A RAndomised controlled trial assessing the clinical and cost-effectiveness of Endovascular vs. Open revascularisation for common Femoral artery steno-occlusive disease. The RAF Trial.

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SIGNATURE PAGE

The undersigned confirm that this protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements.

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

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

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NIHR Portfolio adopted	Yes

CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BHF	British Heart Foundation
CFA	Common Femoral Artery
CI	Chief Investigator
CLTI	Chronic Limb-Threatening Ischemia
CRF	Case Report Form
CRN	Clinical Research Networks
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
EDC	Electronic Data Capture
GCP	Good Clinical Practice
HES	Hospital Episode Statistics
HTA	Health Technology Assessment
ICF	Informed Consent Form
ISF	Investigator Site File
JLA	James Lind Alliance
LCTU	Leicester Clinical Trials Unit
MDT	Multi-Disciplinary Team
NHS R&D	National Health Service Research & Development
ONS	Office for National Statistics
PAD	Peripheral Arterial Disease
PAD SIG	Peripheral Arterial Disease Specialist Interest Group
PI	Principal Investigator
PIC	Participant Identification Centre
PPI&E	Patient and Public Involvement & Engagement
PIS	Participant Information Sheet
PSSRU	Personal Social Service Resource Use Unit Cost
PSP	Priority Setting Partnership
QALY	Quality Adjusted Life Years
QC	Quality Control
QRI	QuinteT Recruitment Intervention

RFS	Research Filestore Service
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UoL	University of Leicester
VSGBI	Vascular Society of Great Britain and Ireland

KEY WORDS

Peripheral arterial disease, endovascular, vascular, common femoral artery

TRIAL SUMMARY

Trial Title	A RAndomised controlled trial assessing the clinical and cost-effectiveness of Endovascular vs. Open revascularisation for common Femoral artery steno-occlusive disease. The RAF Trial.
Trial Design	Multicentre prospective randomised controlled trial (RCT) involving 504 adults with chronic limb threatening ischaemia (CLTI) or lower limb claudication [Rutherford Stage >=3 or Fontaine Stage >= IIb(1)] who have steno-occlusive CFA disease requiring revascularisation, recruited from 24 NHS hospitals nationally (urban/rural areas), randomised 1:1 to receive open surgery or endovascular surgery of the CFA.
Participating Locations:	At least 24 NHS hospital locations in the UK (England, Scotland and Wales)
Trial Participants	Adults (>=18 years of age) with chronic limb threatening ischaemia (CLTI) or severe life-style limiting lower limb claudication [classified as Rutherford Stage >=3 or Fontaine Stage >= IIb(1)] who have steno-occlusive CFA disease requiring revascularisation, recruited from 24 NHS hospitals (secondary care), across a wide geographical spread (urban and rural areas).
Planned Sample Size	504
Recruitment Period	51 months' overall trial duration, allowing 9 months for approvals and pilot set-up, 6-month pilot, 18-month main recruitment phase (with a minimum of 12 months follow-up per individual patient).

Follow Up Duration	Minimum 12 months per individual patient.	
Planned Trial Period	**Grant start date**: 01/09/2025; overall duration: 51 months.	
	Objectives	**Outcome Measures**
Primary	Identify whether open surgery for CFA disease is superior to endovascular treatment in terms of death and reinterventions (including major amputation or arterial revascularisation) over a minimum 1-year follow-up, in a time-to-event analysis.	Primary outcome measure: Composite of death (all-cause) and/or reintervention (major amputation or leg revascularisation) over a minimum of one year (time-to-event analysis)
Secondary	Estimate differences in quality-of-life of patients between arms. Estimate differences in quality adjusted life years and costs between two arms. Evaluate the incremental cost-effectiveness ratios in term of clinical improvement and QALYs gained of intervention compared with the control group.	Secondary outcome measures: • Mortality (all cause) • Hospital admissions (including reason for admission) • Reinterventions (including nature of reintervention) • All lower limb amputations (minor and major i.e. below and above ankle joint) • Quality-of-life using EQ-5D-5L tool • Quality adjusted life years (QALYs) • Healthcare resource-use and cost • Incremental cost per life year gained and per QALY gained

ROLE OF TRIAL SPONSOR

The study has been funded by a grant from the NIHR Health Technology Assessment (HTA) Programme (ref: NIHR151230). Additional support and resources for the study will be provided by the participating Trusts and their corresponding Clinical Research Networks (CRN). The funder will be responsible for funding the study but will not be part of the study conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

The Sponsor, the University of Leicester (UoL), will be responsible for all aspects of the study. The Sponsor will delegate duties to other parties, including Leicester Clinical Trials Unit (LCTU), this delegation will be formally documented. However, like the funder, the Sponsor will not be part of the study conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

RAF TRIAL FLOW CHART

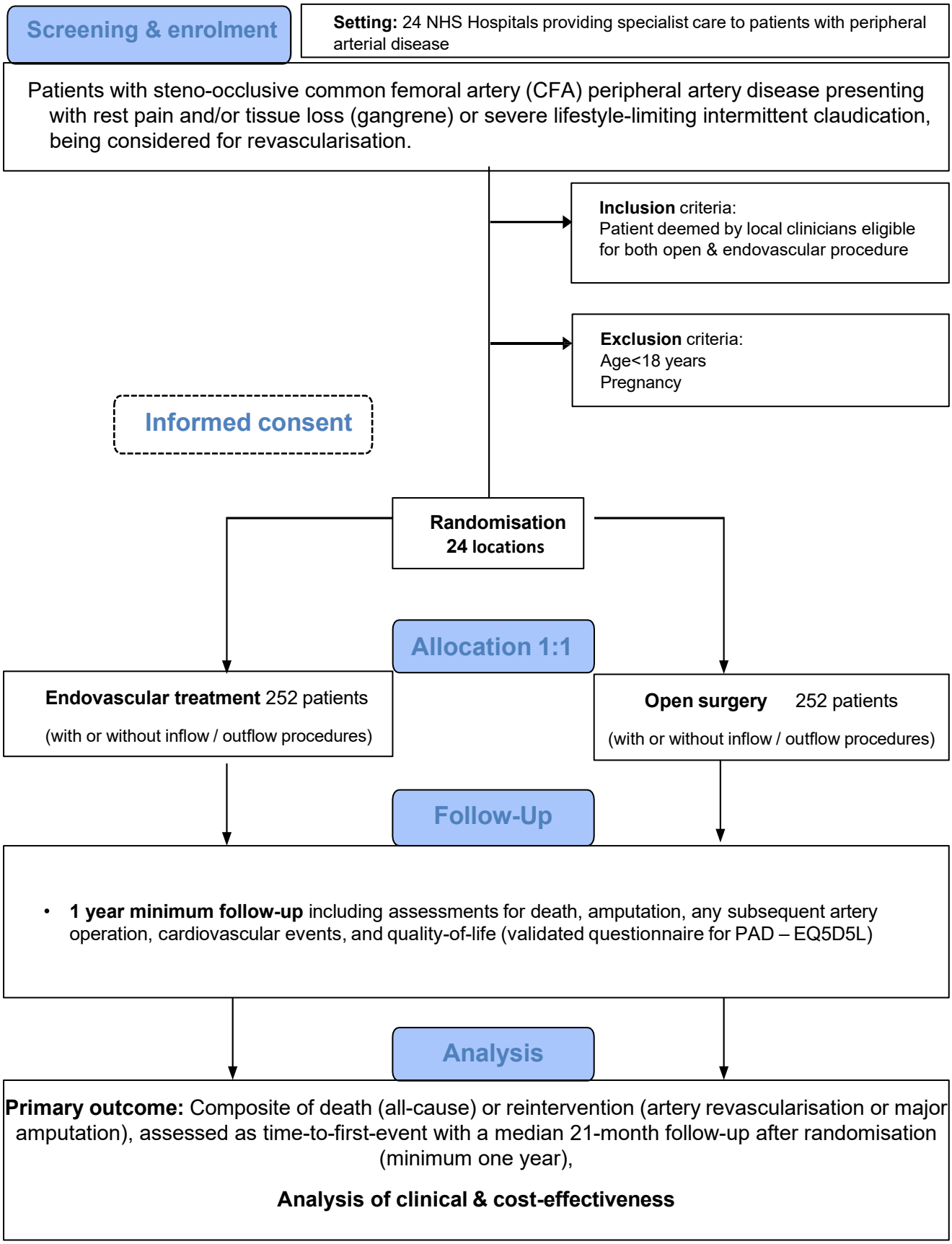

Figure 1. RAF CONSORT diagram

1. BACKGROUND & RATIONALE

Lower limb peripheral arterial disease (PAD) affects 1 in 5 people >55 years of age(2-4). It is the main cause of lower limb amputations in the NHS(5, 6). People who develop symptoms due to PAD typically present with claudication (pain when walking) or leg gangrene (chronic limb threatening ischaemia [CLTI])(2). The common femoral artery (CFA) is the artery most often affected by steno-occlusive atherosclerotic disease in those with CLTI or claudication(7-10); 11,400 people require CFA revascularisation in the NHS yearly(4, 7). Revascularisation of the CFA can be performed via open surgery or newly developed endovascular treatments (minimally invasive)(11). The latter might avoid some surgical complications like wound infections, but is known to be less durable and can be more expensive(8-10, 12). Open CFA surgery vs. endovascular treatment have never been compared head-to-head in a high-quality trial assessing their clinical and cost-effectiveness, leading to unnecessary uncertainty for patients/clinicians, preventable amputations, deaths, and reinterventions across the NHS(7, 13).

Rationale

There is no randomised evidence comparing the clinical and cost-effectiveness of open or endovascular interventions to address steno-occlusive PAD affecting the CFA, which creates great uncertainty for patients with PAD and clinicians. The need to improve outcomes and reduce amputations in this group of patients has been highlighted by the JLA in 2021 as an urgent research priority (14).

Our two lay co-applicants and 42 lay participants in a national survey for this research unanimously agreed on the importance of this trial(7). Most commented on the existing clinical uncertainty for patients and healthcare professionals, noting that this ambiguity causes unnecessary stress and confusion, especially for patients. A James Lind Alliance (JLA) Priority Setting Partnership (PSP) with 122 lay participants nationally, recognised this area as a top research-priority for those with vascular diseases(15, 16).

Healthcare need and clinical effectiveness

Healthcare need. Steno-occlusive disease of the CFA can be treated either with open surgery (usually in the form of CFA endarterectomy) **or** a minimally invasive endovascular procedure. However, these two approaches have never been compared directly in a randomised trial. Our recent NHS-wide surveys showed that equipoise exists amongst radiologists and surgeons in this context and almost all participants supported the conduct of this research, in order to guide NHS care, addressing the current lack of data(7, 16).

Clinical-effectiveness. Endovascular CFA treatment does not require a general anaesthetic or incision allowing for shorter hospital stay, potentially offering advantages over traditional surgery(7, 8, 10, 11). Historically, however, endovascular treatment, primarily using plain balloon angioplasty, was not considered effective in the CFA(7, 11). The past 15 years have seen the introduction of advanced technologies such as atherectomy, lithotripsy, improved imaging, new artery stents and new angioplasty balloons, revolutionising CFA treatment without need for surgery(11). These advancements have enabled efficacious and safe treatment of calcified arterial disease and complex CFA anatomies(7, 17, 18). Such endovascular technologies are now available in the NHS, but their effectiveness remains unproven(8, 10, 11), as per our published literature, surveys/interviews with 121 surgeons/radiologists (for this application), and national observational data(7, 16).

Economic impact and cost effectiveness

Using meta-analyses(19) and NHS data(20), we assessed mortality, amputation, reintervention rates after CFA surgery vs. endovascular treatment with new generation devices. Mortality and amputation rates could not be compared directly due to the greater frailty and older age of patients selected for endovascular treatment in all studies(7, 8, 16, 21). However, wound infections and post-operative complications were more common after surgery (3% vs. 1%), while reinterventions far more frequent after endovascular treatment. We calculated the average peri-operative and device costs at £19,097 for endovascular treatment and £27,846 for surgery. The one-year reinterventions/amputations costs were £46,558 for endovascular treatment and £44,578 for surgery, indicating similar overall cost to the NHS(18, 20, 22). Despite these findings, the extreme heterogeneity of the available data means it is very unclear which treatment is more clinically or cost-effective(7, 22). Unless this study is delivered, we risk adopting expensive devices for endovascular CFA treatment with completely unproven clinical/cost-effectiveness in the NHS.

Sustained interest and intent

PAD affecting the CFA is highly prevalent in the UK, particularly in those with diabetes or those experiencing socioeconomic deprivation(23). Amputations due to PAD are also on the rise(23, 24). This study will be the first effectiveness-driven randomised trial (RCT) in this context, informing clinical practice in the NHS and worldwide.

Capacity to generate new knowledge

This will be the first randomised trial assessing clinical and cost-effectiveness in this clinical context worldwide.

Evidence and literature

CFA trials: In June 2024, we searched all online trial-repositories (ISRCTN, clinicaltrials.gov, WHO database) and reviewed published guidelines related to PAD, including those from the National Institute for Care Excellence (NICE). We found **no completed or ongoing effectiveness-driven randomised trials** in this area and most international guidelines supported the conduct of this randomised study.

Observational evidence: We updated a meta-analysis, including our own data, published a multicentre study, and accessed NHS-wide datasets(7, 8, 11, 13, 25, 26) to support this research.

Key findings:

1) Widespread use of modern devices for CFA treatment(s): Modern CFA endovascular devices (stents, balloons, lithotripsy, atherectomy) are now available in the NHS, enabling minimally invasive treatment of the CFA. These devices mitigate the risks of complications due to arterial calcification and the risk of deep femoral artery (a branch of the CFA) occlusion, which are the main issues faced when using plain angioplasty (the older version of endovascular treatment) to treat the CFA. These modern CFA technologies have proven efficacy but completely unknown effectiveness(7-9, 11, 12). Our **ongoing NIHR HTA EVOCC trial cannot address this issue**, due to fundamental differences in design/anatomy/eligibility criteria (EVOCC focusses on aortic disease and CLTI, using very different endovascular technologies).

2) Eligibility for proposed trial: 87% of NHS patients with CFA disease would be eligible for our proposed trial(7), as we showed in a multicentre cohort study in the NHS.

3) Comparative patency rates and safety: A small efficacy-driven RCT involving patients with CFA disease, called TECCO(17), assessed older-generation endovascular devices vs. open surgery, but failed to address clinically-meaningful differences between treatments. At the same time, the TECCO RCT and our cohort studies(27-30) have shown similar patency rates for surgery and endovascular CFA treatment and have confirmed the safety of modern endovascular technologies. In all observational data to date, surgery is associated with higher rates of wound infection and longer hospital-stays. Importantly, all these studies are biased and did not prospectively assess clinically meaningful outcomes such as amputations rates or reinterventions.

4) Both treatments are now performed in the NHS: Between 2016-2021, an average of 8,150 NHS patients underwent open CFA surgery annually, compared to 3,290 who received endovascular treatments, based on our own audits, National Vascular Registry data, and our recently published cohort studies(20, 31).

Survey conducted to design RAF: We completed a **national survey** specifically for RAF in 2023-24; 90% of the 121 NHS clinicians taking part felt there is an urgent need for this RCT, with 57% indicating that they would randomise patients(16). Additionally, the 42 patient participants unanimously agreed on

the importance of this question, all felt randomisation is acceptable, and provided guidance on outcomes and eligibility-criteria. Most importantly, they felt the RAF trial should assess the superiority of open surgery vs. endovascular treatment. They would only accept open surgery of the CFA if it was proven to be better than endovascular treatment by at least a third, in saving legs and preventing reintervention.

Evidence supporting the need for the trial and study design based on PPI&E and staff views

This research is urgently needed, as highlighted by expert bodies and a JLA PSP. Currently, there is a significant gap in our understanding of the most effective treatments for patients with PAD. This lack of knowledge leads to clinic uncertainty and potentially unnecessary deaths, amputations, lower quality of life, and high NHS costs. By providing definitive evidence, this research aims to resolve these uncertainties and substantially improve care delivery.

Patient/Public Involvement & Engagement (PPI&E) supporting the need for this research: A JLA PSP in 2022-23 found that improving outcomes after PAD intervention/surgery is the highest research-priority for UK patients with vascular diseases (122 responses from people with vascular health issues in the UK). Our PPI&E for this proposal strongly supports this(7, 16). Patients in our PPI&E for RAF strongly supported the notion that they would only accept having open CFA surgery if it was found to be superior to the newer endovascular treatment, which has guided RAF design.

2. RESEARCH QUESTION, OBJECTIVES AND OUTCOME MEASURES

Research question

Is the clinical and cost-effectiveness of open surgery for steno-occlusive common femoral artery (CFA) disease superior to endovascular (minimally invasive) treatment?

Primary objective

Identify whether open surgery for CFA disease is superior to endovascular treatment in terms of death and reinterventions (including major amputation or arterial revascularisation) over a minimum 1-year follow-up, in a time-to-event analysis

Secondary objectives

- Estimate differences in quality-of-life of patients between arms
- Evaluate the cost-effectiveness of each intervention/arm.

- Evaluate the incremental cost-effectiveness ratios in term of clinical improvement and QALYs gained of intervention compared with the control group.

Primary outcome

Composite of death (all-cause) and/or reintervention (major amputation or lower limb revascularisation) over a minimum of one year (time-to-event analysis).

Major amputation is defined as any amputation above the level of the ankle joint in the ipsilateral lower limb.

Revascularisation is defined as any arterial revascularisation in the ipsilateral lower limb.

Secondary outcomes

Secondary outcome measures are:

- Mortality (all cause)
- Hospital admissions (including reason for admission)
- Reinterventions (including nature of reintervention)
- All lower limb amputations (minor and major i.e. below and above ankle joint)
- Quality-of-life using EQ-5D-5L which is validated for PAD and liked/preferred by our PPI&E groups/lay co-applicants
- Healthcare resource-use and costs (participant medical notes)
- Review of medical notes will be used to ensure capture of post-operative appointments in primary/community care. Further, telephone remote follow-up (centrally) will be used to capture missing information regarding amputations, reinterventions, readmissions, and mortality (relating to the primary outcome)

Trial Design and setting

The RAF trial is a two-arm prospective, superiority, multicentre (national), randomised controlled trial (RCT) comparing two modes of treatment which are already routine NHS care, in approximately 24 UK locations (NHS hospitals which already provide care for PAD to patients). Open surgery will be compared to the newer treatment (intervention) using established methodology and pre-specified plans by the CTU team and statisticians. This will address the existing uncertainty whether surgery is superior (clinical and cost-effectiveness) to endovascular treatment. Blinding is impossible in this setting given the completely different nature of the two trial treatments. The target population is individuals ≥18 years with steno-occlusive CFA disease presenting with ischaemic lower limb rest pain and/or tissue loss and/or lifestyle limiting claudication to NHS vascular hospital networks. Patients will be screened and recruited across all secondary care settings in those hospitals (clinic, ward, on-call, remote referrals). Randomisation will take place as soon as the patient provides written informed

consent and baseline assessment is performed. Patients undergoing these treatments in the NHS are usually discussed at multidisciplinary (MDT) team meetings. The patients will be approached for consent once the treating clinicians feel are in equipoise regarding the treatments. Equipoise amongst surgeons/radiologists was confirmed and RAF trial design was planned based on a two-year mixed-methods' study (CONFESS), delivered by our team in order to design RAF(7, 16).

Participating locations

The Coordinating Centre will maintain a list of participating locations. At least 24 UK locations will be involved. Hub and spoke NHS organisations whom have agreed service level agreements may be approached and selected, appropriate contractual agreements will be agreed between Hub (lead trial site) and spoke (other trial site) in accordance with UK (or national governing body equivalent) regulatory guidelines. Participant Identification Centres (PIC) can be utilised in site setup where appropriate. This will be governed by a PIC contractual agreement and will be applicable where one site identifies and refers potentially suitable participants to a recruiting site (governed by mNCA contractual agreement) and where this is the only trial related research activity the PIC will be responsible for. If more than participant identification is required, the appropriate regulatory contractual agreement(s) will be guided by sponsor.

Internal pilot and progression criteria

Key assumptions about recruitment, inclusivity and adherence will be tested in an internal pilot. The RAF trial internal pilot will take place over six months.

Progression criteria, per red-amber-green 'traffic-light' system:

Progression criteria	**Red (<50%)**	**Amber (≥50% <100%)**	**Green (≥100%)**
Number of locations opened	<6	≥6 & <12	≥12
Total number of participants recruited	<24	≥24 & 47	≥48

If the progression criteria are met, we will recruit from at least 24 NHS locations over an additional 18 months (24 months total). Accounting for staggered locations' opening, 2 locations per month from the start of recruitment, 1.136 patients per site per month will be required to reach the required sample size (504 participants). Each of the 24 locations is of similar size with an estimated 40 eligible patients per month(7), of which we expect ~50% to be offered randomisation(7, 16), requiring a consent rate of 6-7% at each site, shown to be feasible in the recent BASIL-3 and our ongoing EVOCC RCTs.

Upon completion of the pilot, we will host a national hybrid PPI&E/expert event inviting participants/PPI&E members/NHS-staff to present pilot findings and qualitative QuinteT Recruitment

Intervention (QRI) results. We will discuss equipoise and recruitment optimisation strategies, which will be implemented in the main recruitment phase.

3. ELIGIBILITY CRITERIA

Main trial criteria

3.1.1 Inclusion criteria

- Age ≥18 years
- CLTI (rest pain and/or tissue loss) or severe life-style limiting claudication (Rutherford Stage ≥3 or Fontaine Stage ≥ IIb)
- Patient deemed suitable for CFA open surgery or endovascular treatment by the treating clinicians (pragmatic design).

For participants with bilateral disease, the leg with more severe symptoms will be designated as trial leg, as per other RCTs(28). Adjunctive inflow/outflow procedures will be permitted, with decisions regarding these left to the discretion of operators (pragmatic design).

3.1.2 Exclusion criteria

- Asymptomatic PAD
- Pregnancy

Communication study (patients) criteria

3.1.3 Inclusion criteria

- Patient willing and able to give consent
- An ability to understand written English or availability of a translator to explain the study documentation
- Identified as potentially eligible to participate in the RAF study
- Involved in discussions about RAF participation with nurses and/or doctors that have provided consent for the HCP Communication Study (where related to audio-recording of research visits)

Communication study (healthcare providers) criteria

3.1.4 Inclusion criteria

- Willing and able to give consent
- Involved in discussions about participation in RAF with patients that have provided consent for the Communication Study (where related to audio-recording of research visits)

PLEASE NOTE: Participants must meet all eligibility criteria to be considered for the RAF trial. There are NO eligibility waivers.

4. TRIAL INTERVENTIONS

Open Surgery

Open surgical revascularisation is an established treatment strategy for patients with symptomatic PAD and CFA disease in the NHS. The exact configuration of the open surgical revascularisation will be left to the clinicians who offer the treatment at each site.

Endovascular Treatment

Endovascular treatment is an established treatment strategy for patients with symptomatic PAD and CFA disease in the NHS. The exact type of procedure offered to each patient will be decided locally, based on clinicians' preferences and patient characteristics. Any type of angioplasty device, stent, vessel preparation strategy, or other adjunct endovascular procedure can be used, at the discretion of the clinicians at each trial site. Inflow and outflow procedures, including open surgical access to arteries or open surgical reconstruction to ensure adequate inflow/outflow will be allowed.
For both open surgery and endovascular treatment, inflow and outflow procedures (e.g. adjunct open surgery when undergoing endovascular treatment or vice versa) will be left to the treating clinicians to decide/offer.

Patients with any type of concomitant aortoiliac, femoropopliteal, or crural disease (in either lower limb) are allowed to take part and can be offered any type of concomitant inflow/outflow revascularisation, regardless of RAF trial arm.

Medical and lifestyle therapy before/after intervention will be left to the discretion of the clinicians and is not dictated by the RAF trial protocol.

Reintervention

A reintervention will be classed as a major reintervention if the procedure meets any of the listed criterion in Table 1.

Table 1. Criterion for definition of major reintervention.

Criterion	Examples
New open arterial surgery on either lower limb or within the aortoiliac vasculature (either side)	Any new bypass graft, interposition graft, or surgical reconstruction involving the treated arterial segment, its inflow, or outflow, performed after the index procedure.
Treatment of any arterial occlusion requiring thrombectomy or thrombolysis on either lower limb or within the aortoiliac vasculature (either side)	Surgical thrombectomy, mechanical thrombectomy, catheter-directed thrombolysis, or hybrid

	thrombectomy/thrombolysis, bypass graft, stent, or stent-graft.
Conversion from allocated endovascular strategy to an alternative strategy (hybrid or open surgery) because of failure of the original endovascular procedure (intra-operatively or post-operatively)	Open bypass or endarterectomy after failed endovascular treatment to salvage the original failed arterial reconstruction.
Unplanned surgery of any description requiring surgical femoral exposure with or without additional endovascular or other arterial reconstruction on either lower limb or within the aortoiliac vasculature (either side)	Surgical groin exploration with thrombectomy plus iliac/SFA/profunda intervention (open or endovascular), patch/graft revision with adjunctive stenting, or hybrid salvage of a failed arterial reconstruction or surgical groin exploration due to infection/bleeding (including pseudoaneurysms) on either side

5. TRIAL PROCEDURES

Participant identification and recruitment for pilot and main RCT

The RAF trial CONSORT diagram (Figure 1) demonstrates the recruitment process in addition to the treatments and follow-up schedule. The recruitment phase will commence as soon as there is ethical, research governance and regulatory approval, local site capacity and capability and only after the Sponsor green light has been issued.

Potentially eligible participants are identified by the clinical care team through surgical waiting lists, clinics (elective or emergency), on calls, through multi-disciplinary team (MDT) meetings or by the patient's direct clinical care team.

Following identification by the clinical team, the patients will be approached by a delegated member of the clinical team. The potential participant will be provided with the Participant Information Sheet (PIS) either in person, by post, by e-mail or electronically via REDCAP (as per their preference). The potential participant will be given as much time as they feel necessary in order to consider taking part.

QuinteT Recruitment Intervention (QRI) (known as Communication Study on patient facing materials)

Recruitment to RAF will be optimised through the inclusion of a QRI, led by experts in qualitative analysis from the University of Bristol. The overarching aim of the QRI is to support recruitment to RAF by identifying and addressing sources of recruitment difficulty and optimising informed consent(32-35). Drawing on lessons learned from working with more than 70 RCTs, the QRI team will apply evidence-based recruitment strategies to create patient-facing materials and prepare training for site initiations(33, 34, 36). Following this preparatory work, the QRI will focus on understanding recruitment issues specific

to RAF. The QRI employs mixed-method approaches to understand recruitment issues rapidly (Phase 1) and then uses this evidence to design and implement tailored strategies to optimise recruitment processes (Phase 2).

The QRI will be integrated from the outset of the trial, through the pilot phase and into the main RCT, with learning shared throughout.

Phase 1: Understanding recruitment

Phase I aims to understand trial recruitment processes and how these may differ across participating locations. A multi-faceted, flexible approach will be employed, including one or more of the following research activities:

a) Semi-structured interviews with: (i) members of the Trial Management Group (TMG) (ii) clinicians or researchers involved in trial recruitment ('recruiters') (n=20-30), and (iii) eligible patients who have been approached to take part in the trial (n=5-15). Interviews with members of the TMG and recruiters will explore their perspectives on the evidence underpinning the trial; perceptions of uncertainty/equipoise; views on the appropriateness of eligibility criteria, and (where relevant) experiences of recruitment successes and challenges. Interviews with patients will explore their views on the presentation of trial information, their understanding of trial processes (e.g. randomisation), and reasons underlying their decisions to accept or decline participation. Patients will be purposefully sampled to achieve maximum variation in age, biological sex, trial centre, and their decision about trial participation (i.e. accept or decline). Interviews will be conducted via telephone or a secure web-conference facility (e.g. MS Teams, Zoom or Google Hangouts) according to participant preference. Some interviews with recruiting staff may be undertaken in person.

b) Analysis of audio-recorded recruitment discussions: Site staff will be provided with encrypted audio recorders and instructions for their use. With participant permission, 'recruitment consultations' between recruiters and potential participants will be audio-recorded. This will be a core component of data collection, as it allows an opportunity to investigate actual (rather than perceived) recruitment behaviours. The audio recordings will be analysed to examine how the trial treatments and trial processes (e.g., randomisation) are explained to patients, how equipoise is conveyed, and how patients respond to the information provided. Audio-recordings of recruiter-patient consultations do not require the presence of the QRI researcher. If recruitment consultations need to be conducted remotely via telephone, equipment will be provided to enable recruiters to securely record these discussions (upon receipt of appropriate consent). Approximately 4-8 centres at a time will be provided with an audio recorder, beginning with pilot locations. Thereafter, recorders may be moved to other locations.

c) Scrutiny of trial screening logs and mapping of recruitment pathways: working in close collaboration with LCTU, a comprehensive screening log will be designed to capture numbers of patients screened, eligible, approached, randomised, and those accepting their randomised allocation. Data from the screening logs and interviews (described above) will be used to construct flowcharts depicting patient pathways for optimum recruitment at RAF locations. Screening data will be compared across centres and considered in relation to estimates specified in the grant application/trial protocol. This process will be regularly repeated to identify bottlenecks in the recruitment pathway and inform further data collection through interviews and/or analysis of consultations.

Phase 2: Development and implementation of recruitment intervention strategies

Working closely with the Chief Investigator (CI) and TMG, action plans will be developed and agreed, consisting of specific strategies designed to improve recruitment and informed consent processes. These plans will be informed by Phase 1 evidence and are likely to include generic and site-specific interventions. Generic interventions may include written guidance documents that provide suggestions on how to explain the trial to patients in a balanced way (i.e. conveying equipoise). Supportive feedback forms a key component of the plan, with its nature and timing tailored to the issues that arise. For example, feedback may be offered to individual centres through amalgamated cross-site feedback or confidentially to individual recruiters. All feedback will be supported with anonymised data extracts from interviews and recruitment consultations.

Although the QRI has been presented as two distinct phases for clarity, the phases will overlap in practice. New avenues of enquiry will arise as data collection progresses and new centres open, and the feedback sessions themselves may highlight new issues that warrant further investigation. Screening logs will be monitored throughout the recruitment period, with particular attention to figures and patterns observed before and after Phase 2 interventions. This will help assess the impact of the QRI and identify whether further investigation or additional interventions are needed. Findings from the QRI will be shared with the CI, TMG, and relevant oversight committees to support ongoing trial management.

QRI consent processes

Healthcare professionals (HCPs) involved in RAF trial recruitment will receive a copy of the 'QRI Healthcare Professional Information Sheet' at Site Initiation Visits (SIVs) from the trial team or via email from the QRI researcher. This will outline the QRI procedures described above (specifically, the audio-recording of recruitment discussions and participation in interviews). Written consent will be obtained from HCPs by research nurses or the QRI researcher. HCPs may choose to participate in one, both, or neither of these QRI elements (interview and/or audio-recording of patient consultations).

Within patient-facing materials, the QRI will be referred to as the Communication Study. Information about this study will be included in the main RAF PIS, rather than provided as a separate document. This approach reduces the number of documents that site staff need to distribute and helps ensure that patients are consistently informed about the Communication Study.

The main RAF PIS describes the audio-recording of recruitment discussions and the option of having a follow-up interview after their consultation. As with HCPs, patients may choose to take part in one, both, or neither element of the Communication Study (interview and/or audio-recorded consultation). A two-step consent process may be used for participation in the Communication Study. This approach recognises that patients often receive the RAF PIS shortly before or during their first consultation, which is the discussion the QRI aims to record. To enable inclusion of these initial discussions, HCPs may obtain verbal consent at the time of the consultation. The HCP will complete a verbal consent form to document this consent, and written consent will then be obtained at a later stage, typically during consent for the main RAF trial or at a subsequent baseline visit. If written consent is not provided, any recordings made under verbal consent will be securely deleted.

QRI data analysis

All qualitative interviews will be audio-recorded using encrypted digital recorders, transcribed verbatim, and edited to ensure anonymity. Audio-recordings will be transcribed either by internal University of Bristol staff or by an external transcription company which has signed the required University of Bristol confidentiality agreements. Transcripts will be pseudonymised. Interview data will be managed using NVivo software (QRS International) and analysed thematically, drawing on constant comparative approaches adopted from Grounded Theory. Audio-recorded recruitment consultations and follow-up discussions will be analysed using a combination of content analysis, thematic analysis, and targeted conversation analysis. There will be a focus on aspects of information provision that are unclear, disrupted, or potentially detrimental to recruitment and/or adherence. Standard strategies to enhance rigour, such as double-coding, triangulating, and identifying ‘negative cases’, will be employed throughout the analysis.

Qualitative Process Evaluation sub-study

Randomised RAF patients from three clinical centres (Leicester, Hull, London – to provide a range of populations) will be invited to consider participating in semi-structured interviews as part of a qualitative process evaluation at two time points: post-treatment, and at approximately 12 months after the initial interview.

We will seek to undertake semi-structured interviews (telephone or video) with approx. 12-18 randomised patients (6-9 allocated to each of the two study arms) to understand information delivery,

experience and acceptability of the interventions, satisfaction with the procedure and wound dressing. The two time points will provide an in-depth understanding of how the RAF treatments and procedures are being delivered and received in practice and over time.

Interviews will be audio-recorded and transcribed verbatim. Transcripts will be coded by a qualitative researcher from the University of Bristol, and analysed thematically. A sub-set of transcripts will be independently coded by the QRI lead (Dr Marcus Jepson), with discussion taking place to refine the coding system and address any discrepancies. Data collection and analysis will be iterative, taking place concurrently and informing further sampling. The exact sample size will depend on when the sample has delivered sufficient information. Qualitative findings will be used to aid understanding of how the results of the RAF trial can be implemented.

The three clinical centres participating in this sub-study will be provided with participant information and consent forms and asked to seek patients' informed consent at the time of the randomisation discussion. Contact details of those consenting will be shared with the University of Bristol researcher who will make contact with the patients and arrange times for their interview.

Co-enrolment

Co-enrolment is permitted in line with the inclusion and exclusion criteria of the RAF protocol as well as the corresponding trial being considered for co-enrolment with. Approval of co-enrolment to each study will be discussed and confirmed by C.I/P.I's of each study involved.

Consent

The Principal Investigator (PI) retains overall responsibility for the conduct of research at their site, this includes the obtaining of informed consent of participants at their site. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If delegation of consent is acceptable then details should be recorded in the Delegation of Authority Log.

Telephone, electronic or written informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial and are out-with standard routine care at the participating site (including the collection of identifiable participant data).

The right of a participant to refuse participation without giving reasons must be respected.

The option of electronic consent and telephone consent has been developed as an alternative to face-to-face methods. This model has been developed where it is not in the best interests of the patient to bring them back to hospital for research purposes, the patient does not want to or is unable to come into

the hospital. It is anticipated that the majority of potential participants will wish to have a face-to-face visit. The electronic consent process will mirror the content of the paper documents, including an electronic PIS, and will be supported by the REDCap platform provided by LCTU (University of Leicester). This will be supported by a Video/Telephone Consent Form to be completed by the researcher or delegated site person performing consent, confirming that the participant has understood the information and consent process. The electronic consent system will only be accessible by appropriate personnel active on the study who will only be able to view consents for their site. The system will notify of any errors in a submitted consent form which can be rectified by the participant, as well as produce a PDF for the participant, research and medical records. Where appropriate, electronic consent will be supported either over the telephone or by video conference between the participant and the clinician/researcher. The remote consent process will also mirror the content of the paper documents. The Video/Telephone Consent Form will be completed by the researcher or delegated site person receiving informed consent, confirming that the participant has understood the information and has capacity to consent. The remote consent process will only be performed by delegated personnel at each site.

The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing their further treatment and must be provided with a contact point where they may obtain further information about the trial. Data collected up to the point of withdrawal will be retained and used. Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner.

A PIS will be provided to facilitate this process. The PI or their delegate will ensure that they adequately explain to the participant the aim, trial intervention, anticipated benefits and potential risks of taking part in the trial.

The participant will be given time to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial. They will be given sufficient time to make their decision. Informed Consent will then be obtained through the available methods by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The original signed ICF will be retained at the trial site within the Investigator Site File (ISF). A copy of the signed Informed Consent will be given to participants and a copy retained in the participant medical notes. The outcome of the conversation, i.e., provided informed consent and have been randomised to the trial, will be recorded in the trial screening log. This will be necessary for assessing recruitment feasibility.

The ICF contains optional items relating to consent for the use of data held by central NHS bodies (see below) and the retention of contact information to enable future contact for consideration of participation in follow-up studies. Participants may provide or decline consent for any of these items independently.

Should new and important information, particularly relating to safety, become available during the trial, participants may be required to re-consent to the trial via an updated PIS and ICF.

Once the participant is randomised, their Participant ID Number will be populated and recorded on the ICF and all Case Report Forms (CRFs) going forward.

Details of the informed consent discussions should be recorded in the participant's medical notes in accordance with Good Clinical Practice (GCP). This should include date of discussion, the name of the trial, outcome of the discussion, version number of the PIS given, version number of ICF signed and date consent received.

5.4.1 Optional consent for linkage of NHS routine clinical datasets

RAF includes an optional consent to allow linkage to patient data available in NHS routine clinical datasets, such as the Hospital Episode Statistics (HES) and mortality data from the Office of National Statistics (ONS) through The Health and Social Care Information Centre and other central UK NHS bodies. This consent will also allow access to other new central UK NHS databases that may appear in the future so that relevant long-term outcomes and health resource usage data can be recorded to extend the follow-up of participants without needing to contact them further. This is important as it will link 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. The linkage and analysis of routine clinical datasets will be optional and dependant on securing future funding, if obtained the linkage of data will be performed within 6 years of the end of the trial (estimated November 2035).

Randomisation

After the consent form has been signed, and the baseline assessment performed, the participant will be randomised to receive one of the two arms; open surgery or endovascular treatment. Participants will be randomised via the 24-hour, web-based service, Sealed Envelope.

Random allocations will have a 1:1 ratio, will be minimised by the following variables: age above 65 years, sex, site, and presence of tissue loss (yes/no). Randomisation forms should be completed alongside online randomisation. After a participant is randomised, the user is presented with the allocated treatment group and the unique Participant ID Number is generated. An automated notification email will be sent to the person conducting the randomisation, copying in LCTU via the RAF trial mailbox. The Participant ID number must be entered onto the participant signed ICF and all CRFs from this point forward and will link the participant details to the trial data. Any errors in the randomisation process should be reported to LCTU as soon as reasonably possible after being identified.

Trial assessments

5.6.1 Baseline Visit (Day 0)

Once informed consent has been obtained, the baseline visit can take place. This visit can be performed remotely. During this visit, participants will complete participant questionnaires, undergo a review of their medical history (including previous surgical interventions), cardiovascular risk factors, PAD anatomy, eGFR, HbA1C, LDL and cholesterol levels (where performed clinically). If a female is thought to be pregnant, a urine pregnancy test will be performed as part of usual care ahead of surgery and not as part of the trial procedures. Where a female participant is found to be pregnant, participation will be excluded as per exclusion criteria. Baseline visit biochemistry assessments/bloods to be taken in line with clinical pathway and matching the research schedule as closely as possible. It is understood that because these bloods are clinical, that there may be occasions where these bloods are taken ahead of the research baseline timepoint. The blood sample used for the study should be the closest available to baseline visit. Please refer to Table 2 for further details about the Baseline visit, follow up visits and assessments. To ensure consistency, the CRFs we will use will be based on the CRFs we have developed for the EVOCC trial (already in use across the NHS, ISRCTN14591444), based on the successful BASIL trials (similar disease area, ISRCTN27728689). The anatomy of the CFA bifurcation will be recorded, alongside information regarding the presence of calcification. All anatomical details will be collected based on cross-sectional imaging (duplex and computed tomography), which is routinely used in the NHS for people with CFA disease.

5.6.2 Review of Clinical Events – Day of Discharge, Day 30 and Months 6, 12, annually thereafter until month 36**.

A review of clinical events, particularly those related to the cardiovascular system, will be undertaken at the above trial visits including reintervention and other surgical procedures, admission to hospital, death, myocardial infarction, stroke and new heart failure leading to admission. Leg Ulcers: Size, episode of infection, course of antibiotics, and service utilisation, including primary/community and secondary care (use of patient diaries and review of medical notes at each appointment). Follow up visits will coincide with routine appointments where possible.

For visits at day 30, months 12, 24 and 36, data collection may be performed either by telephoning the participant or retrieving the information from their medical notes. For visit month 6, the participant is preferred to attend clinic in person. However, if the participant cannot attend in person, as this is a pragmatic study this information can instead be collected remotely via telephone or through acquiring information through participant medical records. **All participants will have a final follow up in the last month of the study follow-up period (with an additional review of clinical events taking place if their 12, 24 or 36-month follow-up does not fall in this period).

All assessments which can be completed remotely (via telephone) may take place remotely, with supplemental information collected from patients' records (physical and electronic notes).

5.6.3 EuroQOL 5D 5L Questionnaire – Baseline and Months 6, 12, 24 and 36.

EuroQOL- 5D (EQ-5D-5L) is a standardised assessment of health status to provide a simple, generic measure of health for clinical evaluation (10, 11). It consists of 2 pages covering 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and the participant is asked to choose an accompanying statement which best describes how much ease or difficulty they have in each of these dimensions (1 is scored as no problems/pain/anxiety/depression, 5 is scored as unable to/extreme anxiety/depression). The questionnaire also asks the participant to indicate on a scale of 1-100 1 = the worst health you can imagine, 100 = the best health you can imagine how their health is on that day.

5.6.4 Table 1. Schedule of Assessments

Visit	Baseline	Trial intervention	Day of Discharge	30 Days[1]	6 months[1]	12 months[1]	24 months[1 2]	36 months / Final[1 3]
Visit window (days) (± number of days this visit can take place ahead or after its due date)	-	-	-	± 7 days	± 30days	± 30 days	± 30 days	± 30 days
Day	0			30	180	365	730	1095
Eligibility check	x							
Obtain informed consent	x							
Randomisation (allocation of treatment)	x							
Demographics	x							
Medical history including cardiovascular risk factors	x				x			
Structured assessment	x			x	x	x		
Details of anatomy (arteries)	x							
Concomitant medications (statins and antithrombotics)	x		x	x	x	x	x	x
Review of clinical events			x	x	x	x	x	x[3]
Days lost from regular activities					x	x	x	x
Estimated Glomerular Filtration Rate (eGFR)	x				x			
Ankle Brachial Pressure Index (ABPI) (if available)	x				x	x	x	x
EQ-5D-5L questionnaire	x				x	x	x	x
Details of intervention (type of surgery or endovascular treatment configuration and devices)		x						
Admission to hospital or visit to primary care					x	x	x	x
Assessment of Adverse Events		x	x	x	x	x	x	x[3]

[1] The follow up trial visits may be undertaken remotely either via telephone or through acquiring information through participant medical records. For 6 months, in the first instance please try to bring the patient in for a face-to-face appointment. If this is not possible then this follow-up visit may also be undertaken remotely via telephone or through acquiring information through participant medical records.

[2] Participants will not always be expected to complete these follow up timepoints. For example – those randomised during the main trial phase may only reach the minimum 12 month follow-up timepoint before follow-up period ends.

[3] Participants still in active follow-up i.e has not withdrawn will have their clinical and adverse events data assessed in the final month of trial follow up perio

Follow-up

The minimum follow-up period for participants is 12 months after the time of randomisation. All follow up data will be collected from the date of randomisation. Participants that are recruited after the first year of recruitment may not complete all follow up assessments, for those participants in active follow up during the final month of the trial follow up period will have a 'Final' assessment which will match the activities performed at month 36 in Table 2.

Withdrawal of consent

Participants may withdraw their consent to participate further in the trial at any time, without prejudice for future care and they do not need to provide a reason why. However, if they are willing to provide a reason, it should be recorded on the relevant CRF. Participants will be asked to what extent they wish to withdraw their consent from the trial.

There are varying levels of withdrawal of consent available:

- Withdrawal from active follow-up (questionnaire completion and remote contact)
- Withdrawal from patient record data collection
- Withdrawal from collection of trial related data from NHS England or equivalent routinely collected dataset(s)
- Complete withdrawal (no further data collection will be carried out)

Withdrawal status will be documented on trial CRF and medical records. It is important to note that the data already collected prior to the point of withdrawal can still be analysed and included in the trial dataset.

Assessment and management of risk

All clinical trials can be considered to involve an element of risk and in accordance to LCTU operating procedures, RAF has been assessed for any risks relating uniquely to this trial. Both surgical interventions are routinely used to treat this patient population therefore it has been concluded that the trial carries no higher risk than that of standard medical care.

Pandemic adaptations

In the event of a pandemic, or local/national lockdowns which may affect RAF participants, locations should check ahead of scheduled trial visits that participants are able to attend in line with local Trust policy. Participants should follow government guidelines regarding testing and self-isolation and MUST inform the Research Nurse/trial team if they are experiencing symptoms, have tested positive and/or must self-isolate. All scheduled trial visits can be rescheduled and certain data/assessments can be collected/performed remotely e.g. over the telephone or through medical notes. Participant safety data will be collected during the course of the trial as usual. In some cases, the data collection may be limited to primary endpoints, i.e., deaths and amputation data.

End of trial

The end of the trial will occur when the last participant has completed their final follow up/final assessment and the trial statistician has confirmed data lock for analysis.

6. SAFETY REPORTING

Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence (including clinically significant abnormal laboratory findings), in a study participant.
Adverse Reaction (AR)	Any untoward medical occurrence (including clinically significant abnormal laboratory finding), in a study participant that is **related (possibly, probably, definitely)** to a participant's involvement in the study. The assessment of relatedness **must be** undertaken by a delegated medically qualified professional.
Serious Adverse Event (SAE)	A SAE is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. **NOTE:** The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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.
Serious Adverse Reaction (SAR)	Any untoward medical occurrence that meets the above referenced serious criteria and, is believed to be **related (possibly, probably, definitely**) to a participant's involvement in the study.
Suspected Unexpected Serious Adverse Reaction	Any untoward medical occurrence that meets the above referenced serious criteria and, is believed to be related to the study intervention but is not listed within the expected events section below.

(SUSAR)	
Expected SERIOUS Adverse Events	The following events are considered as expected SAEs. For the purposes of this trial such events do **NOT** require reporting to the RAF central team or Sponsor. These events should continue to be recorded in the medical records according to local practice and on the routine follow-up CRFs.

Acute kidney injury
Arterial dissection
Arterial pseudoaneurysm formation
Atrial fibrillation (new)
Bleeding
Chest infection
Diabetes (new diagnosis)
Diabetic foot ulcer (new)
Diabetic ketoacidosis
Endovascular reintervention (reported separately using the relevant form)
Failure of endovascular closure device
Fall
Fasciotomy
Haematoma (at site of surgery or percutaneous puncture)
Heart failure (non-fatal)
Hernia
Hypertension (new diagnosis)
Intermittent claudication (new diagnosis)
Lower limb compartment syndrome
Lower limb oedema
Minor amputation (below the ankle joint)
Myocardial infarction
Need for open surgical access to an artery during the index endovascular procedure
Peripheral embolization
Prescription of antibiotics for lower limb tissue loss (ulcer/gangrene)
Re-admission to hospital within 30 days of randomisation
Requirement for catheterisation (urinary catheter)
Stent or graft occlusion
Stroke

	Surgical reintervention (will have to be reported separately using the relevant form)
	Transient renal replacement therapy
	Urinary retention
	Urine infection
	Use of additional stent or additional endovascular device
	Venous thrombosis (deep and/or superficial)
	Viral infection
	Wound infection

Reporting procedures for All Serious Adverse Events

6.1.1 Reporting procedures for Adverse Events

AEs will not be reported as part of this trial. AEs should be recorded in the medical records according to local practice.

6.1.2 Reporting Procedures for Serious Adverse Events

All Serious Adverse Events/Reactions occurring from the time of randomisation until follow-up completion will be recorded on the SAE log and in the participant medical notes.

SAE/SARs that are assessed by the PI or a delegated medic as **related** (possibly, probably or definitely) to the study procedures, conduct or management, and are listed in section 6.1 as an expected event (i.e., **related and expected**) do not require onward reporting to Sponsor **unless** the severity or frequency is greater than anticipated.

SAE/SARs that are assessed by the PI or delegated medic as **related** (possibly, probably or definitely) to the study procedures, conduct or management and are not listed as expected within section 6.1 (i.e., **related and unexpected** events) will be reported to rgosponsor@le.ac.uk and trial mailbox (RAFTrial@leicester.ac.uk) immediately and within 24 hours of becoming aware of the event.

Any event considered **related and unexpected** to the study will be reported to the relevant Research Ethics Committee concerned. The Research Governance Office will facilitate this process. Fatal or life-threatening events must be reported within 7 days, all other events within 15 days.

For **unrelated** events, no onward reporting to the Research Governance Office is required.

The relatedness of the event to the study will be assessed and signed off by a medically qualified individual listed on the Delegation of Authority and Signature Log.

The CI will inform all investigators concerned of relevant information about related but unexpected events that could adversely affect the safety of participants.

Events will be followed-up until resolution or the event is resolved or considered stable.

The SAE/SAR will be reported using the appropriate forms and according to the Sponsor SOP for reporting serious adverse events (S-1009). Additional information will be provided if requested to the Sponsor and main Research Ethics Committee (REC).

Copies of all documentation and correspondence relating to SAEs will be stored in the TMF and / or ISF (or electronic equivalent) as appropriate.

Please note: No serious adverse reactions (SARs) are anticipated as a unique consequence of participation in the RAF trial.

The trends in serious adverse events will be independently reviewed in addition to the trial safety monitoring and sponsor pharmacovigilance procedures. The decision regarding the frequency of review of individual and cumulative SAEs is to be based on the trial design, risk assessment and advice from the Sponsor / TSC / DMC and will include:

- Clinical review of a line listing of all life threatening or SAEs resulting in death within 1 week of their occurrence performed by the local P.I and/or C.I.
- Clinical review of a line listing of all other SAEs on a monthly basis performed by local P.I and/or C.I.
- Cumulative review of all safety information by the DMC on an annual basis or more often if required

6.1.3 Reporting Urgent Safety Measures

The Sponsor, the CI or the local PI at a research site may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety. If any urgent safety measures are taken, the CI/Sponsor shall be notified immediately, and in any event no later than 7 days from the date the measures are taken. Written notice must be provided to the Sponsor and the relevant REC of:

- The measures taken
- Reason these measures were taken
- The circumstances giving rise to those measures

- Plan for further actions.

7. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision for the trial on behalf of the Sponsor and Funder and to ensure that the trial is conducted to the rigorous standards set out in the Department of Health's UK Policy Framework for Health and Social Care Research and the Guidelines for Good Clinical Practice. The remit of the TSC is to provide advice, focus on trial progress and adherence to study protocol, patient rights, safety and well-being as well as considering new information and its relevance to the research question. The TSC will also ensure that all ethical and regulatory approvals are obtained and agree proposals for substantial protocol modifications.

The TSC will be composed of an Independent Chair, and at least two Independent Clinicians or others with expertise relevant to the trial, along with a lay/PPI&E representative. NIHR and Sponsor Representatives may be invited to attend TSC meetings as observers. The TSC will adopt a charter to define its terms of reference and operations. The TSC will have a majority independent representation, including the Chair, meet on an annual basis, or as required, and send reports and make recommendations/decisions to the TMG/Sponsor/Funder. Members will be required to sign a 'conflict of interests declaration form'.

Data Monitoring Committee (DMC)

The role of the DMC is to monitor outcome data, safety data and other trial data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue. The safety, rights and well-being of the trial participants are of paramount importance, in addition to the validity of the trial data. The DMC will also consider data emerging from other related trials, provided by the Sponsor or Funder.
The DMC will consist of an Independent Chair, an Independent Clinician and an Independent Statistician. The DMC will adopt a charter, based on the principle of Damocles, to define its terms of reference and operation. The DMC will meet annually, or as required, as specified in the charter.

Trial Management group

The TMG will be responsible for the day-to-day management of the trial to ensure the delivery through delegation of tasks to individuals or a group, for all aspects of the trial, including recruitment rate, budget management, safety reporting, protocol compliance and ensuring appropriate action is taken to safeguard trial participants and quality of the trial. The TMG members will meet regularly to ensure all

practical details of the trial are progressing and working well or to produce and implement mitigating strategies when necessary to maintain or improve study performance.

8. STATISTICS AND DATA ANALYSIS

Sample size calculation

Calculations and event rates are based on our published cohort study, reviews, and contemporary NHS event-rates in an analysis using routinely collected data (6, 8, 9, 15, 17). Based on these, the proportion of patients having endovascular treatment who die and/or undergo reintervention (including amputation) at 21 months is 59.1%. Assuming a 2-year recruitment phase with a median follow-up, due to staggered opening of locations, of 21 months (minimum one year, maximum three years) and a conservative 5% loss to follow-up, a total of 504 people will have to be recruited to provide 90% power (2 sided, a=0.05) to detect a hazard ratio of 0.667 (absolute risk reduction at 21 months of 14.2%: 59.1% events in endovascular vs 44.9% in open surgery). Our PPI&E groups/co-applicants specifically fed back that they would like open surgery to be better by a third with regards to the primary for them to accept it as standard of care; NHS staff agreed(6, 9). The sample size was calculated using the 'artsurv' command in STATA, powering for the statistical test of unweighted logrank test (local).

LCTU will lead data management/maintenance/monitoring.

Statistical analysis plan

The LCTU statistician will be responsible for planning, monitoring and carrying out data analyses throughout the study, supervised by the Senior LCTU statistician. Statistical analysis will be undertaken according to a pre-specified statistical analysis plan written prior to database lock and reported following CONSORT statements (37).

Summary of baseline data

Data collected at baseline will be presented as means and standard deviations or medians and ranges if not normally distributed for all continuous variables and/or number and percentage for categorical variables, overall and by randomised group. No formal statistical hypothesis tests will be used to assess normality assumptions or make comparisons of differences between groups.

Primary outcome analysis

The primary analysis will be performed on an intention-to-treat (ITT) basis with the primary estimate defined fully within the statistical analysis plan (SAP). The primary analysis of the primary outcome will compare the randomised groups using a Cox proportional hazards model (or appropriate alternative where assumptions are not met) in the ITT population, adjusting for minimisation factors. The hazard

ratio and 95% confidence intervals will be presented along with Kaplan Meier curves and superiority of Open surgery over endovascular treatment will be declared with a two-sided p-value <0.05.
Participants not experiencing a primary outcome event will have their time to event censored at last follow-up date. Participants withdrawing consent or that are lost to follow-up prior to reaching primary outcome will have their time to event at last contact date.
Secondary analyses of the primary outcome will explore a per-protocol population excluding major protocol deviators.

Secondary outcome analysis

Secondary outcomes will be analysed on a complete case population and reported similarly to the primary outcome using appropriate methodology with point estimates and confidence intervals to compare randomised groups; time to event analysis will be performed using Cox proportional hazard model(s), binary secondary outcomes will be analysed using logistic regression, continuous outcomes using linear regression or where not normally distributed using appropriate nonparametric methods.

8.1.1 Subgroup analyses

An un-powered exploratory subgroup analyses of the primary outcome will be performed to assess associations between types of endovascular treatment (e.g. use of stents and use vs. no use of vessel preparation).

8.1.2 Interim analysis and criteria for the premature termination of the trial

There will be no formal interim statistical assessment for early termination of the trial for safety or efficacy. There are no formal stopping rules associated with DMC reporting (see section 7.2).
Recruitment data collected during the 6-month internal pilot will be presented descriptively in terms of the progression criteria to the oversight committees and funding body and used to assess if it is feasible to continue to recruit to the main study.

8.1.3 Adverse Events Reporting

Unexpected SAEs outside of the list provided in section 6.1, will be reported descriptively in the safety population i.e., participants undergoing trial treatment, presented in groups according to treatment received not as randomised. The number of unexpected SAE's and the number of participants experiencing unexpected SAE's will be presented categorised by common SAE terms. Unexpected SAE's will be presented as line listings and grouped by severity.

8.1.4 Procedure(s) to account for missing or spurious data

Missing data is expected to be minimal given the type and mode of data collected and use of final assessment as described in Table 2. The primary outcome and other time-to-event outcomes should not encounter missing data due the nature of the data. Furthermore, any losses to follow-up should be

minimised by the intended methods to capture long term follow-up through routine data capture where funding is obtained.

8.1.5 Economic evaluation

The economic evaluation will be conducted from the NHS and personal social services perspective, as per National Institute of Care Excellence (NICE) recommendations (21), led by Health Economists with considerable experience in NIHR HTA funded vascular research. Use of hospital and community services will be recorded over the trial time horizon using the trial CRFs.

Quality-of-life will be assessed using the EQ-5D-5L, converted to health utility scores using the UK value set recommended by NICE. QALY will be calculated using area under the curve approached.

Unit costs will be based on manufacturers' prices and national databases such as BHF, National Reference Cost and Personal Social Service Resource Use Unit Cost (PSSRU). Days lost from work and activities will be recorded and used in a secondary analysis.
The differences in costs and QALY between groups will be estimated using bootstrap methods. The extent and pattern of missing data will be assessed and appropriate methods employed, for example, multiple imputation.
Bootstrapping methods will be employed to estimate the incremental cost – effectiveness ratio.

If the trial finds a clinically meaningful difference in outcomes or costs over the study time horizon, a decision model will be developed to extrapolating the cost effectiveness beyond the trial period. s. A state-transition decision model (Markov model) will estimate costs and QALYs over the lifetime of the cohort. The recommended discount rate of 3.5% per year will be used. Parametric survival curves will be used to estimate rates of death, cardiovascular disease and amputation events. Long term rates of events will be estimated based on the results from the trial and supplemented from literature. Outcomes or states of the model will be decided based on consultation with experts and review of previous economic evaluations in PAD. Sensitivity analyses will be conducted by varying key variables with high uncertainty. The model will be constructed, analysed, and reported, according to CHEERS guidelines (22).

9. DATA MANAGEMENT

Data flow diagram

Please refer to **Appendix 2** for the trial Data Flow Diagram.

Data handling and record keeping

All data handling and record keeping will be kept in adherence to UoL's and NHS Organisation(s) policies and SOPs.

9.1.1 National Data Opt-out

The national data opt-out was introduced on 25th May 2018 enabling patients to opt out from the use of their data for research or planning purposes in line with the recommendations of the National Data Guardian in their review of Data Security, Consent and Opt-outs. As from 1st August 2022, all NHS Trusts are now compliant with the national data opt-out operational policy guidance document; for further information please visit https://digital.nhs.uk/services/national-data-opt-out/operational-policy-guidance-document.

9.1.2 Data Collection Tools and Source Document Identification

LCTU will be responsible for Data Management for the trial and will undertake data validation, database queries/reviews in line with their SOPs.

ICH E6 R3 defines source records as "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)."

The basic concept of source data is that it permits not only reporting and analysis but also verification at various steps in the process for the purposes of confirmation, quality control (QC), audit or inspection. A number of attributes are considered of universal importance to source data and the records that hold those data. These include that the data and records are:

- Accurate
- Legible
- Contemporaneous
- Original
- Attributable
- Complete
- Consistent
- Enduring
- Available when needed

Source Data is defined as the first place where data is recorded, this will include:

- Medical Records
- Paper CRFs
- Participant reported outcome questionnaires
- Laboratory reports

- Printouts from equipment
- Field notes
- Audio-recordings

Data collection tools will comprise of:

- REDCAP Database (transcribed from paper CRFs have been used) and direct source data entry
- Participant reported outcome questionnaires

Audio recordings of clinical consultations taken as part of the research undertaken by the QRI team will be captured on encrypted audio-recording devices, which the QRI team will provide to locations (with instructions). Recordings will be periodically transferred securely to the University of Bristol research team using a Trust-approved secure data transfer system. The recordings will be transcribed and de-identified by the University of Bristol or a University of Bristol approved contracted transcribing service that has signed the University of Bristol's Confidentiality Agreements. Transcripts and recordings will be held up to 6 years from the end of the trial on a secure database at the University of Bristol which will only be accessed by authorised members of staff in the QRI team. Any paper copies of the transcripts will be stored securely in a locked filing cabinet at the University of Bristol and destroyed 6 years after the end of the trial.

Digital recordings and transcripts taken as part of the process evaluation will be managed in the same way as those undertaken for the Communication Study.

9.1.3 Data Handling and Record Keeping

Records of trial participant data will be made on trial specific electronic CRFs. Trained member(s) of the site research team will enter data directly into a commercially available web based electronic data capture (EDC) system provided by the LCTU, called REDCap. If the EDC is unavailable at any point during the trial, paper CRF's will be used and later transcribed into the EDC. On-entry validation checks will be applied where required and data entered will be checked for completeness, accuracy and timeliness by the site research team/trial manager, with queries managed using the data clarification functionality within the EDC system.

A sticker will be placed on the cover of the notes (or inside cover) detailing the trial title, contact details of the PI and the fact that the notes should not be destroyed for 6 years from the end of the trial. Where electronic or hybrid medical notes are used it is expected that electronic flags, scanned documents and annotation are included in the medical notes.

All data collected will be stored in securely locked filing cabinets and in password-protected databases. After the trial is complete, all data of participants will be securely archived and will be destroyed after six years, sponsor approval to destroy will be obtained prior to destruction. Anonymised data will be stored in secure specialist data centre/repository relevant to this subject area and available for future research, should the participant consent to data storage.

According to the ICH guidelines for Good Clinical Practice, the trial management team may check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. LCTU will develop a monitoring plan for source data verification (SDV) checks. The ICF will include a statement by which the participant allows the Sponsor and LCTU's duly authorised personnel, the Ethics Committee, and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (e.g., participant's medical file, appointment books, original laboratory records, etc.) in the event that this trial is monitored. These personnel must maintain the confidentiality of all personal identity and/or personal medical information (according to confidentiality and personal data protection rules).

A Data Management Plan (DMP) will be created with specific details on data handling and record keeping.

Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution, LCTU, and the regulatory authorities to permit trial-related monitoring, audits and inspections in line with participant consent.

All trial documentation will be retained in a secure location during the conduct of the trial. Personal identifiable data will be retained by each participating site for a maximum of 6 years following the end of the trial, after which it will be destroyed, unless participants have expressed an interest in being invited to the results dissemination event and/or receiving a copy of the trial newsletter. In these circumstances, personal identifiable details such as names and contact details will be retained on a password protected database until required, and then destroyed. The UoL will also hold pseudonymised data for potential future data linkage in the EDC, to assess future outcomes (amputation or mortality) for up to 6 years.

All electronic data will be stored on secure network systems, to which only the relevant trial personnel will have access.

For the purposes of this trial, the UoL will act as the Data Controller for data held on the EDC. The University of Bristol will act as the Data Controller for data generated as part of the qualitative analysis. The UoL will act as the data controller for the data held on the NVivo qualitative data indexing software as part of the process evaluation. NVivo transcription data is encrypted both in transit and at rest and only the account owner has access to and control over the data.

Archiving

Personal identifiable data generated by the trial will be retained for 6 years following the notification of the end of the trial before being destroyed in a confidential manner. Sponsor authorisation will be requested prior to destruction.

Following completion of the trial data analysis, data and essential trial records, including the final trial report, will be archived in a secure location for at least 6 years after the completion of the trial, in accordance with LCTU SOPs. No trial-related records, including hospital medical notes, will be destroyed unless or until the Sponsor gives authorisation to do so.

Details of the UoL archiving Standard Operating Procedure can be found at: http://www2.le.ac.uk/offices/ias.

10. MONITORING, AUDIT & INSPECTION

The UoL, as Sponsor, operates a risk-based monitoring and audit programme, to which this trial will be subject. The LCTU operates a risk-based Quality Management System (QMS), which will apply to this trial with quality checks and quality assurance audits performed as required.

As part of the quality management process, the trial will be subject to a risk assessment which will be developed by the LCTU in association with the Sponsor. The trial manager will undertake quality checks and assurance audits to ensure compliance with protocol, ICH GCP, and regulatory requirements.
All source data, trial documents, and participant notes will be made available for monitoring, audits and inspections by the Sponsor (or their delegate), NHS Host Organisation and the regulatory authorities, should a monitoring visit be undertaken.

11. ETHICAL AND REGULATORY CONSIDERATIONS

Research Ethics Committee (REC) review and reports

Once the initial Sponsor review process is complete and a Sponsor reference number has been allocated and all requested documentation has been received and checked, authorisation from the UoL's Research Governance Office (RGO) will be issued to book further reviews of the proposed research. The NHS Research Ethics Committee and the Health Research Authority will then review the proposal. Agreement in principle is subject to the research receiving all relevant regulatory permissions. Submission for regulatory approvals will be submitted via Integrated Research Application System (IRAS). The Chief Investigator will ensure that all regulatory approvals, confirmation of capacity and capability from NHS locations and Sponsor greenlight are in place before participants are approached.

For any required modifications to the trial, the Chief Investigator, in agreement with the Sponsor will submit information to the appropriate body in order for them to issue approval for the modification. Modifications will be implemented upon receiving Sponsor Green Light. The Research Governance Office's Standard operational procedures will be followed for the duration of the trial. Modification will be submitted to the Sponsor in the first instance for review and approval.

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

An (e)trial master file (TMF) will be maintained for the duration of the trial and will be stored for 6 years after the trial has ended, if this is not possible a physical TMF will be used as an interim measure.

Peer review

The trial design and protocol have undergone a high-quality peer-review both internally (UoL) and externally by two lay individuals and two experts, as well as the NIHR HTA panel which funded this research.

Public and Patient Involvement & Engagement (PPI&E)

11.1.1 PPI&E to support trial design

The RAF trial is based on formal qualitative work undertaken over the course of two years in our published CONFESS study. All components of the RAF trial design are based on the views/opinions of lay people with lived experience and their families/carers. We convened two PPI&E groups (51 participants) specifically for RAF (one in Leicester and one online, to allow participants across the UK to take part), as part of the Vascular Society Peripheral Arterial Disease Specialist Interest Group (PAD SIG) national lay-involvement activities, following a national PPI&E survey and interviews of NHS staff

involved in treating PAD/CFA disease (CONFESS study). We also convened a third online workshop with our lay co-applicants and four patients with PAD/CFA disease, to finalise our replies to the Committee and this Stage 2 application.

In the PPI&E working groups and surveys, we explored RAF trial inclusion criteria, best outcomes to use, follow-up duration, acceptability of trial assessments, and clinically important differences. To do this, we presented our literature reviews to patients taking part, using infographics and simple slides and presented them with different scenarios regarding outcomes, and clinically important differences. Patients supported inclusion of both people with claudication and CLTI (chronic limb threatening ischaemia – the more advanced manifestation of PAD) in RAF with a primary outcome measure that should include mortality, amputations, and major reinterventions i.e. the things feared the most (equal weight) by them. They asked us to assess quality of life and preferred the EQ-5D-5L tool over other questionnaires. They unanimously supported a superiority design, only accepting the more invasive open surgery if it was better at saving legs, lives, and associated with less reinterventions over a minimum 1-year, by at least a third. We also qualitatively explored barriers and facilitators for RCT-delivery, which shaped our design, as presented in our CONFESS study publications. From the PPI&E focus groups convened for RAF, we recruited our formal lay co-applicants, who both have had CFA endovascular treatment and then arterial surgery (reintervention); one suffered with claudication and one with CLTI when they had CFA disease diagnosed. They prepared the Plain English Summary, which was approved by the independent PAD Leicester PPI group.

The PPI&E groups convened for RAF included participants with various types of symptomatic PAD (e.g. CLTI or claudication), and diverse characteristics, including people from South Asian communities, Afro-Caribbean communities, urban areas, rural areas, smokers (current and ex-smokers), and people who previously had amputations due to PAD. We followed INVOLVE guidance to complete our PPI&E activities in terms of developing RAF and all participants were supported by our experienced PPI&E/lay co-ordinator (Miss Black) based in the NIHR Leicester Biomedical Research Centre, working closely with the CI on several NIHR PAD studies. We also involved families and carers, to ensure PPI&E views represent those who provide care for eligible participants, as people with PAD are often older and frail. Finally, to ensure applicability of our PPI&E input across the nation, we purposively interviewed four lay individuals from Hull, Brighton (coastal communities), Manchester, and Glasgow) prior to the Stage 2 application, as per latest NIHR INVOLVE and other PPI/EDI guidance. They also approved the PES, and final protocol/proposal.

11.1.2 PPI&E during trial delivery

The RAF trial includes lay co-applicants as core team members, who have lived disease experience (both CLTI and claudication) and have been involved in preparing the research protocol and delivery

plan. Separate to the co-applicants, an independent RAF-specific support PPI&E advisory group (SPAG) will meet regularly (at least six monthly) to advise all co-applicants/team-members, and all trial committees. The membership of the SPAG has been finalised via our national PPI&E work prior to RAF and includes people with PAD across the nation, including coastal communities, South Asians, Afro-Caribbeans, people with diabetes and prior research-advisory experience (from the Leicester Diabetes Centre ((LDC)), people who had amputations due to PAD, carers, and families of individuals who had PAD surgery before.

The lay co-applicants, supported by the SPAG, will take part in trial meetings, advise the TMG/TSC, and prepare study documents. They will also prepare a six monthly (or more regular) study update in lay format, shared via existing PAD Facebook and X profiles and disseminated via professional societies (surgery, radiology, primary care, anaesthetics). Final results will be summarised by our PPI&E supporters and shared with traditional media outlets, on a trial-specific website and social media as well as NHS professional societies. GRIPP 2 reporting checklists will be used when/where necessary to support PPI&E reports during the trial and upon completion.

Our team already has extensive experience in involving PPI&E participants in PAD-related trials (e.g. EVOCC trial, BASIL trials) and we will use our networks as well as experience using INVOLVE guidance to ensure RAF meets the expectations of patients during delivery and upon completion.
We have costed for an experienced PPI&E co-ordinator who will be based in Leicester (with the CI and CTU). We will use state-of-the art NIHR Leicester BRC meeting rooms and software to host PPI&E activities both face-to-face and in hybrid format, allowing participation of collaborators nationally. The LDC and Centre for Ethnic Health Research (CEHR) will support our PPI&E plans, offering advice, infrastructure for meetings, document preparation, and involvement of hard-to-reach communities (including those who cannot speak English). Translation services for our PPI&E groups are available in our BRC and CEHR. The BRC and CEHR already work with the CI on multiple PAD-related NIHR-funded projects.

With regards to documents and support of people with frailty or other barriers, our PPI&E co-applicants and SPAG will use templates from our NIHR-funded CHABLIS study and EVOCC (NIHR HTA trial) to adapt them accordingly for RAF. CHABLIS specifically designed research documents for people with severe PAD facing barriers (e.g. frailty) in terms of participating in research.

With regards to technology support for better PPI&E-delivery, we will host a trial-specific website in lay and expert language, involve Vascular Research UK (YouTube channel for vascular UK research), prepare infographic with expert graphic designers in the UoL (supported by our SPAG), video animation and post regular lay updates (including infographics and videos) online (social media and

trial website). Lay updates/summaries will be available in the six most common languages in the UK, also including South Asian and Eastern European languages, as we have found that these two groups are more likely to need CFA surgery, presenting with severe PAD (in our CONFESS study).

Regulatory Compliance

Before the start of the trial, approval will be sought from a REC for the trial protocol, ICF and other relevant documents. Any substantial modifications that require review by REC will not be implemented until the REC grants a favourable opinion for the trial. All correspondence with the REC will be retained in the TMF.

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

Protocol compliance

Prospective, planned deviations or waivers to the protocol are **not** permitted under the UK regulations on Clinical Trials and must not be used e.g., it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol. However, accidental protocol deviations can happen at any time and they must be adequately documented on the relevant forms and reported to the Chief Investigator immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

If a protocol breach occurs, then the CI will document this in adherence to the University's Standard Operational Procedure SOP Identifying and Reporting Deviations and Serious Breaches of GCP and/or the Protocol for Trials. The CI will seek advice from the research supervisors and the Sponsor. All serious breaches must be reported to Sponsor immediately and within 24 hours of identification.

Financial

This trial has been awarded a grant from the NIHR and financial support will be available for participating locations for trial related research costs.

Local Research Delivery Network (RDN) support should be available to support the entry of participants into this trial including PI consent.

PPI*&E* representatives who attend scheduled trial visits or focus groups / interviews will be reimbursed with regards to expenses for travel up to £50. Lay individuals who take part in PPI&E groups will be reimbursed at a maximum of £25 per hour as per NIHR INVOLVE principles.

Indemnity

Sponsorship and insurance for trial design and management will be provided by the University of Leicester. If a participant is harmed due to negligence, this will be covered by the local NHS Trust(s) indemnity arrangements for all participants in clinical trials. If a trial participant wishes to make a complaint about any aspects of the way they have been treated or approached during the research project, the standard National Health Service complaint system will be available to them. Details of this are made available to participants the PIS.

Post trial care

Following completion of trial follow-up, participants will resume their regular routine NHS care and follow-up/surveillance as per local clinical pathways.

Access to the final trial dataset

The Chief Investigator will have access to the full dataset. Direct access will be granted to authorised representatives from the Sponsor and host institutions for monitoring and/or audit of the trial to ensure compliance with regulations.

12. DISSEMMINATION POLICY

Dissemination will take place in lay and expert format, via networking events in the form of a hybrid (online and face-to-face) workshop for both lay audiences and experts from all vascular healthcare backgrounds. This will be a one-day event, led by the RAF trial team, NIHR Leicester BRC staff and PPI partners, with support from the PPI co-ordinator and LCTU.

Six monthly lay and expert updates will be shared on a trial website and social media (e.g., X, Facebook), prepared by the PPI partners and RAF trial team, including infographics and videos.
We will ensure the widest possible dissemination of both lay and expert outputs to vascular healthcare professionals via the Vascular Society PAD group, which includes members from all disciplines involved in vascular care. Our strategy of publishing outputs in lay and expert format on a trial-specific website, social media and directly communicating these to NHS and vascular healthcare societies, will ensure the widest possible reach during RAF and on trial completion. Patient support groups such as the James Lind Alliance (JLA) or Self Help UK will be given lay summaries regularly and will be asked to disseminate amongst their networks. We will ensure that the findings of the trial are immediately disseminated to NICE, since the CI is also a member of a NICE Technology Appraisal Committee. Via our links (co-applicants) to all vascular healthcare societies in the UK, the findings will immediately be disseminated to NHS vascular professionals using mailing/emailing lists.

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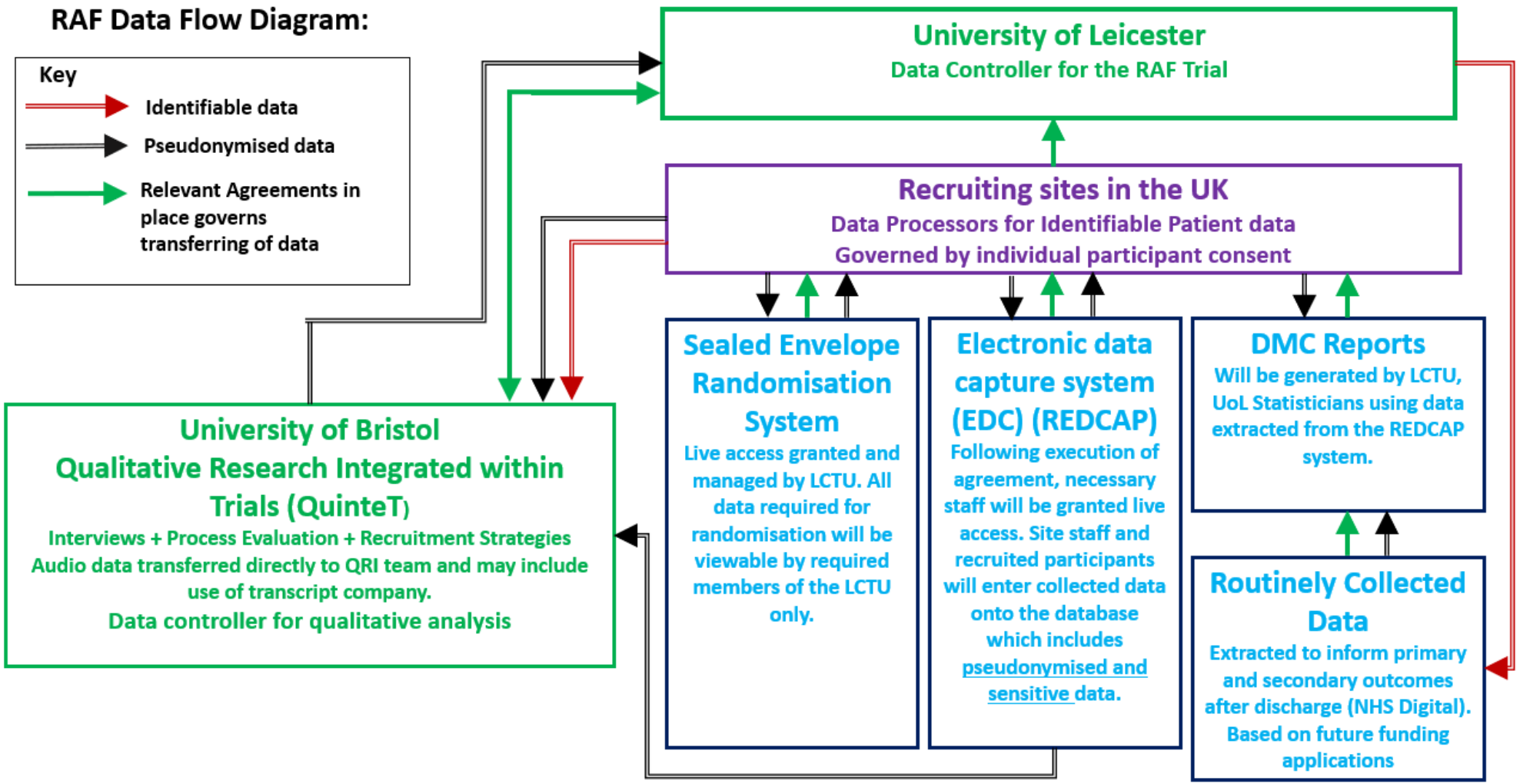
14. APPENDICES

APPENDIX 1 - Modification History

Modificiation No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
N/A	1.0	10/03/2026	Luke Ingram	Initial version created.
N/A	1.1	03/06/2026	Luke Ingram	Changes as recommended by initial research ethics committee (REC) review. Definition of major reintervention, end of trial and updates to section aligning the GDPR requirements and data management.

APPENDIX 2 – Data Flow Diagram



RAF Data Flow Diagram_v1.0_10_03_2026