Bypass vs. Angioplasty in Severe Ischaemia of the Leg-2

Trial Registration: ISRCTN27728689

Statistical Analysis Plan

SAP Version Number	Protocol Version Number
2.0	7.0

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Table 1: Statistical Analysis Plan Amendments

SAP version number	SAP section number	Description of and reason for change	Timing of change with respect to interim analysis/ final analysis/ database lock	Blind Reviewer	
2.0	NA	Review of SAP prior to final analysis, decision made to transfer to new BCTU template which is a more comprehensive document. Text from previous SAP copied over to appropriate sections in new template. New sections in template (essentially sections 1-4), uses template text and/or text taken directly from SAP v1.0 or the latest protocol (7.0).	Prior to final analysis/database lock	Name:	
				Signature:	
				Date:	
	5.1	P-values only reported for the primary outcome.	Prior to final analysis/database lock	Name:	
				Signature:	
				Date:	
	9.3	Multiple imputation will not be performed to assess the impact of missing data. For the primary outcome, which is a time to event outcome analysed using a Cox model,	Prior to final analysis/database lock	Name:	

SAP version number	SAP section number	Description of and reason for change	Timing of change with respect to interim analysis/ final analysis/ database lock	Blind Reviewer	
		participants will be censored at the point their clinical status was last known. Whilst it is now not custom to perform sensitivity analyses (for missing data) for secondary outcomes, the same holds true for the following clinical secondary outcomes (time to major amputation, overall survival, time to first major adverse limb event and time to first major adverse cardiac event). Continuous outcomes will be modelled using a repeated measured framework and therefore all available data will be included in the models.		Signature:	
				Date:	
	9	All analysed will be performed using adjusted regression models.	Prior to final analysis/database lock	Name:	
				Signature:	
				Date:	
	4.6	HADS was removed as a secondary outcome from protocol 4.0. Healing of minor amputations was removed as a secondary outcome from protocol 7.0. Time to major amputation added as a secondary outcome to protocol 7.0	Prior to final analysis/database lock	Name:	
				Signature:	

SAP version number	SAP section number	Description of and reason for change	Timing of change with respect to interim analysis/ final analysis/ database lock	Blind Reviewer	
				Date:	
	9.8	Subgroup variables expanded to include previous (permissible) intervention to the trial leg, intention for a hybrid procedure, Ankle to Brachial Pressure Index and Toe to Brachial Pressure Index. Previous (permissible) intervention to the trial leg and intention for a hybrid procedure were added as minimisation variables partway through recruitment in BASIL-2.	Prior to final analysis/database lock	Name:	
				Signature:	
				Date:	
	NA	Analyses which look at differences in alternative endovascular options and analyses which examine whether failed BET appears to impact negatively upon the success of subsequent surgeries (and vice-versa) removed from statistical analysis plan due to lack of availability of data.	Prior to final analysis/database lock	Name:	
				Signature:	
				Date:	
	4.7	Exploratory outcomes added	Prior to final analysis/database lock	Name:	

SAP version number	SAP section number	Description of and reason for change	Timing of change with respect to interim analysis/ final analysis/ database lock	Blind Reviewer	
				Signature:	
				Date:	

Abbreviations & Definitions	
Abbreviation/Acronym	**Meaning**
ABPI	Ankle to Brachial Pressure Index
AE	Adverse Event
AFS	Amputation Free Survival
AKA	Above Knee Amputation
BCTU	Birmingham Clinical Trials Unit
BET	Best Endovascular Treatment
BIC	Bayesian information criterion
BKA	Below Knee Amputation
CABG	Coronary Artery Bypass Graft
CI	Confidence Interval
CKD	Chronic Kidney Disease
CLTI	Chronic Limb Threatening Ischemia
cm	Centimetres
CONSORT	Consolidated Standards of Reporting Trials
CTA	Computed Tomography Angiography
DARS	Data Access Request Service
DM	Diabetes Mellitus
DMC	Data Monitoring Committee
DP	Dorsalis Pedis
DSA	Digital Subtraction Angiography
eGFR	estimated Globular Filtration Rate
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
ICECAP-O	ICEpop CAPability measure for Older people
IP	Infra-popliteal
IQR	Interquartile Range
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to Treat
kg	Kilograms
m	Metres
MACE	Major Adverse Cardiovascular Event
MALE	Major Adverse Limb Event
MI	Myocardial Infarction
ml	Millilitres
MRA	Magnetic Resonance Angiography
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSAID	Non-Steroidal Anti-Inflammatory Drugs
ONS	Office National Statistics
OS	Overall Survival
PAD	Peripheral Artery Disease
PCI	Percutaneous Coronary Intervention
PEDIS	Perfusion, Extent, Depth, Infection and Sensation
PP	Perforating peroneal
PT	Posterior Tibial
RCT	Randomised Controlled Trial
RD	Risk Difference
RR	Risk Ratio
RUSAE	Related Unexpected Serious Adverse Event
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-12	Short Form-12

Abbreviations & Definitions	
Abbreviation/Acronym	**Meaning**
TBPI	Toe to Brachial Pressure Index
TIA	Transient Ischaemic Attack
TKA	Through Knee Amputation
US	Ultrasound
VAS	Visual Analogue Scale
VascuQoL	Vascular Quality of Life Questionnaire
VB	Vein Bypass
WIFI	Wound, Ischemia and Foot Infection
Term	**Definition**
International Standard Randomised Controlled Trial Number	A clinical trial registry
Protocol	Document that details the rationale, objectives, design, methodology and statistical considerations of the study
Randomisation	The process of assigning trial subjects to intervention or control groups using an element of chance to determine the assignments in order to reduce bias.
Statistical Analysis Plan	Pre-specified statistical methodology documented for the trial, either in the protocol or in a separate document.

TABLE OF CONTENTS

1. Introduction

This document is the Statistical Analysis Plan (SAP) for the BASIL-2 trial, and should be read in conjunction with the current trial protocol. This SAP details the proposed analyses and presentation of the data for the main paper(s) reporting the results for the BASIL-2 trial.

The results reported in these papers will follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (e.g. to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (e.g. transformation of data prior to analysis), but they are intended to establish rules that will be followed, as closely as possible, when analysing and reporting data.

Any deviations from this SAP will be described and justified in the final report or publication of the trial (using a table as shown in Appendix A). The analysis will be carried out by an appropriately qualified statistician, who should ensure integrity of the data during their data cleaning processes.

2. Background and rationale

The background and rationale for the trial are outlined in detail in the protocol. In brief, BASIL-2 is a multi-centre randomised controlled trial (RCT) to compare the clinical and cost-effectiveness of a 'Vein Bypass (VB) first' with a 'Best Endovascular Treatment (BET) first' revascularisation strategy for Chronic Limb Threatening Ischemia (CLTI) due to Infra-popliteal (IP) arterial disease.

3. Trial objectives

The primary objective is to assess whether a 'VB first' or a 'BET first' revascularisation strategy represents the most clinical and cost-effective treatment for CLTI due to IP arterial +/- more proximal Peripheral Artery Disease (PAD) disease.

4. Trial methods

4.1. Trial design

BASIL-2 is an individually randomised, parallel, multi-centre, pragmatic, two-arm, superiority, 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 (refer to section 4.11 for progression rules) and a within-trial economic evaluation. Participants will be recruited from secondary care hospitals in the United Kingdom, Denmark and Sweden [1]. See Appendix B for trial schema.

4.2. Trial interventions

The two interventions being assessed in the BASIL-2 trial are:

- VB – where the person's own vein is used to bypass the diseased arteries.
- BET – which involves opening up the diseased arteries with balloons and small metal tubes called stents.

4.3. Randomisation

Participants will be randomised at the level of the individual, in a 1:1 ratio to either VB or BET. Randomisation will be performed centrally at the Birmingham Clinical Trials Unit (BCTU) using a web-based randomisation service (with a telephone back-up service) with a minimisation algorithm incorporating the following factors:

- Age (≤60, 61-70, 71-80, >80 years).
- Gender (male, female).
- Diabetes Mellitus (DM) and Chronic Kidney Disease (CKD) (DM, CKD*, DM and CKD*, neither).
- Severity of clinical disease (ischaemic rest/night pain only, tissue loss only, both).
- Previous (permissible) intervention to the trial leg (yes, no).
- Intention for a hybrid procedure (yes, no).

**CKD will be defined as stage 3 or worse based on estimated Globular Filtration Rate (eGFR) of <60 ml/min/1.73m^2.*

A 'random element' will be included in the minimisation algorithm, so that each participant has a probability (unspecified here), of being randomised to the opposite intervention that they would have otherwise received. Full details of the algorithm used will be stored in a confidential document at BCTU.

4.4. Timing of outcome assessments

The schedule of trial procedures and outcome assessments are given in Appendix C.

4.5. Primary outcome measure

Amputation Free Survival (AFS), defined as the time to major limb (above the ankle) amputation of the index (trial) leg or

death from any cause. See Appendix D: Data manipulations for how the primary outcome will be derived.

4.6. Secondary outcome measures

The secondary outcomes are as follows:

- Overall survival (OS).
- Time to first major (above the ankle) amputation of the trial leg.
- In-hospital 30-day (from the date of the first revascularisation intervention to the trial leg) morbidity and mortality.
- Major Adverse Limb Event (MALE) defined as time to major (above the ankle) amputation of, or any major vascular revascularisation to, the trial leg (time to first MALE will also be included).
- Major Adverse Cardiovascular Event (MACE) defined as CLTI and/or major amputation affecting the non-trial leg, Myocardial Infarction (MI), Transient Ischemic Attack (TIA), or stroke (time to first MACE will also be included).
- Relief of ischaemic rest/night pain (Visual Analogue Scale (VAS), medication usage).
- Health Related Quality of Life (HRQoL) using generic (EuroQoL EQ-5D-5L [2], Short Form-12 v2 (SF-12) [3], ICEpop CAPability measure for Older people (ICECAP-O) [4]) and disease specific (Vascular Quality of Life Questionnaire (VascuQoL) [5]) tools.
- Further interventions: 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 Perfusion, Extent, Depth, Infection and Sensation (PEDIS) classification system [6] and the Wound, Ischemia and Foot Infection (WIFI) classification system [7].
- Haemodynamic measurements; absolute ankle and toe pressures, Ankle to Brachial Pressure Index (ABPI), Toe to Brachial Pressure Index (TBPI).

See Appendix D: Data manipulations for how the secondary outcomes will be derived.

4.7. Exploratory outcome measures

Exploratory outcomes are as follows:

- MACE (non-leg related): defined as MI, TIA, or stroke (time to first MACE (non-leg related) will also be included).
- MACE (non-leg related)-death: defined as MI, TIA, stroke or death from any cause (time to first MACE (non-leg related)-death will also be included).
- Major non-trial leg event: CLTI and/or major amputation affecting the non-trial leg (time to first major non-trial leg event will also be included).
- MALE-death: MALE (defined as time to major (above the ankle) amputation of, or any major vascular revascularisation to, the trial leg) or death from any cause (time to first MALE-death will also be included).

See Appendix D: Data manipulations for how the exploratory outcomes will be derived.

4.8. Sample size

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 participant. Non-event rates for the primary outcome (AFS) were assumed to be 0.72, 0.62, 0.53, 0.47 and 0.35 at the end of Years 1-5 based on the original BASIL-1 trial [8].
Based on the above, and allowing for 10% attrition (the lost to follow-up rate in BASIL-1 was around 1%) a trial of 600 participants would have 90% power to detect a reduction in AFS of one-third (Hazard Ratio (HR)=0.66 equivalent to a 12% absolute difference in AFS at Year 3) at the 5% significance level.

Revised Sample Size

The initial assumptions made in BASIL-2 concerning recruitment rates were not achieved. The number of randomised participants 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 participants needed to reach this target with two years minimum follow-up.

4.9. Framework

The objective of the trial is to test the superiority of one intervention to another. The null hypothesis is that there is no difference in AFS between the intervention groups. The alternative hypothesis is that there is a difference in AFS between the intervention groups.

4.10. Interim analyses and stopping guidance

A separate Data Monitoring Committee (DMC) reporting template will be drafted and agreed by the DMC including an agreement on which outcomes will be reported at interim analyses. The statistical methods stated in this SAP will be

followed for the outcomes included in the DMC report, where possible. 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.

4.11. Internal Pilot Progression Rules

The following internal pilot progression targets were assessed after 12 months of recruitment:

- At least 2/3rds of open centres recruiting.
- At least 60 participants randomised.
- At least 80% of participants receiving their allocated treatment.
- At least 2/3rds of centres recruiting two participants per month from month four onwards.

4.12. Timing of final analysis

The final analysis for the trial will occur after all participants have been followed up for a minimum of two years and the corresponding outcome data has been entered onto the trial database and validated as being ready for analysis.

4.13. Timing of other analyses

Not applicable.

4.14. Trial comparisons

All references in this document to 'group' refer to VB or BET.

5. Statistical Principles

5.1. Confidence intervals and p-values

All estimates of differences between groups will be presented with two-sided 95% confidence intervals (CIs), unless otherwise stated. A p-value will be reported from a two-sided test at the 5% significance level for the primary outcome only.

5.2. Adjustments for multiplicity

No correction for multiple testing will be made.

5.3. Analysis populations

All primary analyses (primary, secondary and safety outcomes) will be based on the intention-to-treat (ITT) principle. Participants will be analysed in the intervention group to which they were randomised, and all participants will be included whether or not they received their allocated intervention. This is to avoid any potential bias in the analysis. A per protocol analysis will also be carried out for the primary outcome (AFS). Refer to section 5.4 for a definition of adherence and the per-protocol cohort (section 9.9 provides further details on these sensitivity analyses).

5.4. Definition of adherence

Adherence to the allocated intervention will be monitored using the trial intervention forms (specifically the surgical bypass form and the BET summary forms). We will define adherence as those who receive their allocated intervention for their first intervention post-randomisation (further interventions are anticipated in this cohort). Subsequent interventions (following the first intervention) will not be considered for our adherence definition (these are captured as per our secondary outcomes). Participants who are regarded as adherent will be considered as the per-protocol cohort. There will also be a further analysis where participants are analysed as per what they actually received for their first intervention (VB or BET) which will be regarded as an 'as treated' analysis (section 9.9 provides further details on these sensitivity analyses).

5.5. Handing protocol deviations

A protocol deviation is defined as a failure to adhere to the protocol such as errors in applying the inclusion/exclusion criteria, the incorrect intervention being given, incorrect data being collected or measured, follow-up visits (clinical follow-up) conducted outside the visit window (as per Table 2 below) or missed follow-up visits. Any follow-up visits not completed 'on-time' will still be included in all analyses but will be listed as protocol deviations. We will apply a strict definition of the ITT principle and will include all participants as per the ITT population described in section 5.3 in the analysis, in some form, regardless of deviation from the protocol [9]. This does not include those participants who have specifically withdrawn consent for the use of their data.

Table 2

Follow-up time point (post randomisation)	Completion window		
	Early	On-time	Late
1 month*	<2 weeks	2-6 weeks	>6 weeks
3 months[1]	<1 month	1-5 months	>5 months
6 months	<4 months	4-8 months	>8 months
9 months[1]	<7 months	7-11 months	>11 months
12 months	<10 months	10-14 months	>14 months
18 months[1]	<16 months	16-18 months	>18 months
24 months	<22 months	28-32 months	>32 months
30 months[1]	<28 months	22-26 months	>26 months
36 months	<34 months	34-38 months	>38 months
48 months	<46 months	46-50 months	>50 months
60 months	<58 months	58-62 months	>62 months
72 months	<70 months	70-74 months	>74 months
84 months	<82 months	82-86 months	>86 months
96 months	<94 months	94-98 months	>98 months

*Post first revascularisation intervention (if primary revascularisation intervention occurred, otherwise post-randomisation).
[1]Only applicable for protocol versions ≤3.0.

5.6. Unblinding

Not applicable BASIL-2 is an open-label study.

6. Trial population

6.1. Recruitment

A flow diagram (as recommended by CONSORT [10]) will be produced to describe the participant flow through each stage of the trial. This will include information on the number (with reasons) of losses to follow-up (drop-outs and withdrawals) over the course of the trial. A template for reporting this is given in section 3 of the supplementary template report.

6.2. Baseline characteristics

The trial population will be tabulated as per section 6 of the supplementary template report. Categorical data will be summarised by number of participants, counts and percentages. Continuous data will be summarised by the number of participants, mean and standard deviation (SD) if deemed to be normally distributed or number of participants, median and interquartile range (IQR) if data non-normal, and ranges if appropriate. Tests of statistical significance will not be undertaken, nor confidence intervals presented [11].

7. Interventions

7.1. Description of the interventions

A template for reporting information on the interventions is given in section 7 of the supplementary template report.

7.2. Adherence to allocated intervention

A cross-tabulation of allocated intervention by the adherence categories stated in section 5.4 will be produced (proportions and percentages). A template for reporting adherence is given in section 7 of the supplementary template report.

8. Protocol deviations

Frequencies and percentages by group will be tabulated for the protocol deviations as per section 5 of the supplementary template report.

9. Analysis methods

Intervention groups will be compared using regression models to adjust for all covariates as specified in section 9.1, where possible. BET will be considered the reference group for the treatment group parameter in all regression models.

9.1. Covariate adjustment

In the first instance, intervention effects between groups for all outcomes will be adjusted for the minimisation parameters listed in section 4.3 and randomising centre. The minimisation variables: 'previous (permissible) intervention to the trial leg (yes, no)' and 'Intention for a hybrid procedure (yes, no)' were both added to the randomisation algorithm partway through recruitment to BASIL-2. As a result, these variables contain missing data. If 'previous vascular intervention to the trial leg' is no on the baseline medical form, or 'previous vascular intervention to the trial leg' is yes, but 'endovascular' and 'surgery' are both no, then we will assume 'previous (permissible) intervention to the trial leg' is no. Otherwise, missing data will be classed as 'unknown' for adjustment purposes. Therefore, this variable will have three levels: yes, no and unknown. For the variable 'intention for a hybrid procedure', since we cannot collect this data retrospectively (as the clinician's intention at the time of the intervention would not be consistently recorded in clinical notes) all participants with missing data will be classed as 'unknown' for adjustment purposes. Therefore, this variable will have three levels: yes, no and unknown. For the

minimisation variable 'DM and CKD (DM, CKD, DM and CKD, neither)' these will classed as two separate variables for adjustment purposes, DM (yes, no) and CKD (yes, no). Categorised continuous variables (age) will be treated as continuous variables in this adjustment. Randomising centre will be treated as a random effect in the models (randomising centre will be considered a shared frailty variable [with a Gamma distribution] in Cox regression models), and all other factors as fixed effects. EQ-5D-5L, SF-12, ICECAP-O, VascuQoL, ABPI, TBPI, PEDIS and VAS will be further adjusted for baseline value.

In models which include baseline values, if full covariate adjustment is not possible (e.g. the model does not converge), randomising centre will be removed first. If this reduced model (with centre excluded) still fails to converge, the minimisation parameters will be removed next. If this reduced model (which only includes treatment and baseline value) still fails to converge, unadjusted estimates will be produced and it will be made clear in the final report why this occurred (e.g. not possible due to low event rate/lack of model convergence).

In models which do not include baseline value, if covariate adjustment is not possible (e.g. the model does not converge), randomising centre will be removed first. If this reduced model still fails to converge, unadjusted estimates will be produced and it will be made clear in the final report why this occurred (e.g. it is not possible due to low event rate/lack of model convergence).

For binary outcomes only, if the (full) adjusted log-binomial model fails to converge, a Poisson regression model with robust standard errors will be used to estimate the same parameters [12]. If this also fails to converge, estimates will be produced from the log-binomial model (following rules for removal of variables as outlined above). It will be made clear in the final report why this occurred (e.g. not possible due to low event rate/lack of model convergence).

9.2. Distributional assumptions and outlying responses

Distributional assumptions (e.g. normality of data and/or regression residuals for continuous outcomes) will be assessed visually prior to analysis. In the first instance the proposed primary method of estimation in this analysis plan will be followed. If data are considered to be particularly skewed and/or distributional assumptions violated, the impact of this will be examined through sensitivity analysis. This may consist of either transformation of data prior to analysis (e.g. log transformation) or the use of medians and IQRs alongside unadjusted differences in medians using bootstrapping methods (repetition=1000, seed=123456).

9.3. Handling missing data

As every attempt will be made to collect full follow-up data on all study participants; it is anticipated that missing data will be minimal. Since participants in BASIL-2 have varied lengths of follow-up (based on recruitment time), all participants will be included in the primary analysis up to the point where their clinical status (mortality and major amputation) is last known (censored at this point). Therefore, no sensitivity analyses to assess the impact of missing data for the primary outcome (or secondary outcomes) are proposed.

9.4. Analysis methods – primary outcome

See Appendix D: Data manipulations for information on how variables will be derived for the analysis. A template for reporting the primary outcome is given in section 8.1 of the supplementary template report.

The primary outcome (AFS) will be compared between intervention groups using survival analysis methods. The number of participants who experience an event (death or major amputation) will be reported by treatment group, alongside the composite components (death or major amputation). 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 an adjusted HR and 95% CI. Statistical significance of the intervention group parameter will be determined (p-value generated) from this model. Adjustment will be as per section 9.1.

Further analysis of the primary outcome will include assessment of the proportional hazards assumption, assessed graphically using either Kaplan Meier plots or a log(-log(survival)) versus log of survival time plot. The proportional hazard assumption can be further assessed by fitting a time-dependent effect (i.e. treatment by time interaction). If the proportional hazard assumption is found to be violated, time dependent effects will be modelled using restricted cubic splines with varying degrees of freedom (1-10). Additionally, restricted cubic splines will be used to model the baseline log cumulative hazard with varying degrees of freedom (1-10). For the time dependent effects (where non-proportional hazards observed) and baseline log cumulative hazard, different combinations of degrees of freedom will be fitted, where the number of degrees of freedom for the baseline hazard is always higher than the degrees of freedom for the time dependent effect. The Bayesian information criterion (BIC) will be computed for each model. The model with the lowest BIC value will be considered the 'best' fit.

9.5. Analysis methods – secondary outcomes

See Appendix D: Data manipulations for information on how variables will be derived for the analysis. A template for

reporting the primary outcome is given in section 8.2 of the supplementary template report.

Time to event outcomes (time to major amputation, OS, time to first MALE and time to first MACE) will be presented and analysed as per the primary analysis for AFS (with the exception that no p-value will be reported).

Outcome measures that are based on a continuous scale (EQ-5D-5L, SF-12, ICECAP-O, VascuQoL, ABPI, TBPI, PEDIS and VAS) will be summarised using means and SDs 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 95% CIs at the primary time points (1, 12 and 24 months) will be estimated through the use of mixed effect repeated measures [13] models. All assessment times will be included in the model, with baseline value included as a covariate in the model. Time will be included as a categorical (fixed) variable in the model. To allow for a varying treatment effect over time, a time by treatment interaction parameter will be included in the model as standard (estimates of differences between groups at the relevant time will be taken from the model including this interaction parameter). A general 'unstructured' covariance structure will be assumed.

Binary outcome measures (MALE, MACE, further interventions, in hospital 30 day morbidity and mortality) will be summarised using frequencies and percentages. A log-binomial model will be used to generate adjusted risk ratios (and 95% CIs). Adjusted risk differences (RD) (and 95% CIs) will also be presented (using an identity link function).

Other binary outcome measures which are measured at multiple assessment times (medication usage and WIfI) will be summarised using frequencies and percentages at each assessment. Odd ratios and associated 95% confidence intervals at the primary time points (1, 12 and 24 months) will be estimated through the use of mixed effect repeated measures [13] logistic regression models. All assessment times will be included in the model, with baseline value included as a covariate in the model. Time will be included as a categorical (fixed) variable in the model. To allow for a varying treatment effect over time, a time by treatment interaction parameter will be included in the model as standard (estimates of differences between groups at the relevant time will be taken from the model including this interaction parameter). A general 'unstructured' covariance structure will be assumed.

Adjustments for secondary outcomes will be as per section 9.1.

9.6. Analysis methods – exploratory outcomes and analyses

MACE (non-leg related), MACE (non-leg related)-death, major non-trial leg event and MALE-death will be analysed as per the methods outlined above (MALE and MACE in secondary outcomes).

Any other data that does not form a pre-specified primary, secondary or safety outcome will be presented using simple summary statistics by intervention group (i.e. numbers and percentages for binary data and means (or medians) and SDs (or IQRs) for continuous normal (or non-normal) data.

A flow diagram will be produced to illustrate the participant flow in regards to received revascularisation interventions (endovascular, bypass surgery or non-bypass vascular surgery), major amputations and mortality in the first 12 months post-randomisation by group.

An exploratory analysis will be performed for composite time to event primary and secondary outcomes (AFS, MALE and MACE) using a win ratio approach [15]. Ordering of events will be as per Table 3.

Table 3

	Outcome		
	AFS	**MALE**	**MACE**
Most severe	Death	Major amputation to trial leg	Stroke
	Major Amputation	Further revascularisation	MI
			Major amputation to non-trial leg
			CLTI to non-trial leg
Least severe			TIA

9.7. Safety data

The number and percentage of participants experiencing any serious adverse events (SAEs) and related unexpected serious adverse events (RUSAEs) within 30 days post-first revascularisation intervention will be presented by intervention group alongside the number of events reported. Statistical significance will be determined (p-value generated) through

examination of the associated chi-squared statistic. A template for reporting is given in section 9 of the supplementary template report.

9.8. Planned subgroup analyses

Interpretation of subgroup analyses will be treated with caution (output will be treated as exploratory rather than definitive [14]). Analyses will be limited to the primary outcome only, and the following subgroups:

- Age (≤60, 61-70, 71-80, >80 years).
- Gender (male, female).
- DM (yes, no).
- CKD (yes, no).
- Severity of clinical disease (ischaemic rest/night pain only, tissue loss only, both).
- Previous (permissible) intervention to the trial leg (yes, no, unknown).
- Intention for a hybrid procedure (yes, no, unknown).
- ABPI (<0.8, 0.8-1.2, >1.2 or non-compressible)
- TBPI (<0.6, ≥0.6 or non-compressible)

The effects of these subgroups will be examined by including a treatment group by subgroup interaction parameter in the regression model. P-values from tests for statistical heterogeneity will be presented alongside the effect estimate and 95% CI within each subgroup. In addition to this, a ratio(s) (and 95% CI(s)) will be provided to quantify the difference between the treatment effects estimated within each subgroup. For gender, DM, CKD and TBPI as these subgroup variables contain only two levels, one ratio will be provided ('male', 'no', 'no', and '≥0.6 or non-compressible' will be regarded as the reference groups respectively). For age, which has four levels, '≤60' will be considered as the reference group and three ratios will be provided for the other levels in comparison to this reference. For severity of clinical disease, previous (permissible) intervention to the trial leg, intention for a hybrid procedure and ABPI, which have three levels, 'ischaemic rest/night pain only', 'no', 'no' and '>1.2 or non-compressible' will be considered as the reference groups respectively and two ratios will be provided for the other levels in comparison to this reference. A template for reporting the subgroup analyses for the primary outcome is given in section 8.1.5 of the supplementary template report.

9.9. Sensitivity analyses or supportive analyses

Sensitivity/supportive analyses will consist of:

- A per-protocol (adherent) analysis (population described in section 5.4) for the primary outcome only.
- An as treated analysis (population described in section 5.4) for the primary outcome only.
- A sensitivity to assess distributional assumptions (where applicable, as described in section 9.2) for continuous secondary outcomes.

10. Analysis of sub-randomisations

Not applicable.

11. Health economic analysis

As indicated in the protocol there will also be an economic analysis. The details of this analysis are documented separately.

12. Statistical software

Statistical analysis will be undertaken in the following statistical software packages: Stata (version 17.0 or higher) and SAS (version 9.4 or higher).

13. References

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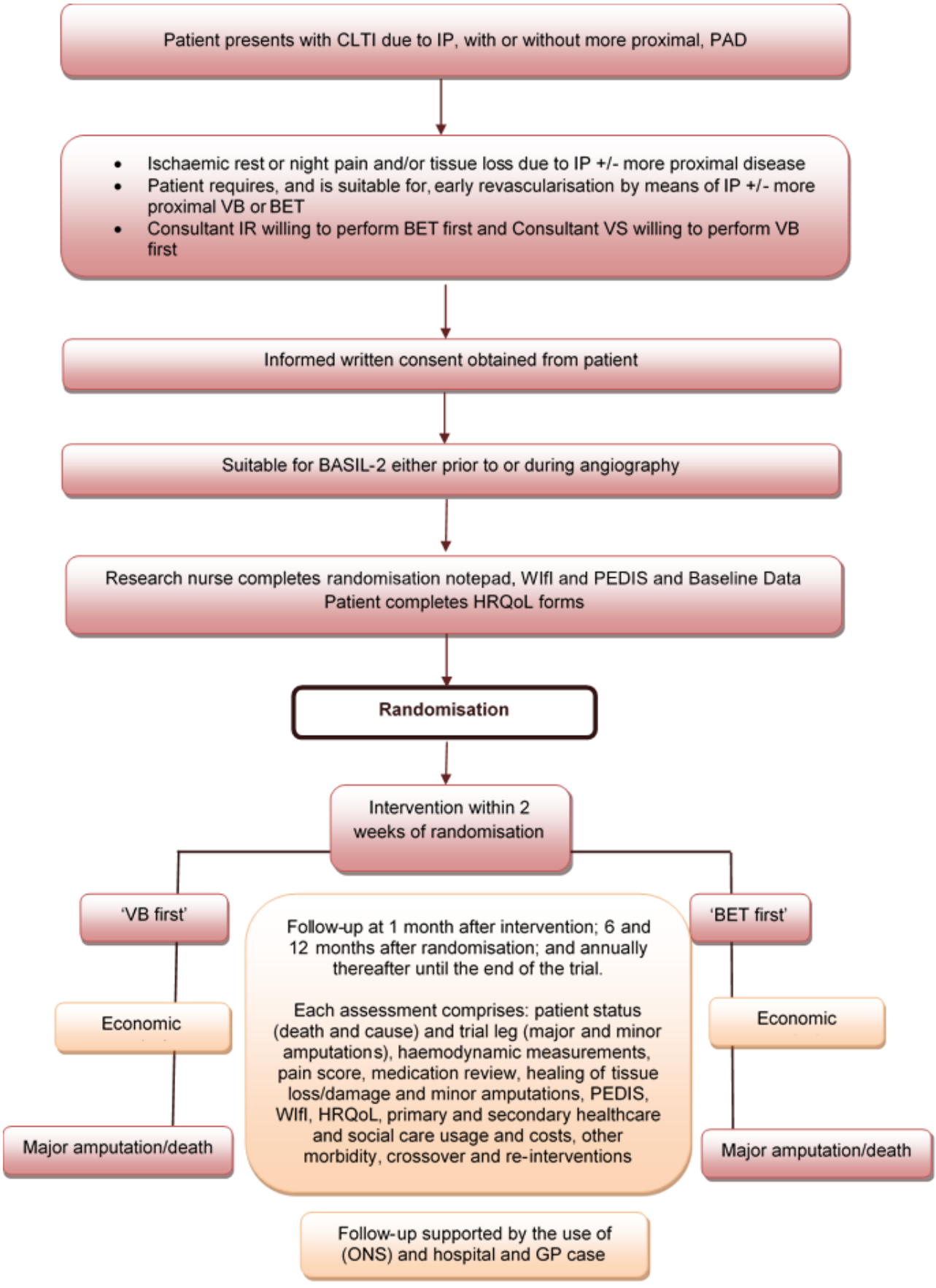
Appendix A: Deviations from SAP

This report below follows the statistical analysis plan version <x.0> dated <insert effective date of latest SAP> apart from following:

Section of report not following SAP	Reason
<insert section >	<insert, e.g. exploratory analyses request by TMG>

Appendix B: Trial schema



Appendix C: Schedule of assessments

	Completed by	Screening	Baseline	Randomisation	Intervention (within 2 weeks)	Follow-up (1, 6, 12 months and annually)
Informed Consent	Participant	X	X			
History	Participant/Case notes	X	X			
Physical examination	Case notes		X			X
Imaging	Case notes		X			X
Wound assessment	Case notes		X			X
VAS	Participant		X			X
WIfI/PEDIS	Case notes		X			X
EQ-5D-5L	Participant		X			X
ICECAP-O	Participant		X			X
VascuQoL	Participant		X			X
Haemodynamic indices	Case notes		X			X
Amputation assessment	Case notes				X	X
Randomisation	Case notes			X		
Revascularisation interventions	Case notes				X	X
Resource usage	Participant/Case notes		X			X
Pain relief medication	Participant/Case notes		X			X
SAE review	Participant/Case notes				X	X

Appendix D: Data manipulations

The Trial Statistician will derive the following measures as follows:

Primary and secondary outcome measures

- **AFS**

  During follow-up, if a participant has a major amputation or dies from any cause, this will be recorded on the amputation form or exit form respectively (death data will also be captured via Office National Statistics (ONS) data, and amputations via Data Access Request Service (DARS) data). A major amputation is defined as an amputation above the ankle (below knee amputation (BKA), through knee amputation (TKA), or an above knee amputation (AKA)). Major amputation or death from any cause will be regarded as an event. Date of amputation or date of death will be used as the date of the event. If a participant has experienced a major amputation and then subsequently dies, the major amputation date will be used (i.e. the first event). Time to major amputation/death will be calculated as the number of years between the date of randomisation and the date of event as follows:

  Time to major amputation/death (years) = ((Date of major amputation/death)-(Date of randomisation))/365.25.

  If a participant does not report a major amputation or death, their date last seen (for censoring) will be obtained from the date of their most recent clinical assessment (see below*). Censoring time will be calculated as follows:

  Censoring time (years) = ((Date last seen)-(Date of randomisation))/365.25.

  If a participant has no follow-up post randomisation or their event occurred on the date of randomisation then their time will be considered as one day (1/365.25 years).

  *If ONS/DARS data is available then date last seen will be 'most recent date of data extraction period' (unless a participant has had a clinical contact post this date, as defined below). If ONS/DARS data is unavailable then date last seen will be date of their most recent (last) clinical contact (date of visit on the follow-up form**, date of discharge for an inpatient admission*** or date of amputation).

  **If the date of visit on the follow-up form is missing, use date of form completion.

  ***If the date of discharge for an inpatient admission is missing, use date of admission (or earliest date of any procedure/complication recorded on the form if date of admission also missing).

- **OS**

  During follow-up in BASIL-2 if a participant has died this will be recorded on the exit form (or captured via ONS data). Death from any cause will be regarded as an event. Time to death will be calculated as the number of years between the date of randomisation and the date of death as follows:

  Time to death (years) = (Date of death)-(Date of randomisation)/365.25.

  If a participant remains alive, their date last seen (for censoring) will be obtained from the date of their most recent assessment (see below*). Censoring time will be calculated as follows:

  Censoring time (years) = ((Date last seen)-(Date of randomisation))/365.25.

  If a participant has no follow-up post randomisation or their event occurred on the date of randomisation then their time will be considered as one day (1/365.25 years).

  *If ONS is available then date last seen will be 'most recent date of data extraction period' (unless a participant has had a clinical contact post this date, as defined below). If ONS data is unavailable then date last seen will be date of their most recent clinical contact (date of visit on the follow-up form**, date of discharge for an inpatient admission***, date of completion of HRQoL [EQ-5D, VascuQoL, SF-12 or ICECAP-O], or date of amputation).

  **If the date of visit on the follow-up form is missing, use date of form completion.

***If the date of discharge for an inpatient admission is missing, use date of admission (or earliest date of any procedure/complication recorded on the form if date of admission also missing).

- **Time to first major (above the ankle) amputation of the trial leg**

During follow-up, if a participant has a major amputation this will be recorded on the amputation form (or captured via DARS data). A major amputation is defined as an amputation above the ankle (BKA, TKA or AKA). Major amputation will be regarded as an event. Time to major amputation will be calculated as the number of years between the date of randomisation and the date of event as follows:

Time to major amputation (years) = ((Date of major amputation)-(Date of randomisation))/365.25.

If a participant does not report a major amputation, their date last seen (for censoring) will be obtained from the date of their most recent clinical assessment (see below*). Censoring time will be calculated as follows:

Censoring time (years) = ((Date last seen)-(Date of randomisation))/365.25.

If a participant has no follow-up post randomisation or their event occurred on the date of randomisation then their time will be considered as one day (1/365.25 years).

*If DARS data is available then date last seen will be 'most recent date of data extraction period' (unless a participant has had a clinical contact post this date, as defined below or has a death prior to this date in which case date of death will be used). If DARS data is unavailable then date last seen will be date of their most recent clinical contact (date of visit on the follow-up form**, date of discharge for an inpatient admission*** or date of amputation).

**If the date of visit on the follow-up form is missing, use date of form completion.

***If the date of discharge for an inpatient admission is missing, use date of admission (or earliest date of any procedure/complication recorded on the form if date of admission also missing).

- **In-hospital 30-day morbidity and mortality**

Morbidity

Morbidity will be defined as any adverse event (AE) which occurs within 30 days of the participant's first revascularisation intervention post-randomisation. This includes minor/major amputations to either leg, intervention to the non-trial leg, further intervention to the trial leg (following first intervention), complications such as MI, TIA, stroke or other or any SAE (derived as per Table 4 below).

Table 4

AE	Form	Data rule	Date of morbidity event
Minor/major amputation to the trial leg	Amputation form	Hallux, other toes, transmetatarsal, forefoot, below knee, through knee, above knee or other=yes	Date of amputation
Minor/major amputation to the non-trial leg	Inpatient/Daycase form	Vascular intervention(s) to the non-trial leg=yes and Minor amputation or major amputation=yes	Date of admission
Intervention to the non-trial leg	Inpatient/Daycase form	Vascular intervention(s) to the non-trial leg=yes and Surgical or endovascular=yes	Date of admission
Further intervention to the trial leg	~	~	~
Complications	Inpatient/Daycase form	Myocardial infarction, TIA, stroke or other complication=yes	Date of MI/Date of TIA/Date of stroke/Date of other complication*
SAE	SAE form	Any SAE reported	Date classified as serious by reporting site

~Derived as per 'further interventions' below.

*If date of other complication is missing, date of admission will be used (unless this is pre the date of the participant's first revascularisation intervention [or pre- randomisation if no revascularisation intervention] in which case date of first revascularisation intervention [date of randomisation] will be used).

Time to morbidity will be calculated as the number of days between the date of intervention (first) and the date the morbidity event occurred as follows:

Time to morbidity (days) = (Date of morbidity event)-(Date of Intervention[1])

If time to morbidity ≤30 days for any AE this will be regarded as an event. If time to morbidity is >30 days for all AEs or no AEs reported this will not be regarded as an event.

[1]If a participant does not receive a revascularisation intervention post-randomisation then date of randomisation will be used.

Mortality
During follow-up in BASIL-2 if a participant has died this will be recorded on the exit form (or captured via ONS data). Time to death will be calculated as the number of days between the date of intervention (first) and the date of death as follows:

Time to death (days) = (Date of death)-(Date of Intervention[1])

If time to death ≤30 days this will be regarded as an event. If time to death is >30 days or death is not reported this will not be regarded as an event.

[1]If a participant does not receive a revascularisation intervention post-randomisation then date of randomisation will be used.

- **MALE**
MALE is defined as either a major amputation or any major revascularisation (following first intervention) to the trial leg (derived as per Table 5 below).

Table 5

MALE component	Form	Data rule	Date of MALE event
Major amputation to the trial leg	Amputation form	Below knee, through knee or above knee=yes	Date of amputation
Further intervention to the trial leg	~	~	~

~Derived as per 'further interventions' below.

If a participant has had any of the events listed above this will be regarded as an event. If a participant has experienced more than one MALE, the earliest event date will be used. Time to first MALE will be calculated as the number of years between the date of randomisation and the date of event as follows:

Time to first MALE (years) = ((Date of MALE event)-(Date of randomisation))/365.25.

If a participant does not have a MALE, their date last seen (for censoring) will be obtained from the date of their most recent clinical assessment (see below*). Censoring time will be calculated as follows:

Censoring time (years) = ((Date last seen)-(Date of randomisation))/365.25.

If a participant has no follow-up post randomisation or their event occurred on the date of randomisation then their time will be considered as one day (1/365.25 years).

*Date last seen will be date of their most recent clinical contact (date of visit on the follow-up form**, date of discharge for an inpatient admission***, or date of amputation).

**If the date of visit on the follow-up form is missing, use date of form completion.

***If the date of discharge for an inpatient admission is missing, use date of admission (or earliest date of any procedure/complication recorded on the form if date of admission also missing).

- **MACE**

MACE is defined as either a major amputation to the non-trial leg, MI, stroke, TIA or CLTI in the non-trial leg (derived as per Table 6 below).

Table 6

MACE component	Form	Data rule	Date of MACE event
Major amputation to the non-trial leg	Inpatient/Daycase form	Vascular intervention(s) to the non-trial leg=yes and Major amputation=yes	Date of admission
MI	Inpatient/Daycase form	Myocardial infarction=yes	Date of MI
Stroke	Inpatient/Daycase form	Stroke=yes	Date of stroke
TIA	Inpatient/Daycase form	TIA=yes	Date of TIA
CLTI to the non-trial leg	Baseline clinical form and clinical follow-up form(s)	If ischaemic rest/night pain=yes or tissue loss=yes in the non-trial leg at a given time point (at or below the ankle~) this will be regarded as having developed CLTI (at that time point). CLTI in the non-trial leg will be regarded as an event if a new case of CLTI develops, that is, if at a given time point CLTI=no and then at a later time point CLTI=yes, this will be regarded as a new case of CLTI and will be considered an event.	Date of visit (At the earliest visit where the new case of CLTI occurs)

~Tissue loss yes on either the ankle, hind foot, forefoot, other toes or hallux.

If a participant has had any of the events listed above this will be regarded as an event. If a participant has experienced more than one MACE, the earliest event date will be used. Time to MACE will be calculated as the number of years between the date of randomisation and the date of event as follows:

Time to first MACE (years) = ((Date of MACE event)-(Date of randomisation))/365.25.

If a participant does not have a MACE, their date last seen (for censoring) will be obtained from the date of their most recent clinical assessment (see below*). Censoring time will be calculated as follows:

Censoring time (years) = ((Date last seen)-(Date of randomisation))/365.25.

If a participant has no follow-up post randomisation or their event occurred on the date of randomisation then their time will be considered as one day (1/365.25 years).

*Date last seen will be date of their most recent clinical contact (date of visit on the follow-up form**).

**If the date of visit on the follow-up form is missing, use date of form completion.

- **Relief of ischaemic rest/night pain (VAS)**

Relief of ischaemic pain is measured using a VAS, which is measured on a scale of 0-10 where 0 corresponds to no

pain and 10 corresponds to the worse possible pain.

- **Relief of ischaemic rest/night pain (medication usage)**
  Medication usage is recorded on the baseline clinical form and clinical follow-up forms. If a participant receives opiates this is defined as receiving medication for pain relief at that visit.

- **EQ-5D-5L**
  The current National Institute for Health and Care Excellence (NICE) guidelines (updated October 2019 [16]) for EQ-5D-5L index scoring recommend not to use the most recent value set for England published by Devlin et al. 2018 [17] but instead use the crosswalk approach developed by Van Hout et al. 2012 [18]. This approach maps the 5L responses onto the 3L value set. The Van Hout crosswalk is based on international datasets, with mapping between response options. For participants recruited to BASIl-2 in the UK, the UK value set will be used. For participants recruited to BASIL-2 in Denmark or Sweden, the Danish value set will be used.

  For the UK value set, the EQ5D (5 level) index score ranges from –0.594 to 1, where a score of 1 implies perfect health, a score of 0 implies a health status of death and negative scores imply a health status worse than death. No missing data items are permitted in order to compute a score.
  For the Danish value set, the EQ5D (5 level) index score ranges from –0.624 to 1, where a score of 1 implies perfect health, a score of 0 implies a health status of death and negative scores imply a health status worse than death. No missing data items are permitted in order to compute a score.

  The EQ5D (5 level) health state score ranges from 0 to 100, where a score of 0 implies worst health, a score of 100 implies best health. No missing data items are permitted in order to compute a score.

- **SF-12 (v2)**
  The SF-12 response scales will be coded as follows:

  - Question 1: Excellent=5, Very good=4.4, Good=3.4, Fair=2, Poor=1.
  - Questions 2a, 2b: Yes, limited a lot=1, Yes, limited a little=2, No, not limited at all=3.
  - Questions 3a, 3b, 4a, 4b, 6a, 6b, 6c, 7: All of the time=1, Most of the time=2, Some of the time=3, A little of the time=4, None of the time=5.
  - Question 5: Not at all=5, A little bit=4, Moderately=3, Quite a bit=2, Extremely=1.

  The SF-12 domain scores listed below will be derived as follows:

  - Physical function=(100*(((SUM(2a, 2b))-2)/4))
  - Role limitation due to physical problems=(100*(((SUM(3a, 3b))-2)/8))
  - Role limitation due to emotional problems=(100*(((SUM(4a, 4b))-2)/8))
  - Social functioning=(100*(((Question 7)-1)/4))
  - Mental health=(100*(((SUM(6a, 6c))-2)/8))
  - Energy/vitality=(100*(((Question 6b)-1)/4))
  - Pain=(100*(((Question 5)-1)/4))
  - General health perception=(100*(((Question 1)-1)/4))
  - Mental component summary score=50+[((A*-0.22999)+(B*-0.12329)+(C*-0.09731)+(D*-0.01571)+(E*0.23534)+(F*0.26876)+(G*0.43407)+(H*0.48581))*10]
  - Physical component summary score =

50+[((A*0.42402)+(B*0.35119)+(C*0.31754)+(D*0.24954)+(E*0.02877)+(F*-0.00753)+(G*-0.19206)+(H*-0.22069))*10]

Where,

- A=[(100*(((SUM(2a, 2b))-2)/4))-81.18122]/29.10588.
- B=[(100*(((SUM(3a, 3b))-2)/8))- 80.52856]/27.13526.
- C=[(100*(((Question 5)-1)/4))- 81.74015]/24.53019.
- D=[(100*(((Question 1)-1)/4))- 72.19795]/23.19041.
- E=[(100*(((Question 6b)-1)/4))- 55.59090]/24.84380.
- F=[(100*(((Question 7)-1)/4))- 83.73973]/24.75775.
- G=[(100*(((SUM(4a, 4b))-2)/8))- 86.41051]/22.35543.
- H=[(100*(((SUM(6a, 6c))-2)/8))- 70.18217]/20.50597.

SF-12 domain scores range from 0 to 100, where higher scores are good. No missing data items are permitted.

- **SF-12 (v1)**

The SF-12 component summary scores listed below will be derived as follows:

- Mental component summary score=SUM(physical component weight A-AU*)+57.65693
- Physical component summary score=SUM(mental component weight A-AU*)+60.58847

Component weights as per

Table 7. SF-12 mental component summary scores range from 2.7897 to 69.18291 and physical component summary scores range from 13.95879 to 74.14425. Higher scores are good. No missing data items are permitted.

Table 7

SF-12 item	Indicator variable	Physical component weight	Mental component weight
Question 1			
Excellent	A	0	0
Very good	B	-1.31872	-0.06064
Good	C	-3.02396	0.03482
Fair	D	-5.56461	-0.16891
Poor	E	-8.37399	-1.71175
Question 2			
Yes limited a lot	F	-7.23216	3.93115
Yes, limited a little	G	-3.45555	1.86840
No, not limited at all	H	0	0
Question 3			
Yes limited a lot	I	-6.24397	2.68282
Yes, limited a little	J	-2.73557	1.43103
No, not limited at all	K	0	0
Question 4			
Yes	L	-4.61617	1.44060
No	M	0	0
Question 5			
Yes	N	-5.51747	1.66968
No	O	0	0
Question 6			
Yes	P	3.04365	-6.82672
No	Q	0	0
Question 7			
Yes	R	2.32091	-5.69921
No	S	0	0
Question 8			
Not at all	T	0	0
A little bit	U	-3.80130	0.90384
Moderately	V	-6.50522	1.49384
Quite a bit	W	-8.38063	1.76691
Extremely	X	-11.25544	1.48619
Question 9			
All of the time	Y	0	0
Most of the time	Z	0.66514	-1.94949
A good bit of the time	AA	1.36689	-4.09842
Some of the time	AB	2.37241	-6.31121
A little of the time	AC	2.90426	-7.92717
None of the time	AD	3.46638	-10.19085
Question 10			
All of the time	AE	0	0
Most of the time	AF	-0.42251	-0.92057
A good bit of the time	AG	-1.14387	-1.65178
Some of the time	AH	-1.61850	-3.29805
A little of the time	AI	-2.02168	-4.88962
None of the time	AJ	-2.44706	-6.02409
Question 11			
All of the time	AK	4.61446	-16.15395
Most of the time	AL	3.41593	-10.77911
A good bit of the time	AM	2.34247	-8.09914
Some of the time	AN	1.28044	-4.59055
A little of the time	AO	0.41188	-1.95934
None of the time	AP	0	0
Question 12			
All of the time	AQ	-0.33682	-6.29724
Most of the time	AR	-0.94342	-8.26066
Some of the time	AS	-0.18043	-5.63286
A little of the time	AT	0.11038	-3.13896
None of the time	AU	0	0

- **ICECAP-O**

  The ICECAP-O response scales will be coded as follows:

- Question 1: I can have all of the love and friendship that I want=0.2535, I can have a lot of the love and friendship that I want=0.2325, I can have a little of the love and friendship that I want=0.1340, I cannot have any of the love and friendship that I want=-0.0128

- Question 2: I can think about the future without any concern=0.1788, I can think about the future with only a little concern=0.1071, I can only think about the future with some concern=0.0661, I can only think about the future with a lot of concern=0.0321

- Question 3: I am able to do all of the things that make me feel valued=0.1923, I am able to do many of the things that make me feel valued=0.1793, I am able to do a few of the things that make me feel valued=0.1296, I am unable to do any of the things that make me feel valued=0.0151

- Question 4: I can have all of the enjoyment and pleasure that I want=0.1660, I can have a lot of the enjoyment and pleasure that I want=0.1643, I can have a little of the enjoyment and pleasure that I want=0.1185, I cannot have any of the enjoyment and pleasure that I want=0.0168

- Question 5: I am able to be completely independent=0.2094, I am able to be independent in many things=0.1848, I am able to be independent in few things=0.1076, I am unable to be at all independent=-0.0512

The ICECAP-O score can be derived from summing all responses, as follows:

ICECAP-O score = SUM(1-5)

The ICECAP-O score ranges from 0 to 1, where high scores are good. No missing data items are permitted in order to compute a score.

- **VascuQoL**

The VascuQoL response scales will be coded as follows:

- Question 1, 2, 5, 6, 7, 12, 13, 17, 19, 21, 23, 25: All of the time=1, Most of the time=2, A good bit of the time=3, Some of the time=4, A little of the time=5, Hardly any of the time=6, None of the time=7

- Question 3, 8, 20: A very great deal of discomfort or distress=1, A great deal of discomfort or distress =2, A good deal of discomfort or distress =3, A moderate deal of discomfort or distress =4, Some discomfort or distress=5, Very little discomfort or distress=6, No discomfort or distress=7

- Question 4, 10, 14, 15, 16, 22: Totally limited=1, Extremely limited=2, Very limited=3, Moderately limited=4, A little limited=5, Only very slightly limited=6, Not at all limited=7

- Question 9: Not at all=1, A little=2, Somewhat=3, Moderately=4, A good deal=5, A great deal=6, A very great deal=7

- Question 11, 24: A very great deal=1, A great deal=2, A good deal=3, Moderately=4, Somewhat=5, A little=6, Not at all=7

- Question 18: Severely limited=1, Very limited=2, Moderately limited=3, Slightly limited=4, Very slightly limited=5, Hardly limited at all=6, Not limited at all=7

The VascuQoL domain scores and total score listed below will be derived by taking the mean of the items in that domain, as follows:

- Pain=SUM(1, 7, 13, 20)/4

- Symptoms=SUM(3, 5, 8, 17)/4

- Activities=SUM(4, 9, 10, 14, 16, 18, 22, 24)/8

- Social=SUM(6, 15, 12)/3
- Emotional=SUM(2, 11, 12, 19, 21, 23, 25)/7
- Total=SUM(1-25)/25

The VascuQoL scores range from 1 to 7, where low scores are bad and high scores are good. No missing data items are permitted.

- **Further interventions: Re- and cross-over revascularisation intervention**
  Further interventions are defined as a further revascularisation procedure (endovascular, bypass surgery or non-bypass vascular surgery) following the first revascularisation procedure post-randomisation (regardless if a participant is adherent with their allocated procedure). Further interventions can be either an endovascular procedure, surgical bypass, or non-bypass vascular surgery. A further intervention is regarded as a re-intervention if this is the same procedure as their first revascularisation procedure post-randomisation. Whereas a further intervention is regarded as a cross-over procedure if this is an alternative revascularisation procedure as their first revascularisation procedure post-randomisation (as per Table 8 below). If a participant does not receive a first revascularisation procedure post-randomisation then further intervention will be regarded as no.

Table 8

First revascularisation intervention	Subsequent revascularisation intervention	Cross-over to re-intervention	Date of subsequent revascularisation intervention
Endovascular	Endovascular	Re-intervention	Date of Intervention[1]
	Surgical bypass	Cross-over	Date of bypass surgery[1]
	Non-bypass surgery*	Cross-over	Date of non-bypass vascular surgery[3]
	None	No further intervention	
Surgical bypass	Endovascular	Cross-over	Date of Intervention[1]
	Surgical bypass	Re-intervention	Date of bypass surgery[1]
	Non-bypass surgery*	Cross-over	Date of non-bypass vascular surgery[3]
	None	No further intervention	
Non-bypass surgery*	Endovascular	Cross-over	Date of Intervention[1]
	Surgical bypass	Cross-over	Date of bypass surgery[1]
	Non-bypass surgery*	Re-intervention	Date of non-bypass vascular surgery[3]
	None	No further intervention	
None	-	No further intervention	

*Thrombectomy, thrombolysis, endarterectomy, fasciotomy or other revision of anastomosis.
[1]From BET summary form (or best segmental treatment form if BET summary form missing).
[2]From surgical bypass form.
[3]From non-bypass vascular surgery form.

- **Healing of tissue loss (WIfI)**
  Tissue loss is reported on the baseline clinical assessment form and the follow-up form. For participants with tissue loss on or below the ankle (ankle, hind foot, forefoot, other toes or hallux) on the trial leg then a WIfI form is to be completed. The WIfI response scales will be coded as follows:
  - Wound status: Grade 0=0, Grade 1=1, Grade 2=2, Grade 3=3
  - Ischaemic status: Grade 0=0, Grade 1=1, Grade 2=2, Grade 3=3
  - Foot Infection: Grade 0=0, Grade 1=1, Grade 2=2, Grade 3=3.

  The WIfI values can then be classified as clinical stage 1-4, where:
  - Clinical stage 1=Very low risk of amputation at one year

- Clinical stage 2=Low risk of amputation at one year
- Clinical stage 3=Moderate risk of amputation at one year
- Clinical stage 4=High risk of amputation at one year.

The clinical stages can be derived from the wound status, ischaemic status and foot infection scores as per Table 9 below:

Table 9

		Ischaemic status															
		0				1				2				3			
Wound Status	0	1	1	2	3	1	2	3	4	2	2	3	4	2	3	3	4
	1	1	1	2	3	1	2	3	4	2	3	4	4	3	3	4	4
	2	2	2	3	4	3	3	4	4	3	4	4	4	4	4	4	4
	3	3	3	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
		Foot Infection															

For participants with no tissue loss or tissue loss above the ankle only (on the trial leg, as reported on the baseline clinical assessment and the follow-up form) a WIfI clinical stage of 1 will be imputed for that corresponding time point.

For the purposes of analyses, clinical stage 1 and 2 will be considered as one group (low risk) and clinical stage 3 and 4 will be grouped to form another (moderate/high risk).

- **Healing of tissue loss (PEDIS)**
  Tissue loss is reported on the baseline clinical assessment form and the follow-up form. For participants with tissue loss on or below the ankle (ankle, hind foot, forefoot, other toes or hallux) on the trial leg then a PEDIS form is to be completed. The PEDIS response scales will be coded as follows:

  - Perfusion status: Grade 1=0, Grade 2=1, Grade 3=2
  - Extent of tissue loss: Skin intact (0cm²)=0, <1cm²=1, 1-3cm²=2, >3cm²=3
  - Depth of tissue loss: Grade 1=1, Grade 2=2, Grade 3=3
  - Infection: Grade 1=0, Grade 2=1, Grade 3=2, Grade 4=3
  - Sensation: Grade 1=0, Grade 2=1.

  The PEDIS score will be derived by taking the sum of all questions, as follows:

  PEDIS Score = SUM(Perfusion status, Extent of tissue loss, Depth of tissue loss, Infection, Sensation).

  The PEDIS scores ranges from 0 to 12, where low scores are good and high scores are bad. No missing data items are permitted.

  For participants with no tissue loss or tissue loss above the ankle only (on the trial leg, as reported on the baseline clinical assessment and the follow-up form) a PEDIS score of 0 will be imputed for that corresponding time point.

- **Haemodynamic measurements (ABPI)**
  ABPI can be calculated at each time point from the haemodynamic data, which is recorded on the baseline clinical form and clinical follow-up forms. ABPI for the trial leg can be computed as follows:

ABPI (trial leg)=Highest ankle pressure (trial leg)/Highest arm pressure*

Where highest ankle pressure (trial leg) is derived as follows:

Highest ankle pressure (trial leg)=maximum(Dorsalis Pedis (DP) pressure (trial leg), Posterior Tibial (PT) pressure (trial leg), Perforating peroneal (PP) pressure (trial leg))

ABPI for the non-trial leg can be computed as follows:

ABPI (non-trial leg)=Highest ankle pressure (non-trial leg)/Highest arm pressure*

Where highest ankle pressure (non-trial leg) is derived as follows:

Highest ankle pressure (non-trial leg)=maximum(DP pressure (non-trial leg), PT pressure (non-trial leg), PP pressure (non-trial leg))

*Highest arm pressure=maximum(left brachial systolic blood pressure, right brachial systolic blood pressure).

Note: If a DP, PT or PP pressure is found to be 'not found' then that pressure is 0. Further, if any of the DP, PT or PP pressures are found to be 'not compressible' this means an ABPI cannot be calculated.

- **Haemodynamic measurements (TBPI)**
  TBPI can be calculated at each time point from the haemodynamic data, which is recorded on the baseline clinical form and clinical follow-up forms. TBPI for the trial leg can be computed as follows:

  TBPI (trial leg)=Hallux pressure (trial leg)/Highest arm pressure*

  TBPI for the non-trial leg can be computed as follows:

  TBPI (non-trial leg)= Hallux pressure (non-trial leg)/Highest arm pressure*

  *Highest arm pressure=maximum(left brachial systolic blood pressure, right brachial systolic blood pressure).

  Note: If a hallux pressure is found to be 'not found' then hallux pressure is 0. Further, if a hallux pressure is found to be 'not compressible' this means a TBPI cannot be calculated.

<u>Exploratory outcome measures</u>

- **MACE (non-leg related)**
  MACE (non-leg related) is defined as either MI, stroke or TIA (derived as per Table 10 below).

Table 10

MACE component	Form	Data rule	Date of MACE event
MI	Inpatient/Daycase form	Myocardial infarction=yes	Date of MI
Stroke	Inpatient/Daycase form	Stroke=yes	Date of stroke
TIA	Inpatient/Daycase form	TIA=yes	Date of TIA

If a participant has had any of the events listed above this will be regarded as an event. If a participant has experienced more than one MACE (non-leg related), the earliest event date will be used. Time to MACE (non-leg related) will be calculated as the number of years between the date of randomisation and the date of event as follows:

Time to first MACE (years) = ((Date of MACE event)-(Date of randomisation))/365.25.

If a participant does not have a MACE (non-leg related), their date last seen (for censoring) will be obtained from the date of their most recent clinical assessment (see below*). Censoring time will be calculated as follows:

Censoring time (years) = ((Date last seen)-(Date of randomisation))/365.25.

If a participant has no follow-up post randomisation or their event occurred on the date of randomisation then their time will be considered as one day (1/365.25 years).

*Date last seen will be date of their most recent clinical contact (date of visit on the follow-up form** or date of discharge for an inpatient admission***).

**If the date of visit on the follow-up form is missing, use date of form completion.

***If the date of discharge for an inpatient admission is missing, use date of admission (or earliest date of any procedure/complication recorded on the form if date of admission also missing).

- **MACE (non-leg related)-death**
  MACE (non-leg related)-death is defined as either MI, stroke, TIA or death from any cause (derived as per Table 11 below).

Table 11

MACE component	Form	Data rule	Date of MACE event
MI	Inpatient/Daycase form	Myocardial infarction=yes	Date of MI
Stroke	Inpatient/Daycase form	Stroke=yes	Date of stroke
TIA	Inpatient/Daycase form	TIA=yes	Date of TIA
Death	Exit form	If death=yes	Date of death

If a participant has had any of the events listed above this will be regarded as an event. If a participant has experienced more than one MACE (non-leg related)-death, the earliest event date will be used. Time to MACE (non-leg related) will be calculated as the number of years between the date of randomisation and the date of event as follows:

Time to first MACE (years) = ((Date of MACE event)-(Date of randomisation))/365.25.

If a participant does not have a MACE (non-leg related), their date last seen (for censoring) will be obtained from the date of their most recent clinical assessment (see below*). Censoring time will be calculated as follows:

Censoring time (years) = ((Date last seen)-(Date of randomisation))/365.25.

If a participant has no follow-up post randomisation or their event occurred on the date of randomisation then their time will be considered as one day (1/365.25 years).

*Date last seen will be date of their most recent clinical contact (date of visit on the follow-up form** or date of discharge for an inpatient admission***).

**If the date of visit on the follow-up form is missing, use date of form completion.

***If the date of discharge for an inpatient admission is missing, use date of admission (or earliest date of any procedure/complication recorded on the form if date of admission also missing).

- **Major non-trial leg event**
  Major non-trial leg event defined as CLTI and/or major amputation affecting the non-trial leg (derived as per Table 12 below).

Table 12

Component	Form	Data rule	Date of MACE event
Major amputation to the non-trial leg	Inpatient/Daycase form	Vascular intervention(s) to the non-trial leg=yes and Major amputation=yes	Date of admission
CLTI to the non-trial leg	Baseline clinical form and clinical follow-up form(s)	If ischaemic rest/night pain=yes or tissue loss=yes in the non-trial leg at a given time point (at or below the ankle~) this will be regarded as having developed CLTI (at that time point). CLTI in the non-trial leg will be regarded as an event if a new case of CLTI develops, that is, if at a given time point CLTI=no and then at a later time point CLTI=yes, this will be regarded as a new case of CLTI and will be considered an event.	Date of visit (At the earliest visit where the new case of CLTI occurs)

~Tissue loss yes on either the ankle, hind foot, forefoot, other toes or hallux.

If a participant has had any of the events listed above this will be regarded as an event. If a participant has experienced more than one major non-trial leg event, the earliest event date will be used. Time to major non-trial leg event will be calculated as the number of years between the date of randomisation and the date of event as follows:

Time to first major non-trial leg event (years) = ((Date of major non-trial leg event event)-(Date of randomisation))/365.25.

If a participant does not have a major non-trial leg event, their date last seen (for censoring) will be obtained from the date of their most recent clinical assessment (see below*). Censoring time will be calculated as follows:

Censoring time (years) = ((Date last seen)-(Date of randomisation))/365.25.

If a participant has no follow-up post randomisation or their event occurred on the date of randomisation then their time will be considered as one day (1/365.25 years).

*Date last seen will be date of their most recent clinical contact (date of visit on the follow-up form**).

**If the date of visit on the follow-up form is missing, use date of form completion.

- **MALE-death**

MALE-death is defined as either a major amputation or any major revascularisation (following first intervention) to the trial leg or death from any cause (derived as per Table 13 below).

Table 13

Component	Form	Data rule	Date of MALE event
Major amputation to the trial leg	Amputation form	Below knee, through knee or above knee=yes	Date of amputation
Further intervention to the trial leg	~	~	~
Death from any cause	Exit form	If death=yes	Date of death

~Derived as per 'further interventions' above.

If a participant has had any of the events listed above this will be regarded as an event. If a participant has experienced more than one event, the earliest event date will be used. Time to first MALE-death will be calculated as the number of years between the date of randomisation and the date of event as follows:

Time to first MALE-death (years) = ((Date of MALE-death event)-(Date of randomisation))/365.25.

If a participant does not have a MALE-death, their date last seen (for censoring) will be obtained from the date of their most recent clinical assessment (see below*). Censoring time will be calculated as follows:

Censoring time (years) = ((Date last seen)-(Date of randomisation))/365.25.

If a participant has no follow-up post randomisation or their event occurred on the date of randomisation then their time will be considered as one day (1/365.25 years).

*Date last seen will be date of their most recent clinical contact (date of visit on the follow-up form**, date of discharge for an inpatient admission***, or date of amputation).

**If the date of visit on the follow-up form is missing, use date of form completion.

***If the date of discharge for an inpatient admission is missing, use date of admission (or earliest date of any procedure/complication recorded on the form if date of admission also missing).

Other measures

- **Age at randomisation (years)**=(Date of randomisation-Date of birth)/365.25
- **Body mass Index (kg/m^2)**=Weight (kg)/[Height (m)]^2