for such patients has been PBA, with the use of so-called 'bail-out' BMS when PBA alone has been unsuccessful in satisfactorily opening up the artery. More recently, DCB +/- BMS and DES have entered the market and are widely used around the world. These DCB +/- BMS and DES release various drugs which act on the vessel wall and are believed to reduce the risks of the artery narrowing down or blocking off again. However, the evidence base underpinning the use of DCB +/- BMS and DES is weak and they are much more expensive than PBA+/-BMS.

For this reason, NICE and HTA have both recommended RCTs in patients with SLI to determine whether DCB +/- BMS and DES offer additional clinical benefits over PBA+/-BMS and, if so, whether these benefits can be achieved at current willingness to pay thresholds. BASIL-3 directly addresses the HTA call (13/81) by proposing a RCT where patients with SLI due to atherosclerotic FP, +/- IP, PAD will be randomly allocated to DCB +/- BMS or DES or BMS+/-PBA in the first instance.

In the BASIL-3 study, we will invite people affected by SLI due to atherosclerotic FP, +/- IP, PAD and who are considered suitable for DCB +/- BMS, DES and PBA+/-BMS, to be randomly allocated to one of these endovascular treatments in the first instance. If the allocated treatment is unsuccessful, then patients can go on and have one of the other treatments; or go on to have surgery as clinically appropriate. We will follow-up patients for a minimum of 2 years, during which time they will be offered further medical, surgical, and endovascular treatment as required. We will also study the costs of the treatments to see which offers best 'value for money' for the NHS.

4.1.2 DCB+/-BMS, DES and PBA+/-BMS use for FP, +/- IP, PAD

In recent years, a number of "advanced" endovascular technologies (DES, DCB +/- BMS) have become available. These devices are more expensive than PBA +/- BMS and, as yet, there is no evidence that they are more clinically effective, or that they are cost-effective, in patients with SLI (1).

The three treatments currently available for FP SLI are:

1. PBA +/- BMS which involves opening up the diseased arteries with a balloon and if necessary drug-free stents
2. DCB +/- BMS also involves opening up the diseased arteries with balloons and using stents but the balloons in this arm are coated with a drug that may reduce the risk of the artery re-narrowing or blocking off
3. DES involves the placement of stents which release a drug that may reduce the risk of the artery re-narrowing or blocking off

If the first allocated endovascular procedure is unsuccessful, patients may receive alternative treatment which may include repeat and crossover endovascular interventions, bypass surgery or amputation, according to current 'standard of care'. All care after the first allocated

revascularisation will be determined by the responsible VS and IR in the patients' best interest and will not be specified in the study protocol.

The purpose of BASIL-3 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 atherosclerotic FP, +/- IP, PAD.

4.2 BASIL-3 and NICE

There is concern within the UK (recently expressed by NICE in their August 2012 PAD Guidelines) that, if DCB +/- BMS and DES are not associated with a significantly improvement in important clinical outcomes, they may represent a poor use of NHS and Social Care resources. For this reason, the NICE PAD GDG have recommended RCTs comparing DES, DCB +/- BMS, and PBA +/- BMS (NICE CG 147) (http://guidance.nice.org.uk/CG147).

Economic evaluation will be carried out from the perspective of the NHS and Personal Social Services based on the trial outcomes of cost per year of AFS, cost per year of OS, and cost per QALY. Prospective data collection for resource use will include procedure-related care, hospital stay and re-admissions, as well as post-discharge use of health and social services. Modelling beyond the trial endpoint for the outcome of AFS will be considered if appropriate data exist.

4.3 BASIL-3 and the HTA

BASIL-3 directly addresses the research recommendation contained in the BASIL-1 trial HTA monograph (6)

> Examine the clinical and cost-effectiveness of new endovascular techniques and devices (such as stents and stent-grafts) in the management of SLI

And re-expressed in the HTA call 12/81

> "Is the use of DCB +/- BMS or DES clinically and cost-effective in the endovascular treatment of patients with critical limb ischaemia caused by disease of the arteries above the knee?"

4.4 Assessment and Management of Risk

In current NHS practice as recommended by NICE, PBA+/-BMS is regarded as 'standard of care' for most patients, because of uncertainty regarding the clinical and cost-effectiveness of DCB +/- BMS and DES.

Patient experience is the same whether they are randomised to DCB+/-BMS, DES or PBA+/-BMS as all are performed under local anaesthetic.

4.4.1 BASIL-3 and Katsanos Meta-analysis 2018

Katsanos et al. (2018) (2) published a systematic review and meta-analysis in the Journal of American Heart Association (JAHA) in December 2018. This meta-analysis reviewed a total of 28 randomised controlled trials of patients undergoing treatment of femoro-popliteal disease with paclitaxel drug coated balloons (DCB) and drug eluting stents (DES). 89% of these patients had intermittent claudication and no limb threatening ischaemia but it did report an increased risk of all-cause mortality at 2-5 years in patients with peripheral arterial disease who were treated with drug eluting stents and drug coated balloons. (3)

4.4.2 Recruitment Pause

Whilst the population in this meta-analysis differs to the cohort in BASIL-3, the Trial Steering Committee (TSC) decided to pause recruitment in December 2018, pending further information and investigation.

4.4.3 Resumption of Recruitment

The Medicines and Healthcare Regulatory Agency (MHRA) set-up an Expert Advisory Group (EAG) to review the information on these devices (3). In June 2019 the EAG released a report with their recommendations following an investigation. This report recommended the devices should still be considered as a treatment option for patients within critical limb ischaemia. Subsequently, the EAG recommend trials like BASIL-3 should consider re-opening to recruitment (4).

The MHRA released a Medical Device Alert (MDA) MDA/2019/023 (5) which supported the EAG recommendations and stated the risk-benefit profile for patients with other vascular indications may be different to those for intermittent claudication and requires further clinical evidence to be reviewed before any conclusions can be drawn (5). This includes the recommendation that the use of paclitaxel coated DCBs and DESs to still be considered in patients with critical limb ischaemia.

With support from the HTA and the MHRA, the TSC made the decision to re-open the trial to recruitment.

5 Trial Design

BASIL-3 is an individually randomised, multi-centre, pragmatic, three-arm, open trial of three endovascular revascularisation strategies for the management of SLI due to atherosclerotic FP, +/- IP, PAD, incorporating a within-trial economic evaluation. BASIL-3 has been closely based on the currently HTA-funded BASIL-2 trial and will utilise 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 HRQL and health resource usage, patients will be regularly followed up after randomisation.

5.1 Trial Objective

To determine which primary endovascular revascularisation strategy represents the most clinically and cost-effective treatment for SLI, due to atherosclerotic FP, +/- IP, PAD.

5.2 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. The decision to amputate must be taken by a properly constituted, minuted, multi-disciplinary team meeting.

5.3 Secondary Outcome Measures:

- OS
- MALE, defined as amputation (transtibial or above) or any major vascular re-intervention (thrombectomy, thrombolysis, BA, stenting, or surgery)
- In-hospital and 30-day morbidity and mortality
- MACE (SLI and amputation affecting the contralateral limb, ACS, stroke)
- Relief of ischaemic pain (VAS, medication usage)
- Psychological morbidity (using HADS)
- HRQL using generic (EQ-5D-5L, ICECAP-O, SF-12) and disease specific (VascuQoL) tools
- Re- and cross-over intervention rates
- Healing of tissue loss (ulcers, gangrene) as assessed by the PEDIS (7) and the WiFi (8) 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

6 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.

Potentially suitable patients will be identified in minuted, MDT meetings comprising at least two consultants (VS and /or IR), and then approached by a RN who will offer appropriate

verbal and written information. Consent will subsequently be obtained by a 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-3 Delegation and Signature Log**. Please also refer to section 6.1.

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 HRQL data collected, the patient will be randomised (1:1:1) to a PBA+/-BMS, DCB+/-BMS, DES revascularisation first strategy.

This study will include **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 NHS Digital (previously called 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 will 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.

6.1.1 Bilateral SLI

It is anticipated that approximately 25% of eligible patients will have bilateral SLI. 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. Bilateral SLI is not 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

6.1.2 Previous amputation

Prior unilateral amputation is not a contra-indication to randomisation of the remaining contralateral “trial” leg.

6.2 Inclusion Criteria

In order to be considered for randomisation in BASIL-3, patients must:

- Have SLI due to atherosclerotic FP, +/- IP, PAD
- Be judged by the responsible clinicians (at least two consultants (VS and /or IR)) working as part of a MDT to require early FP, +/- IP, endovascular revascularisation in addition to BMT, foot and wound care
- Has adequate 'inflow' to support all trial revascularisation strategies or intervention is planned to restore inflow (either during serial interventions or "hybrid" revascularisation)
- Judged suitable for all trial revascularisation strategies following diagnostic imaging and a documented MDT discussion

6.3 Exclusion Criteria

Patient will be excluded from BASIL-3 if they:

- Have an anticipated life expectancy ≤6 months
- Are, in the opinion of the clinician, unable to provide informed consent
- Are a non-English speaker where local translation facilities are insufficient to guarantee informed consent
- Are judged unsuitable for the endovascular revascularisation strategies by a vascular MDT
- Previous intervention to the target vessel within the past 12 months
- Unable or unwilling to complete the QoL and health economic booklets

7 Trial Procedures and Schedule of Assessments

7.1 Informed Consent Procedure

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

Informed consent will be obtained by a suitably trained member of the local research team who is listed on the **BASIL-3 Delegation and Signature Log**. The patient will previously have been provided with the MREC approved PIS on NHS Trust-headed paper. Adequate time will be given for consideration by the patient, and where appropriate their family, before being approached to give consent to randomisation. 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. The original signed form will be retained at the study site in the ISF and a copy placed in the medical notes. A copy will also be sent to the BASIL-3 Trial Office. With the participant's prior consent, their GP will also be informed using a standard letter. Details of the informed consent discussions will be recorded in the participant's medical notes.

7.1.1 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. Reaffirmation of continuing consent should be documented on attendance of each follow-up session. Further guidance concerning time to consent is available from the National Research Ethics Service's Single Issue Ethical Debate paper, "Time to Consent" available from http://www.hra.nhs.uk/documents/2013/09/issues-and-arguments-time-to-consent.pdf and included as Appendix I.

7.1.2 Withdrawal

Patients may withdraw from the trial at any time if they choose not to continue or the responsible VS and IR feel that continued participation is inappropriate.

There are four different types of withdrawal:

- The patient would like to withdraw from the randomised treatment allocation, but is willing to be followed-up according to the trial protocol (i.e. has agreed that follow-up data can be collected)
- The patient does not want to attend trial specific follow-up visits but has agreed to be followed-up according to standard practice (i.e. has agreed that follow-up data can be collected at standard clinic visits or accessed remotely using electronic patient records or medical records)

- The patient is not willing to be followed up for trial purposes at any further visits (i.e. has agreed that any data collected prior to the withdrawal of consent can be used in the trial final analysis)

If withdrawal is healthcare professional-initiated, then the reason(s) for withdrawal will be recorded on the CRFs; otherwise, a simple statement reflecting patient preference will suffice. Patients who withdraw from trial treatment but continue with on-going follow-up and data collection will be followed-up in accordance with the protocol.

7.2 Baseline Assessments

All patients presenting to participating vascular units with SLI, and who are being considered for revascularisation (whether inside or outside trial), will already have undergone the following as part of their 'standard of care' prior to be being approached about BASIL-3:

- 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
    - Recording of peripheral pulses
    - Measurement of ABPI and/or TBPI (if appropriate)
- 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)
- Assessment of ischaemic night/rest pain using a VAS
- Discussion by VS and IR in an MDT

In patients who have consented to take part in BASIL-3, these data will be transferred to the **Baseline Assessment Form**.

Prior to randomisation, and after giving consent, participating patients will be asked to complete the **Baseline HRQL Booklet** containing EQ-5D-5L, SF-12, HADS, ICECAP-O, VascuQoL.

A copy of the diagnostic imaging study on which the decision to randomise was taken will be forwarded to the BASIL Trial Office for Bollinger Scoring (9)

Patients with wounds on their legs will be assessed and scored according to the PEDIS (7) and WiFi (8) classification systems.

7.3 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 HRQL 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
- CKD*
- Severity of clinical disease (ischaemic rest / night pain only, tissue loss, both rest pain and tissue loss)
- Artery being treated (superficial femoral, popliteal, both)
- Hospital Trust
- Has previous permissible intervention to the trial leg (either to the target vessel >12 months ago or to another vessel within the trial leg)
- Hybrid procedure planned

*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)

7.3.1 Telephone and online randomisation

Patients can be randomised into BASIL-3 via a secure 24/7 internet-based randomisation service (https://www.trials.bham.ac.uk/basil3) or by telephone (number **0800 9530274**). Telephone randomisation is available Monday-Friday, 09:00-17:00. For the secure internet randomisation, each site and each researcher will be provided with a unique log-in username and password.

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 9530274**). The randomisation list will be produced using a random length block design.

7.4 Interventions

7.4.1 Timing of Interventions

The allocated intervention should be scheduled **within two weeks** of the date of randomisation where possible and clinically appropriate.

7.4.2 Nature of Interventions

The trial procedures will be performed under LA, usually via an US-guided puncture of the CFA; occasionally intravenous sedation may be given and, rarely, a GA may be required. Success will be established by palpation of foot pulses and measurement of ABPI and TBPI.

All trial devices must be CE marked and will be supplied via NHS procurement.

The brand name, type and product characteristics will be recorded

7.5 Amputation

The **Amputation Form** will capture data on the level and type of amputation. The decision to amputate must be taken by a properly constituted, minuted, multi-disciplinary team meeting.

7.6 In-patient Follow-up

An **In-patient Form** will be completed every time a patient is admitted to hospital for any reason and will capture a summary of the hospital admissions details, verify if any complications occurred, and confirm if a trial intervention occurred. **An intervention Form** will also be completed for each intervention to the trial leg (endovascular, surgical bypass, non-bypass vascular surgery, amputation).

7.7 Follow-up Visit

Patients will be followed-up at 1 month after intervention, 6 and 12 months after randomisation and annually thereafter until a sufficient number of events have occurred to permit analysis..

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
- Clinical status of trial leg and contra-lateral leg
- Haemodynamic status of trial leg
- Functional status
- Patient HQoL and resource use forms.

The above follow-up schedule should be adhered to for each patient as closely as possible however it is noted, that due to the patient group, strict adherence may not be possible for all trial participants. In cases where participants are unable to attend a follow-up visit (e.g. due to illness), the clinical follow-up data should be collected from hospital records (where available) and attempts should be made for the QoL and health economic booklet to be completed as close as possible to the trial-mandated time point (such as by post and /or telephone).

7.7.1 Enhanced Follow-up

The HTA have requested a plan to be included in the protocol for enhanced follow–up of BASIL-3 patients in line with the recommendations from the EAG and MHRA. Some patients will be followed up for up to five years until enough events are achieved to permit analysis. However primary end point data will still be collected on patients yet to reach a primary end point for period of five years from the date of randomisation. The data will be collected via secondary care data (Hospital Episode Statistics; HES) and mortality data from the Office of National Statistics (ONS) through NHS Digital and other central UK NHS bodies.

The HTA have stated they will decide whether to implement this plan at a later date.

7.8 Trial Duration

The interventional phase of the trial will end when the last patient has completed the allocated trial intervention. The direct follow-up phase of the trial will cease when the last participant recruited has undergone 24 months of follow-up but patients entering the trial do consent to be followed up for a longer period via NHS databases and records.

7.9 Assessment Schedule (Table 1)

Table 7.5

	Completed From	Baseline	Intervention (Within 2 Weeks where possible)	Follow-up Month: 1, 6, 12 and annually thereafter until the end of the trial
Informed Consent	Patient	✓		
History	Case Notes	✓		
Physical	Case Notes	✓		✓
Imaging	Case Notes	✓		
Wound Assessment	Case Notes/Patient	✓		✓
Ischemic Pain VAS	Case Notes/Patient	✓		✓
WiFi and PEDIS	Case Notes/Patient	✓		✓
EQ-5D-5L	Patient	✓		✓
SF-12	Patient	✓		✓
VascuQoL	Patient	✓		✓
Haemodynamic changes	Case Notes	✓		✓
Ulcer and Gangrene Assessment	Case Notes/Patient	✓		✓
Amputation Assessment	Case Notes	✓	✓	
Endovascular Intervention and Stents Used	Case Notes		✓	
Vascular Re-intervention Review	Case Notes		✓	
Resource Usage	Patient			✓
Pain Relief Medication	Case Notes/Patient			✓
Economic Health Analysis Forms	Patient			✓
SAE Review	Case Notes/Patient			✓ ✓

8 Recording and Reporting of Adverse Events

The collection and reporting of AEs and SAEs will be in accordance with GCP and the Research Governance Framework 2005.

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-3 and all of the revascularisation techniques being tested in this trial are part of current UK 'standard of care'; therefore no (S)AEs are anticipated as a unique consequence of participation in BASIL-3.

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

8.1 Safety Reporting Procedures

Due to the nature of the patient population, most of the AEs occurring in BASIL-3, whether serious or not, will be 'expected' in the sense that they are recognised and accepted complications / consequences of SLI, and the three revascularisation procedures.

Non-serious AEs will, therefore, be recorded in the medical records according to local practice and may be recorded on the specific relevant trial forms.

If any trial-related SAEs do occur they will require reporting on a trial-specific **SAE Form** and will follow the procedure/timeframes outlined in this section of the protocol.

8.2 AE Definition

The AE definition for this trial is as below:

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.

8.3 SAE Definition and Reporting

SAE: Any adverse event (as defined above) which:

- results in death;
- is life-threatening*;
- requires hospitalisation** or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity; or
- or, is otherwise considered medically significant by the Investigator

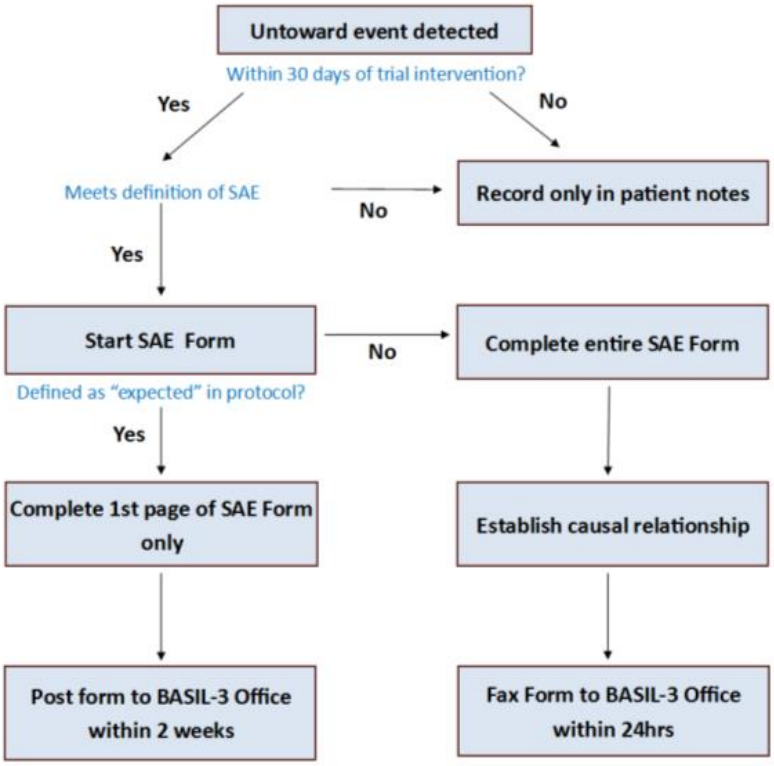
.*The term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** 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 investigationor 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*

Events identified as SAEs require completion of an **SAE form.**

8.4 Summary of Safety Reporting Procedure for BASIL-3



8.5 Expected SAEs

The following SAEs are recognised and accepted complications / consequences of SLI and BET and therefore can be **excluded from expedited notification** during the course of the trial:

Any events occurring more than 30 days after the trial intervention, unless of specific concern to the local clinical lead.

Any admissions to a hospital or other institution for general care, not associated with any deterioration in trial intervention-related symptoms

Expected complications of BET that do not require expedited notification are:

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
10	Anaesthesia: nausea, vomiting, epidural haematoma, dental injury

Events that meet the above trial definition of Expected SAE only part A, B and D of the SAE form to be completed. These should be sent to the BASIL-3 Trial Office as per any other CRF. ie within 2 weeks of completion.

These events should continue to be recorded in the medical records according to local practice and will still be collated by the BASIL-3 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).

Site Investigators should also notify their own institutions of any SAEs in accordance with their institutional policies

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

8.5.1 SAEs for Expedited Notification to the Trial Office

SAEs that occur within 30 days of the trial intervention and which do not meet the criteria of 'expected', as above, will be notifiable to the BASIL-3 Trial Office via **SAE forms immediately and within 24hours of 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 sections of the SAE form (parts A, B, C and D)to be completed. The causality assessment should be made by the PI (or delegated medically-qualified doctor) on a five-point scale in-line with the BASIL-3 SAE reporting form and as follows:

1. Unrelated to the trial intervention
2. Unlikely to be related to the trial intervention
3. Possibly related to the trial intervention
4. Probably related to the trial intervention
5. Definitely related to the trial intervention

Points 3-5 describe an event which is "related".

Completed expedited SAE forms should be faxed to the BASIL-3 Trial Office on

0121 415 9135

Or sent as scanned documents to BASIL-2@trials.bham.ac.uk

On receipt of an SAE form from a clinical centre, the BCTU trials team will allocate each SAE form with a unique reference number and enter this onto the SAE form in the section for office use only. The SAE form (containing the unique reference number completed) will be forwarded to the site as proof of receipt within 1 working day. The SAE reference number will be quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the TMF. The PI at each site will be required to respond to any related queries raised by the BASIL-3 Trial Office as soon as possible. Expedited SAEs will immediately be referred to the CI or delegated deputy on receipt by the BASIL-3 Trial Office. The CI will review the causality assessment and make an assessment of the expectedness of the event.

8.6 Expedited reporting to the Main Research Ethics Committee

8.6.1 Related and Unexpected SAEs

SAEs occurring to a research participant will be reported to the REC where in the opinion of the Chief Investigator the event was:

- "Related" – that is, it resulted from administration of any of the research procedures,

And

- "Unexpected" – that is, the type of event is not listed in the protocol as an expected occurrence.

The CI (or delegated deputy) will undertake urgent review of all such SAEs and may request further information immediately from the clinical team at site. The CI will not overrule the causality or seriousness assessment given by the site PI but may add additional comment on these. Reporting of related and unexpected SAEs to the REC will occur within 15 days after the Trial Office has been notified. The BASIL-3 Trial Office (on behalf of the CI) will inform all PIs of relevant information about SAEs that could adversely affect the safety of participants.

8.6.2 Annual Progress Reports

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

8.7 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 MREC of the measures taken and the circumstances giving rise to those measures.

8.8 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 MREC 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.

9 Data Management and Quality Assurance

9.1 Confidentiality

All data will be handled in accordance with the General Data Protection Regulation and Data Protection Act 2018. CRFs, other than the **Patient Contact Form** (where applicable) and **Consent Form**, will not bear the participant's name. For all other forms the participant's initials, date of birth and trial number, will be used for identification.

9.2 Data Collection

The BASIL-3 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 pre-arranged, clinically indicated, hospital visits. 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 then 6, and 12 months, after randomisation and annually thereafter until the end of the trial as outlined in Tables 1& 2.

The primary outcome will be collected at the end of the trial where this is beyond 24 months. Where possible, outcome data will be extracted from patient case notes and care records.

Outcomes will be collected by RNs and entered onto paper CRFs, these must be completed, signed/dated and returned to the BASIL-3 Trial Office by the PI or an authorised member of the site research team (as delegated on the **BASIL-3 Trial Signature & Delegation Log**) within the timeframe listed in Table 2. 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 CRFs will comprise, but will not necessarily be limited to, the following forms:

Table 2: Form Table

Form Name	Schedule for Submission
Screening Log	Monthly
Randomisation Form	Collected at Randomisation
Baseline Clinical Assessment Form	Collected at Randomisation

Baseline Medical Assessment Form	Collected at Randomisation
In-patient Form	Where applicable, asap after each hospitalisation
Intervention Form	Where applicable, asap after each intervention
Endovascular Form	Number of forms to match that indicated on the above. Returned as per above
Surgical Bypass Form	Where applicable, asap after each intervention (accompanied with an associated intervention form)
Non- Bypass Surgical Form	Where applicable, asap after each intervention (accompanied with an associated intervention form)
Amputation Form	Where applicable, asap after each intervention (accompanied with an associated intervention form)
Follow-up Form	Asap after each follow-up assessment time point
HRQL Booklets	Asap after each follow-up assessment time point
PEDIS Form	Asap after each follow-up assessment time point, where applicable
WIFI Form	Asap after each follow-up assessment time point, where applicable
Exit Form	Where applicable, asap after knowledge of exit
Non-Expedited SAE Form	Asap upon knowledge of event
Expedited SAE Form	Faxed within 24hrs of research staff becoming aware of the event

The design of CRFs may be amended by the BASIL-3 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 on receipt.

9.3 Data Clarification Process

Missing or ambiguous data will be queried by the BASIL-3 trial team on Data Clarification Forms. These multi-page reports are sent from BCTU to each clinical centre as a PDF. The staff at each site should print the report and write the response to each query on the report in black ballpoint pen. Each individual query should be signed and dated by the individual completing them (who should be delegated to do so). The first page of each report consists of a PI declaration to be completed by the PI prior to returning the document to BCTU. Original paper CRFs should not be altered; BCTU will amend the data contained within the trial database in accordance with the DCF responses received.

10 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 Organisation's policy. All essential documents will be archived for a minimum of 20 years after completion of trial in-line with the University of Birmingham's Code

of Conduct for Research. Destruction of essential documents will require authorisation from the BCTU on behalf of the Sponsor.

11 Statistical Considerations

11.1 Outcome Measures

These have been described above at Sections 3.2 and 3.3.

11.2 Sample Size and Recruitment

11.2.1 Original sample size calculation

The sample size for this trial was computed based on a time-to-event analysis making two key comparisons between standard care and the new treatments (PBA+/-BMS vs. DES; and PBA+/-BMS vs. DCB+/-BMS). To maintain an overall 5% Type I error rate, each comparison will be tested at a significance level of 2.5% to account for the increase in the risk of type I error associated with making two key comparisons. The total trial duration is 5 years with 3 years recruitment (20% of participants are to be recruited in Year 1, and 40% in Years 2 and 3 respectively) and two-years of follow-up resulting in a mean follow-up of 3.3 years per patient. The study will be closed and analysis for the primary outcome undertaken two-years after completion of recruitment.

The sample size calculation is based on estimated event rates in the PBA+/-BMS arm taken from the angioplasty arm of the original BASIL-1 trial (observed to be 0.70, 0.64, 0.52, 0.46 and 0.36 at the end of Years 1-5 respectively). The study is powered at 90% to detect a hazard ratio of 0.60 for both comparisons reducing the risk of the primary outcome (AFS). Across the three arms, a total of 342 events would be required to detect a hazard ratio of 0.60 (equivalent to an absolute difference in AFS of 13% at Year 2) at the 2.5% significance level. Conservatively, allowing for 5% drop-out for the primary outcome (equivalent to 1% drop out in each year for 5 years) a total of 861 participants are required.

The sample size calculation was computed using the Stata “artsurv” programme (version 1.0.7) designed to calculate sample size and power for complex trial designs with a time-to-event outcome (10, 11)

11.2.2 Sample size revision

An error was identified in the implementation of the macro used to compute the original sample size. This error resulted in an overall increase in the sample size and number of events needed. Using the same parameters as per the original calculation (listed above), the

corrected number of events required is 291 (15% reduction from the original figure of 342). The observed recruitment rates in BASIL-3 have not been as expected; recruitment has been slower than anticipated. As a result, the median follow-up time for the overall cohort has increased, to allow recruitment of a sufficient number of participants to attain the required number of events. The sample size is now based around achieving the required number of events (291), which will be driven by recruitment rates going forward. This will be monitored closely to ensure we recruit a sufficient number of participants to meet this figure.

11.3 Statistical Analysis

A separate **Statistical Analysis Plan** for the BASIL-3 trial provides a detailed description of the planned statistical analyses. A brief outline of these analyses is given below.

11.3.1 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, where all participants will have a minimum of two years follow-up.

The primary outcome (AFS) 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 hazard ratios and corresponding confidence intervals. Each model will be adjusted for the minimisation variables (where possible), with the exception of centre, which will not be included in the model. 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. 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.

11.3.2 Secondary Outcome Analysis

Secondary 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. Difference between group means and associated confidence intervals at the primary time points (1, 12 and 24 months) will be estimated through the use of mixed effect

repeated measures models adjusting for the parameters listed in 6.3. Where necessary, data transformations will be made to fulfil modelling assumptions.

Binary secondary outcome measures (further intervention etc.) will be summarised using frequencies and percentages. A log-binomial model will be used to generate relative risks (and confidence intervals), adjusting for the minimisation parameters (where possible). Other binary outcome measures which are measured at multiple assessment times (WIFI etc.) will be will be summarised using frequencies and percentages at each assessment. Odd ratios and associated confidence intervals at the primary time points (1, 12 and 24 months) will be estimated through the use of mixed effect repeated measures models adjusting for the minimisation parameters (where possible).

The analysis will be undertaken according to the ITT principle, comparing groupings according to their first allocated procedure, regardless of compliance and subsequent procedures. As the pattern of repeat and cross-over procedures is likely to be multiple and complex, these will be measured as outcomes and no attempt will be made to adjust for them.

11.3.3 Repeat and Cross-over Interventions

Further intervention is possible in all arms of the trial, even when the trial endovascular intervention has been successful. This may either be with the same endovascular intervention (re-intervention), one of the alternative endovascular interventions (endovascular cross-over intervention) or surgical intervention (surgical crossover intervention), each of which may be repeated more than once.

Based on clinical experience, and data from the original BASIL-1 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

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 interventions. As in BASIL-1, we will specifically examine whether the failed trial vascular intervention appears to impact negatively upon the success of subsequent vascular interventions.

The trial addresses the question of the choice of the *first* revascularisation strategy. 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 and BASIL-2, BASIL-3 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*. 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 HRQL 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 HRQL.

11.3.4 Planned Sub-group and Additional Analysis

Variation in the treatment effect between subgroups will be limited to pre-specified variables and investigated using appropriate tests for interaction for the primary outcome only. Subgroup variables will include the minimisation parameters listed in section 7.3, with the exception of centre.

11.3.5 Pilot Phase

The pilot phase lasted a year following the first 6 month set up phase and contained a number of criteria to assess if the recruitment target was feasible. The data achieved during the pilot phase was consistent with the targets overall and the pilot phase ceased on that basis.

11.3.6 Interim Analysis

After the first year we aim to assess recruitment, retention, patient burden and completeness of HRQL data.

A full efficacy and safety analysis report will be reviewed by the DMEC on an annual basis or more frequently if required by the DMEC or Trial Management Committee. The DMEC will outline and agree the stopping rules for the trial which will be documented in the DMEC charter. It is likely that the Haybittle-Peto boundary will be used. This approach states that if an interim analysis of the primary outcome shows, with p-value less than 0.001, that the treatments are different, then the trial should be stopped early. This Haybittle-Peto approach will be used as stopping guide, alongside data on important secondary endpoints and all other relevant evidence. A DMEC report and charter outlining the terms of reference (including

information on stopping rules) will be agreed with the DMEC. The report will specify which endpoints are to be included in the reports to the Trial Steering Committee.

11.3.7 Final Analysis

The final analysis for the BASIL-3 trial will occur once the last randomised patient reaches the end of follow-up.

12 Health Economic Analysis

There is considerable uncertainty around the cost-effectiveness of drug-eluting endovascular revascularisation devices. Determining the most cost-effective revascularisation strategy will enable the NHS to ensure that the care provided care represents the most appropriate use of public resources.

The economic analysis will comprise two components: a 'within-study' analysis, based on data obtained within the study, and, conditionally on the availability of relevant data, a 'model-based' analysis, which will extrapolate and compare 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 (12) . 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.

12.1 Within Study Analysis

The 'within-study' analysis will determine the cost-effectiveness of the trial mandated interventions on the basis of the patient-level data obtained during the study period.

12.2 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 (13) the British National Formulary (14) and the NHS Reference Cost Schedules(15) .

12.3 Outcomes

HRQL will be derived from the latest, EQ-5D-5L instrument as well as by means of the EQ-5D VAS which records the patient's self-rated HRQL 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 (16). 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' HRQL will be measured through the Short Form 12 (SF-12) (17). Responses to SF-12 will be converted into single preference-based index values, and subsequently into QALYs, by using the SF-6D classification system (18). 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) (19, 20) As explained above, the assessment of patient burden and completeness planned for year 1 of the study will determine whether the ICECAP-O should continue to be administered (see 10.3.6. Interim analysis). The time points at which quality of life instruments will be collected are: baseline, 1 month after intervention and months, 6, 12, 24, and 36 after randomisation.

12.4 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 (21). 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 (22). 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(23) . 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 each of the revascularisation interventions being cost-effective across a range of possible values of 'willingness to pay' for an additional QALY (24).

12.5 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 the patients' lifetime. A decision analytic 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, supplemented by evidence from the preceding BASIL trial(s) 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 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 (25). 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) (26) 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.

13 End of Trial

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

14 Direct Access to Source Data

The investigator(s)/institution(s) will permit trial-related monitoring, audits and MREC 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.

15 Ethics

The Sponsor will ensure that the trial protocol, PIS, consent form, GP letter and submitted supporting documents have been approved by the MREC, 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 MREC 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 MREC within one year after the end of the trial.

16 Monitoring Requirement for the Trial

Monitoring of BASIL-3 will ensure compliance with GCP. A risk proportionate approach to the initiation, management and monitoring of BASIL-3 will be adopted and outlined in the trial-specific risk assessment. Central monitoring of the trial will be conducted as outlined in the trial specific monitoring plan.

17 Oversight Committees

17.1 TMG

The TMG will comprise the CI, other lead investigators (clinical and nonclinical) and members of the BCTU. The TMG will be responsible for the day-to-day running and management of BASIL-3. It will convene at least once a month, and more frequently when required.

17.2 TSC

An independent TSC will provide overall supervision for the BASIL-3 and advice to the CI. The ultimate decision regarding the feasibility of the trial lies with the TSC. Further details of TSC functioning are presented in the TSC Charter.

17.3 DMC

An independent DMC will meet either prior to or shortly after the trial opens; the frequency of further meetings will be dictated in the DMC charter. The DMC will consider data using the statistical analysis plan and will advise the TSC.

18 Finance

The NIHR HTA Programme is funding this trial.

19 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.

20 Dissemination and Publication

The CI will coordinate dissemination of data from BASIL-3. All publications and presentations, including abstracts, relating to the main trial will be authorised by the BASIL-3 TMG. The

results of the analysis will be published in the name of the BASIL-3 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-3 data to undertake original analyses will be submitted to the TMG for consideration before release. To safeguard the scientific integrity of BASIL-3, trial data will not be presented in public before the main results are published without the prior consent of the TMG.

21 Statement of Compliance

The trial will be conducted in compliance with the approved protocol, the principles of Good Clinical Practice (GCP), the UK Data Protection Act and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

22 References

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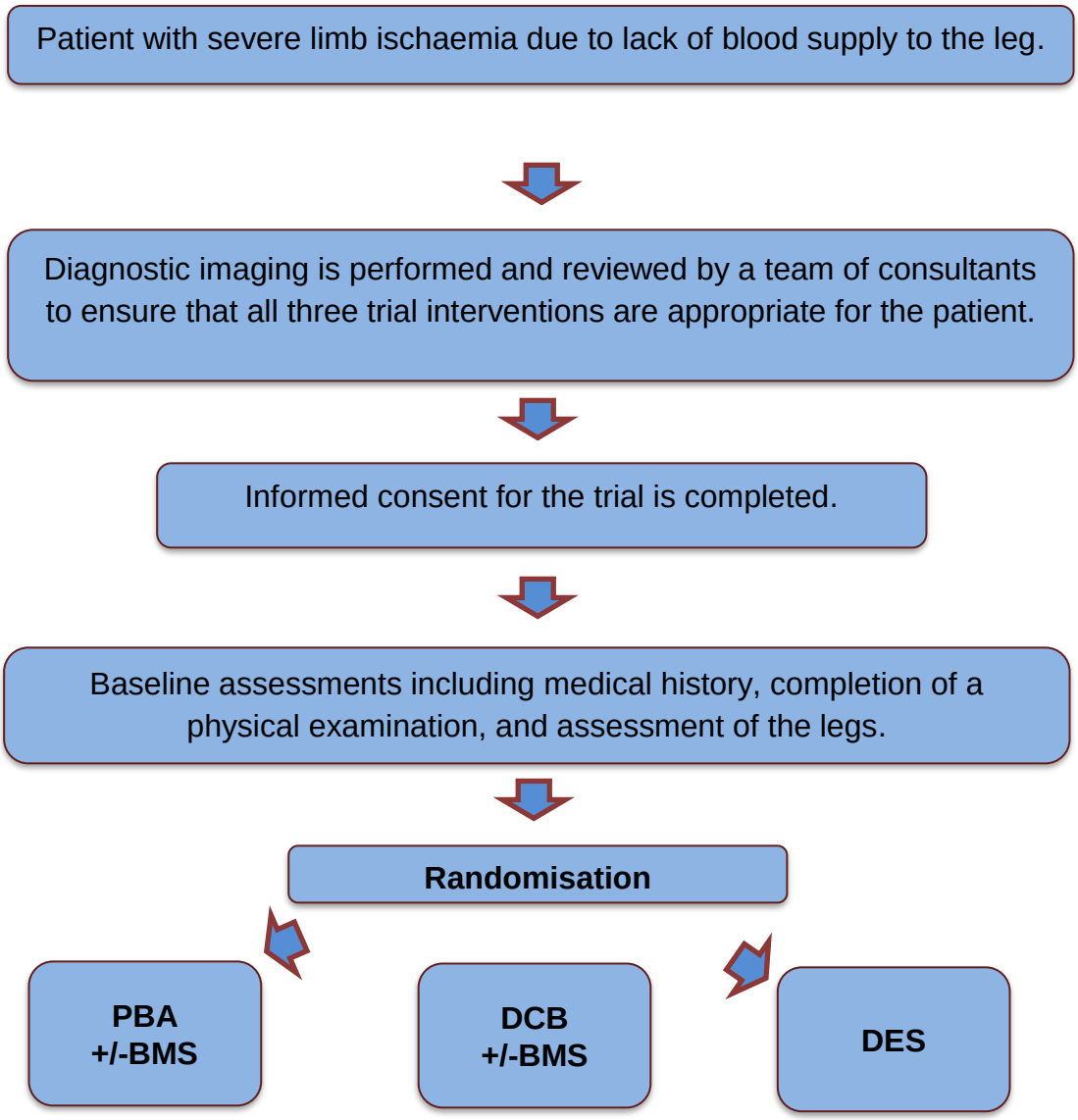
(BASIL 3) Trial Flow Diagram



23 Appendix I

National Patient Safety Agency

National Research Ethics Service

NRES SHARED SINGLE ISSUE ETHICAL DEBATE -

ISSUE PAPER ONE -TIME TO CONSENT

1. Introduction

Issue One was debated by 24 RECs during a single ethical debate. The RECs involved came up with a shared view broadly line with current guidance, they felt consent must be informed, voluntary and time given to consideration to participate needs to be thought through on a case by case basis having considered the influencing factors presented by the research and the participant group. The factors highlighted as influencing decision making are set out in the conclusion to this paper and form a useful template for review.

2. The Issue- How long should potential participants have to consider the invitation to join a research project?

Do we need to delay decisions about participation in research or should the patient have the right to choose to make an immediate decision? What are the deciding factors when making a decision, and are there different rules for different circumstances?

3. Current Guidance

Guidance to applicants in the Integrated Research Application system:

Question A31 Time allowed to decide whether to take part

- *Potential participants need time to consider fully the implications of taking part in research. They should be able to ask questions and reflect. Participants should not be rushed into decisions.*
- *There are no fixed guidelines. Each study should be considered on its own merits, the more burdensome studies will require a longer time for deliberation. Consent for short studies such as questionnaire based studies could be obtained much more quickly. Pragmatic considerations are also needed particularly when subjects have travelled long distances.*

NRES guidance on information sheets

"10.1 Summary

1