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| **FULL/LONG TITLE OF THE STUDY** | Systematic Review and Meta-Analysis of Core Outcomes for people undergoing Major Lower Limb Amputation as a consequence of Peripheral Arterial Disease or Diabetes Mellitus |
| **SHORT STUDY TITLE / ACRONYM** | Systematic review and meta-analysis of core outcomes in dysvascular and diabetes related major lower limb amputation |
| **PROTOCOL VERSION NUMBER AND DATE** | V1.0 March 2024 |
| **IRAS Number:** | N/A |
| **JRES Reference Number** | N/A |
| **Funder Reference Number:** | N/A |
| **St Georges Ethics Registration Reference Number** | SE0129 |
| **PROSPERO Reference Number** | CRD42024497352 |
| **This protocol has regard for the HRA guidance and order of content** | |

# SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor’s SOPs, and other regulatory requirement.

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 investigation without the prior written consent of the Sponsor.

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

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| **Lead Supervisor:** | | |
| Signature:  A black and white drawing of letters  Description automatically generated |  | Date: 14/3/2024 |
| Name (please print):  Mr Iain Roy |  |  |
| Position:  Senior Lecturer in vascular surgery at St George’s University of London |  |  |
| **Chief Investigator:** | | |
| Signature:  A close-up of a signature  Description automatically generated |  | Date: 14/3/2024 |
| Name: (please print):  Mr Robert Leatherby |  |  |

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| KEY STUDY CONTACTS | |
| Chief Investigator | Mr Robert J Leatherby  MD(Res) Student  Molecular and Clinical Sciences Institute  St George’s University of London  Cranmer Terrace, London  SW17 0RE  [Robert.Leatherby@stgeorges.nhs.uk](mailto:Robert.Leatherby@stgeorges.nhs.uk) |
| Study Co-ordinator | Mr Robert Leatherby |
| Sponsor | St Georges University of London  Email: researchgovernance@sgul.ac.uk  St Georges Joint Research & Enterprise Service (JRES), Cranmer Terrace SW17 ORE |
| Funder(s) | Unfunded |
| Key Protocol Contributors | Mr Robert Leatherby and the study group |
| Committees | Study group |

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| **STUDY SUMMARY** | |
| Study Title | Systematic Review and Meta-Analysis of Core Outcomes for people undergoing Major Lower Limb Amputation as a consequence of Peripheral Arterial Disease or Diabetes Mellitus |
| Internal ref. no. (or short title) | Systematic review and meta-analysis of core outcomes in dysvascular and diabetes related major lower limb amputation |
| Study Design | Systematic review and meta-analysis of published studies |
| Study Participants | N/A |
| Planned Size of Sample (if applicable) | N/A |
| Follow up duration (if applicable) | N/A |
| Planned Study Period | November 2023 to November 2024 |
| Research Question/Aim(s) | Understand the frequency of use of the 18 outcomes defined in the core outcome set.  Understand the variability in the standard of reporting for each of the 18 core outcomes.  Establish a contemporary baseline for those core outcomes which are suitable to meta-analysis.  In outcomes in which meta-analysis is possible, perform subgroup analysis for the following if data quality allows:   * Patients with a diagnosis of diabetes vs those without * Level of amputation (above knee vs through knee vs below knee) * Presence of end-stage renal failure * Presence of heart failure |

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| **FUNDING AND SUPPORT** | |
| **FUNDER(S)** | **FINANCIAL AND NON FINANCIALSUPPORT GIVEN** |
| **N/A** |  |

**ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS**

|  |  |
| --- | --- |
| Steering Group | |
| **Chief Investigator** | Mr Robert Leatherby, MD(Res) Student, SGUL |
| **Lead Supervisor** | Mr Iain Roy, Senior Lecturer, SGUL |
| **Supervisor** | Professor Peter Holt, Professor of Vascular Surgery, SGUL |
| **Supervisor** | Mr Bilal Azhar, Clinical Lecturer, SGUL |

**PROTOCOL CONTRIBUTORS**

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| --- | --- |
|  | |
| **Mr Robert Leatherby** | Design of study, writing of protocol, conduct of study, interpretation, writing and dissemination |
| **Mr Iain Roy** | Design of study, writing of protocol, conduct of study, interpretation, writing and dissemination |
| **Professor Peter Holt** | Design of study, writing of protocol, conduct of study, interpretation, writing and dissemination |
| **Mr Bilal Azhar** | Design of study, writing of protocol, conduct of study, interpretation, writing and dissemination |
| **Patient involvement** | No patient involvement has been utilised in the construction of this protocol. However, the core outcome set used in this study was developed by Delphi exercise involving both clinicians and patients. |
| **Sponsorship** | The sponsor will be St George’s University of London |

# STUDY Schematic

October 2023 Formulation of research question and design of study

November 2023 Formulation of search strategy and peer review of search strategy by SGUL librarian

2nd December 2023 Running of search strategy on Embase, Medline and Cochrane libraries

January 2024 Registration of study on PROSPERO

December 2023 – March 2024 Screening of title, abstract and full text for inclusion/exclusion

April 2024 Data extraction

March – June 2024 Blinded second reviewer screening and data extraction check

June – July 2024 Data analysis

August 2024 onwards Writing-up of study

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| **ABBREVIATIONS** | |
| AE | Adverse Event |
| AKA | Above Knee Amputation |
| AR | Adverse Reaction |
| BKA | Below Knee Amputation |
| CI | Chief Investigator |
| CLTI | Chronic Limb Threatening Ischaemia |
| COS | Core Outcome Set |
| CRF | Case Report Form |
| DM | Diabetes Mellitus |
| GCP | Good Clinical Practice |
| GP | General Practitioner |
| HRA | Health Research Authority |
| ICF | Informed Consent Form |
| ISF | Investigator Site File |
| MLLA | Major Lower Limb Amputation |
| NHS | National Health Service |
| NIHR | National Institute for Health Research |
| PAD | Peripheral Arterial Disease |
| PI | Principal Investigator |
| REC | Research Ethics Committee |
| SAE | Serious Adverse Event |
| SGUL | St Georges, University of London |
| SGHFT | St Georges, University Hospitals NHS Foundation Trust |
| TKA | Through Knee Amputation |
| JRES | (St Georges) Joint Research and Enterprise Services |

**STUDY PROTOCOL**

**Systematic Review and Meta-Analysis of Core Outcomes for people undergoing Major Lower Limb Amputation as a consequence of Peripheral Arterial Disease or Diabetes Mellitus**

# 1 BACKGROUND

Lower limb amputations remain an important aspect of vascular practice despite continued advances in limb salvage. Whilst often considered a failure of treatment, a successful amputation can be considered a definitive and reconstructive management option. An aging population along with reported increases in the prevalence of peripheral arterial disease (PAD) (1) and diabetes mellitus (DM) (2) suggest that lower limb amputation will remain an important issue for the foreseeable future.

Lower limb amputations can be divided into minor amputations which are those performed distal to, or at the level of the ankle, and major lower limb amputations (MLLA) which are proximal to the ankle joint. In the UK over 3000 MLLAs are performed for PAD or DM per year (3). Over a 3-year period over 21,000 minor amputations and nearly 8000 MLLAs were undertaken in the diabetic population (4). Variations in classification and reporting of amputation rates make a true assessment of prevalence and temporal change challenging (5), however it is undoubtedly a major health burden.

MLLA is defined as a lower extremity amputation above the level of the ankle and include:

* Trans-tibial or below-knee amputations (BKA)
* Knee disarticulation or through-knee amputations (TKA)
* Trans-femoral or above knee amputations (AKA)
* Hip disarticulation or hemi-pelvectomy

PAD and DM are the most common aetiologies leading to MLLA. The most common indication for MLLA is Chronic Limb Threatening Ischaemia (CLTI), accounting for over 70% of amputations, with infection being the second most common at 15% (6) . Sixty percent of MLLA is performed in the diabetic population, with amputation rates in diabetic patients being 8 times higher than in those without DM (7). Attributing MLLA to a single aetiology is clearly an oversimplification, however, over 90% of MLLAs are performed for ischaemia, infection or a combination of both.

MLLA is undoubtedly a high-risk procedure. Early mortality rates at 30-days are 8.6%, with significantly higher mortality for those undergoing above knee amputation (AKA) at 16.5% versus those having below knee amputation (BKA) at 5.7% (8). Longer term mortality is particularly poor with a 48% mortality rate at 1 year rising to 70% at 3 years (9).

Improving outcomes in patients who undergo amputation has been listed as a priority in vascular research. The Vascular Priority Setting Partnership (PSP) delivered a report in 2021 setting out the top 10 priorities in amputation related research, with investigating and improving outcomes of MLLA, preventing ipsilateral MLLA after minor amputation, and prevention of contralateral amputation after MLLA all listed (10)

Outcomes from MLLA are universally poor. Using mortality as a crude outcome measure, we can see that early mortality after MLLA is high, with 30-day mortality figures ranging from 7% to 22% (11). In patients with DM requiring amputation mortality rates are particularly high, with a median survival of 40-55 months after their first amputation, comparable to patients with systemic malignant disease (12).

Mortality whilst important is not the only outcome measure of interest in MLLA. A recent meta-analysis and Delphi study led to the development of a core outcome set (COS) for patients undergoing MLLA. This set out 18 short- and medium-term core outcomes of importance to patients, carers, and clinicians (13). The core outcomes are as follows:

Short term outcomes

* Death
  + Death within a specified period of time after operation; or survival time after the operation
  + Cause of death
* Leg/stump
  + Problems with amputation stump healing
  + Stump wound infection
  + Development of problems with the other leg
* Quality of life
  + Effectiveness of pain relief
  + Psychological morbidity
* Communication
  + Effective communication between healthcare team and patient/carers
* Additional healthcare
  + Need for readmission to hospital after discharge
  + Need for additional operations
  + Overall peri-operative complications

Mid/long term outcomes

* Leg/stump
  + Problems with amputation stump healing
  + Stump wound infection
  + Development of problems with the other leg
* Quality of life
  + Pain in residual limb/amputations stump/phantom
  + Psychological morbidity
  + Quality of life
* Mobility
  + Patients supplied with a temporary or definitive prosthetic limb
  + Prosthetic limb use, comfort and fitting
  + Level of independent mobility or function achieved
* Social integration/independence
  + Participation in work and social activities
  + Independent living

# 2 RATIONALE

It has now been 5 years since the systematic review was performed to develop the COS for MLLA. No further research into the use of these outcomes, the standardisation of the reporting of these outcomes, nor an overview of the contemporary figures for these outcomes have been produced.

We aim to complete a systematic review and meta-analysis of this COS for patients undergoing MLLA as a consequence of PAD or DM. We aim to establish the use of the outcomes listed in the COS, the variability in frequency and standardisation of reporting for each outcome, and to establish a contemporary baseline for the outcomes. This research will guide future MLLA outcome-based research, aid standardisation, identify areas poorly reported and establish an understanding of the outcomes in contemporary practice.

**3 THEORETICAL FRAMEWORK**

MLLA for DM and PAD is a commonly performed procedure worldwide, and especially in the developed world with an increase in DM and increasing life expectancy. As this procedure and the reporting of its outcomes are common, it lends itself to systematic review and meta-analysis. In addition, this is the only methodological way to determine the frequency and standardisation of the reporting of these outcomes in the published literature. The basis of this study is the core-outcome set developed by Ambler G et al (13). These outcomes were established as being the most important to patients and clinicians via systematic review and Delphi exercise. They have since not been reported on as to their use in contemporary outcomes-based research.

This study aims to address this, establishing the frequency of use for the core outcomes in the contemporary published literature. In addition, the variation of reporting measure will be assessed for each outcome, to assess the standardisation of each outcome’s reporting. This study will also aim to establish a contemporary baseline of these core outcomes for the dysvascular amputee. Meta-analysis previously established high-risk groups will be performed in order to establish more individualised risk profiles for patients undergoing MLLA.

# 4 RESEARCH QUESTION/AIM(S)

To establish the frequency and standardisation of reporting for each core outcome after MLLA. To establish a contemporary baseline for each of the core outcomes.

**4.1** **Objectives**

* Define the frequency of the reporting of the 18 outcomes defined in the core outcome set in the contemporary published literature.
* Define the standardisation of reporting for each of the 18 core outcomes in the contemporary published literature.
* Establish a contemporary baseline of results for each of the core outcomes.
* Meta-analysis of suitable outcomes with performance of sub-group analysis for the following if data quality allows:
  + Patients with a diagnosis of diabetes vs those without
  + Level of amputation (above knee vs through knee vs below knee)
  + Presence of end stage renal failure
  + Presence of heart failure
* Perform time to event analysis for mortality, with subgroup analysis if data allows, with production of a pooled Kaplan Meier plot for this outcome.

**4.2 Outcome**

Primary outcomes of interest are those as defined are “Core Outcomes” in the Development of Core Outcome Sets for People Undergoing Major Lower Limb Amputation for Complications of Peripheral Vascular Disease by Ambler G. et al (13).

1. Death within a specified period of time after operation, or survival time after operation
   1. To allow meta-analysis these will be rounded to the nearest of the following;
      1. peri-operative or 30-days
      2. 3 months or 90-days
      3. 6 months
      4. yearly thereafter.
2. Cause of death
3. Problems with amputation stump healing
4. Stump wound infection
5. Development of problems with the other leg
   1. Defined as need for contra-lateral revascularisation or amputation
6. Effectiveness of pain relief
7. Psychological morbidity
   1. Defined as depression or anxiety post-operatively
8. Effective communication between healthcare team and patient/carers
9. Need for re-admission to hospital after discharge
10. Need for additional operations
    1. Defined as ipsilateral return to theatre, need for revision, proximal revascularisation
11. Overall peri-operative complications
12. Pain in residual limb/amputation stump/phantom
13. Quality of life
14. Patient supplied with a temporary or definitive prosthetic limb
15. Prosthetic limb use, comfort and fitting
16. Level of independent mobility or function achieved
17. Participation in work or social activities
18. Independent living

# 5 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYIS

This study will be a systematic review and meta-analysis of the core outcomes for people undergoing MLLA as a consequence of PAD or DM. It has been registered with PROSPERO (14). We aim to pre-publish the protocol which adheres to PRISMA-P guidelines. The study and all method with be performed in line with the latest PRISMA guidelines (15).

### Types of study

All prospective and retrospective study designs will be considered reporting at least one of the core outcomes. Case reports, case series and small studies inclusive of fewer than 50 patients will be excluded. Review articles and meta-analyses will be excluded along with conference abstracts or non-peer reviewed studies. The literature search will be inclusive of all languages, however studies which do not have a full text in English will be excluded at full text review. The search was limited to 5 years prior to the search date of 2nd December 2023.

### Types of participant

All patients who have undergone MLLA as a consequence of PAD or DM. MLLA is defined as any amputation above the level of the ankle, and studies which do not distinguish major and minor amputation outcomes will be excluded. Studies will be included as long as over 50% of patients have their MLLA secondary to DM or PAD, with “infection” unless specified as being “non diabetes related” being included under DM. With regards to PAD, both patients undergoing MLLA for acute and chronic limb ischaemia will be included. A generally inclusive policy will be utilised with large population studies especially those on vascular registries being assumed to have over 50% of patients having MLLA secondary to PAD or DM.

Studies which solely recruit high or low risk MLLA groups will be excluded (e.g. end stage renal failure) from the meta-analysis. Studies which solely present a propensity matched MLLA group will also be excluded as by definition this will be a high or low risk cohort.

Patients recruited at time of intervention, referral to rehabilitation or from prosthetic centres will all be included in systematic review. These will be analysed and reported as subgroups if data allows as they represent different risk groups.

### Types of intervention

Not applicable. Type of participant is defined above. No comparator group is being used as we are aiming to establish the frequency and standard of use of the core outcome set, and a contemporary baseline of these outcomes.

Subgroup analysis for outcomes suitable to meta-analysis will be performed and the variables of interest will be:

* Presence or absence of DM
* Level of amputation
* Presence or absence of absence of end-stage renal failure
* Presence or absence of heart failure

### Types of outcome measure

Types of outcome measure are those defined as core outcome sets. A liberal approach to what constitutes to the less well-defined outcomes will be utilised. The outcomes are as follows:

1. Death within a specified period of time after operation, or survival time after operation
   1. To allow meta-analysis these will be rounded to the nearest of the following;
      1. peri-operative or 30-days
      2. 3 months or 90-days
      3. 6 months
      4. yearly thereafter.
2. Cause of death
3. Problems with amputation stump healing
4. Stump wound infection
5. Development of problems with the other leg
   1. Defined as need for contra-lateral revascularisation or amputation
6. Effectiveness of pain relief
7. Psychological morbidity
   1. Defined as depression or anxiety post-operatively
8. Effective communication between healthcare team and patient/carers
9. Need for re-admission to hospital after discharge
10. Need for additional operations
    1. Defined as ipsilateral return to theatre, need for revision, proximal revascularisation
11. Overall peri-operative complications
12. Pain in residual limb/amputation stump/phantom
13. Quality of life
14. Patient supplied with a temporary or definitive prosthetic limb
15. Prosthetic limb use, comfort and fitting
16. Level of independent mobility or function achieved
17. Participation in work or social activities
18. Independent living

### Search methods

A search strategy has been devised by an experienced team of researchers with experience in vascular surgery and systematic review/meta-analysis. Part of the search strategy has been peer-reviewed by an information specialist at the Cochrane group as part of a separate study (PAD). A further part of the search strategy (MLLA) uses the same search terminology as used in the systematic review aspect of the core outcome set paper. The complete search strategy was then further defined to be inclusive of patients with DM and the outcomes of interest. The completed search strategy was then reviewed by a librarian experienced in systematic review and meta-analysis at SGUL.

The search strategy was run through OVID Embase and Medline databases and Cochrane. The full search strategy can be found on figshare.

### Selection of studies

The output of all searches will be imported into Rayyan.ai systematic and meta-analysis software. De duplication of results was performed by OVID for Embase and Medline results and then Cochrane duplicates were removed manually via Rayyan’s de-duplicating software.

Once extracted 2 reviewers will blindly and independently assess all studies based on title and abstract against the inclusion and exclusion criteria for full text review. Once complete the 2 reviewers will be unblinded and disagreements in article inclusion for full text review will be attempted to be resolved between them. If disagreements cannot be resolved a third senior reviewer will be used as a tie break. The reviewers will then blindly and independently assess the full text studies against the same criteria, with the same process of unblinding, disagreement resolution and third reviewer tie break used for study selection.

A PRISMA flow chart of study selection will be produced.

### Data extraction and management

The study team will extract data from the study papers and supplementary materials into a pre-populated excel spreadsheet. Data on study design, methodology, demographics and baseline characteristics, level of amputations, aetiology of amputations and relevant outcomes will be extracted. Outcome specific subgroup analysis data will be captured where possible. Data will be extracted by one individual and 10% of this will be independently extracted by a second individual to check for accuracy. A kappa value will be calculated and accepted if this shows strong or almost perfect agreement, if not a further 10% will be checked and this process repeated. Any disagreements will be attempted to be resolved between the two reviewers with a third reviewer brought in for arbitration if required. Microsoft Excel will be used for the database creation and storage and R for statistical analysis.

### Study quality assessment

The methodological quality of the studies include in the meta-analysis will be assessed using the Cochrane risk of bias tool for randomised trials (ROB-2) score for randomised studies (16) and the Newcastle Ottawa Scale (NOS) for non-randomised studies (17).

### Assessment of reporting bias

Publication bias will be assessed visually for studies included in the meta-analysis by use of a funnel plot. If over 10 studies are included, then Egger’s intercept value will be calculated.

### Measurement of treatment effect

For the systematic review of the core outcomes there is no comparator group as such, so the data will be presented as descriptive statistics, and time to event analysis will be performed plotting Kaplan Meier charts for mortality. If subgroup analysis is possible for outcomes this data will be collected as absolute numbers, but if not available hazard ratios and odds ratios will be used as alternatives. This data will be presented as forest plots.

### Unit of analysis

Outcomes is paper level. Unit of analysis is expected to cohort and sub population level, weighted for cohort size.

### Missing data

Only published data will be analysed. Missing data will be considered within the risk of bias assessment. Expected review size makes contacting individual studies for missing results unrealistic.

### Data synthesis

Data analysis will be performed using “R” statistical software. Basic graphical and tabular outcomes will be produced as part of the systematic review aspect of the study with the relative frequency of reporting for each of the core outcomes and the standardisation of reporting for each of the core outcomes being presented. Weighted mean outcomes will be presented for each of the core outcomes to establish the contemporary baseline. Outcomes reported for high-risk subgroups at an acceptable frequency and standardisation will be meta-analysed. Subgroup analysis will be visually presented as Forest plots. Finally time to event analysis will be performed for mortality (with or without subgroups) with this being visually presented using pooled Kaplan Meier plots.

### Sensitivity analysis

Sensitivity analysis will be performed excluding those studies deemed to be of high risk of bias in order to assess whether the exclusion of these studies impacts the final analysis.

# 6 STUDY SETTING

This is a systematic review and meta-analysis and therefore does not require any primary data collection.

**7 SAMPLE AND RECRUITMENT**

**7.1 Eligibility Criteria**

See section 5

**7.1.1 Inclusion criteria**

See section 5

**7.1.2 Exclusion criteria**

See section 5

**7.2 Sampling**

N/A

**7.2.1 Size of sample**

N/A

**7.2.2 Sampling technique**

N/A

**7.3 Recruitment**

N/A

**7.3.1 Participant identification**

N/A

**7.3.2 Consent**

N/A

**Consent provisions for collection and use of participant data and biological specimens**

N/A

7.3.3 **Data collection tool**

Data collection will be via Rayyan.ai systematic review tool for deduplication and screening with data extraction onto a pre-populated excel spreadsheet.

Case Report Forms will be designed by the CI.

* On paper CRFs all data should be entered legibly in black ink. If the Investigator makes an error, it will be crossed through with a single line in such a way to ensure that the original entry can still be read. The correct entry will then be clearly inserted. The amendment will be initialled and dated by the person making the correction immediately. Overwriting or use of correction fluid will not be permitted.
* On eCRF’s the CI will provide logins to relevant and trained site level members of the research team.

It is the Investigator’s responsibility to ensure the accuracy of all data entered and recorded in the CRFs. The Staff Delegation of Responsibilities Log should identify all trial personnel responsible for data collection, entry, handling and managing the database.

7.3.4 **Biological** **Sample Handling**

N/A

# 8 ETHICAL AND REGULATORY CONSIDERATIONS

## This is a systematic review and meta-analysis of previously published data and therefore no additional ethical approval is required.

## **8.1 Assessment and management of risk**

COVID-19 Risk Assessment and Management Strategy

All staff employed by SGUL and/or SGH NHS Foundation Trust are required to complete an ongoing COVID-19 risk assessment prior to undertaking any work on site, which includes research activity. This process is continuously monitored by the responsible line manager.

Participants (unaffected or affected) will not be recruited if they are deemed high risk or are in close contact with someone at risk. The Research Team will contact research participants ahead of scheduled study visits on-site to check for COVID-19 symptoms and the symptom check will be repeated when patients attend the hospital site for the study visit.

Participants will receive information regarding the extra precautions that will be taken in light of the COVID-19 pandemic in the Patient Information Sheet. This will detail steps that patients should take if they have concerns about exposure to COVID-19 through participating in the research, or believe that they are symptomatic or have been in close contact with another person believed to be symptomatic. The Patient Information Sheet will also have contact details for the Research Team for patients to get in touch if they have any concerns or queries about this.

All research personnel are expected to comply with the NHS Trust and University policies on COVID-19.

All patients attending the hospital site for research visits and/or routine clinical follow-up will be expected to abide by the NHS Trust and University policies on COVID-19 which include wearing suitable PPE (provided by the NHS Trust on arrival), adhering to the visitor policy on social distancing and following the one-way routing systems whilst on site.

**8.2 Research Ethics Committee (REC) and other Regulatory review & reports**

Before the start of the study, a favourable opinion will be sought from an appropriate REC for the study protocol, informed consent forms and other relevant documents e.g. advertisements.

**For HRA- NHS REC reviewed research**

* Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site.
* It is the Chief Investigator’s responsibility to produce the annual reports and submit the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.
* The Chief Investigator will notify the REC of the end of the study within one year after the end of the study.
* If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

**Regulatory Review & Compliance**

Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance.

Amendments

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as [amended](http://www.hra.nhs.uk/resources/after-you-apply/amendments/).

**8.3 Peer review**

The study protocol has not been externally peer reviewed. The core outcome set on which this study is based has been peer reviewed prior to publication in the European Journal of Vascular Surgery. In addition, our search strategy has been peer reviewed by the library service at St George’s University of London. All aspects of this protocol have been discussed and reviewed by the research group which is inclusive of clinicians actively involved in these patient’s care and with academic positions within the field.

**8.4 Patient & Public Involvement**

The study itself has not been subject to public or patient review. The core outcome set on which this study is based was however developed by a Delphi exercise which used both clinician and patient input to generate the core outcome set from those found in systematic review. Therefore, the outcomes of our study will be directly of interest to both clinicians and patients who have undergone MLLA.

**8.5 Protocol compliance**

Protocol deviations, non-compliances, or breaches are departures from the approved protocol.

All protocol deviations must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor 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.

### 

**8.6 Data protection and patient confidentiality**

All data should be handled in accordance with the Data Protection Act 2018 (UK implementation of the EU General Data Protection Regulation (GDPR)).

Any Case Report Forms (CRFs) will not bear the participant’s name or other directly identifiable data. The participant’s trial Identification Number (ID) only, will be used for identification. The Subject ID log can be used to cross reference participant’s identifiable information.

8.7 Indemnity

St George’s University of London holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that St George’s has been negligent. This includes negligence in the writing of the protocol, or selection of trial resources.

Where the Trial is conducted in a hospital, the hospital has a duty of care to participants. St George’s University of London will not accept liability for any breach in the hospital’s duty of care, or any negligence on the part of hospital employees. .

If a participant indicates that they wish to make a claim for compensation, this needs to be brought to the attention of St George’s University of London immediately.

Failure to alert St George’s University of London without delay and to comply with requests for information by the sponsor or any designated Agents may lead to a lack of insurance cover for the incident.

**8.8 Access to the final study dataset**

The final dataset will be available to the research group. This is a single centre research group and therefore data will not be available to other sites. No patient identifiable data is held as this study is a systematic review and meta-analysis of previously published data.

### 9 DISSEMINIATION POLICY

### 9.1 Dissemination policy

Publication: “Any activity that discloses, outside of the circle of trial investigators, any final or interim data or results of the Trial, or any details of the Trial methodology that have not been made public by the Sponsor including, for example, presentations at symposia, national or regional professional meetings, publications in journals, theses or dissertations.”

All scientific contributors to the Trial have a responsibility to ensure that results of scientific interest arising from Trial are appropriately published and disseminated. The Sponsor has a firm commitment to publish the results of the Trial in a transparent and unbiased manner without consideration for commercial objectives.

To maximise the impact and scientific validity of the Trial, data shall be consolidated over the duration of the trial, reviewed internally among all investigators and not be submitted for publication prematurely. Lead in any publications arising from the Trial shall lie with the Sponsor in the first instance.

**Before the official completion of the Trial,**

All publications during this period are subject to permission by the Sponsor. If an investigator wishes to publish a sub-set of data without permission by the Sponsor during this period, the **Steering Committee/the Funder** shall have the final say.

Exempt from this requirement are student theses that can be submitted for confidential evaluation but are subject to embargo for a period not shorter than the anticipated remaining duration of the trial.

**Up to 180 days after the official completion of the Trial**

During this period the Chief Investigator shall liaise with all investigators and strive to consolidate data and results and submit a manuscript for peer-review with a view to publication in a reputable academic journal or similar outlet as the Main Publication.

* The Chief Investigator shall be senior and corresponding author of the Main Publication.
* Insofar as compatible with the policies of the publication outlet and good academic practice, the other Investigators shall be listed in alphabetic order.
* Providers of analytical or technical services shall be acknowledged, but will only be listed as co-authors if their services were provided in a non-routine manner as part of a scientific collaboration.
* Members of the Steering Group shall only be acknowledged as co-authors if they contributed in other capacities as well.
* If there are disagreements about the substance, content, style, conclusions, or author list of the Main Publication, the Chief Investigator shall ask the Steering Group to arbitrate.

**Beyond 180 days after the official completion of the Trial**

After the Main Publication or after 180 days from Trial end date any Investigator or group of investigators may prepare further publications. In order to ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the Sponsor for review at least sixty (60) days prior to submission for publication, public dissemination, or review by a publication committee. Sponsor’s reasonable comments shall be reflected. All publications related to the Trial shall credit the Chief and Co-Investigators as co-authors where this would be in accordance with normal academic practice and shall acknowledge the Sponsor and the Funders.

**9.2 Archiving Arrangements**

Each site will be responsible for their onsite level study archiving. The trial essential TMF along with any central trial database will be archived in accordance with the sponsor SOP.

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### 11. APPENDICIES

**11.1** **Appendix 1**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Amendment Log** | | | | |
| **Amendment No.** | **Protocol version no.** | **Date issued** | **Author(s) of changes** | **Details of changes made** |
|  |  |  |  |  |

**11.2 Appendix 2**

**Research Data Protection Impact Assessment (DPIA)**

Data Protection Impact Assessments (DPIAs) are a tool which can help organisations identify the most effective way to comply with their data protection obligations under the Data Protection Act 2018 (DPA 18) and meet individuals’ expectations of privacy.

A DPIA helps identify data privacy risks when planning new, or revising existing, projects and to identify actions to mitigate these risks. In the rare cases where risks cannot be mitigated at all it may be necessary to consult with the Information Commissioner's Office (ICO). Under data protection legislation it is a legal requirement to complete a DPIA in the following circumstances:

* • where data processing is likely to result in a high risk of harm to individuals, e.g. new, invasive technology is proposed
* • when large volumes of personal data are processed, e.g. use of behavioural profiles based on website usage
* • when processing special category personal data on a large scale, e.g. healthcare data, genetic tests to assess and predict the disease/health risks

• where publicly accessible areas are monitored, e.g. CCTV or when filming public areas

Therefore a DPIA will be carried out for both internal and partnership projects which require the collection/processing of personal data in any format for the purpose of research.

The DPIA should be carried out towards the start of the project, in order to identify any associated information risks and mitigate in the early stages, before you start processing.

|  |  |
| --- | --- |
| **Study Title/Acronym:** | Systematic Review and Meta-Analysis of Core Outcomes for people undergoing Major Lower Limb Amputation as a consequence of Peripheral Arterial Disease or Diabetes Mellitus |
| **JRES Reference Number:** | N/A |
| **Chief Investigator Name:** | Mr Robert Leatherby |
| **Chief Investigator Email Address:** | Robert.Leatherby@stgeorges.nhs.uk |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **PROJECT DETAILS** | | | | | |
| **Project / process description:**  **- include / attach processing operations (include a flow diagram or another way of explaining data flows), the purpose and, where applicable, what St George’s lawful basis is for the processing of the information.** | | | | | |
| Systematic review and meta-analysis of already published studies within the past 5 years reporting at least one of the outcomes listed within the core outcomes set. | | | | | |
| **What personal data do you intend to use, and why? (List all categories)** | | | | | |
| No patient level personal data will be utilised as all data is to be taken from already published studies | | | | | |
| **Will the personal data be identifiable, pseudonymised or anonymised (if a mix tick accordingly)** | | | | | |
| Identifiable |  |  | | | |
| \*Pseudonymised |  |  | | | |
| Anonymised | X |  | | | |
| *\*Confirm that the key to this data is kept securely away from the used data with strict controlled access* | | | | | |
| **List all organisations / agencies which will have access to the personal data collection used for this project / process** | | | | | |
| N/A | | | | | |
| **Length of the study – include an assessment of the necessity and proportionality of the processing in relation to the purpose. Also include who, internally & externally, has been consulted in the preparation of this DPIA.** | | | | | |
| Study will run from October 2023 to October 2024. | | | | | |
| **If external organisations / agencies are involved, is there a contract or information sharing agreement in place with suitable clauses for data protection and data incident reporting,? If not why not?** | | | | | |
| N/A | | | | | |
| **RISK** | | | | | |
| **Can you achieve your objectives using anonymised data? – see ICO Code of Practice on Anonymisation** | | | | | |
| Yes | X |  | | | |
| No |  | Why not? |  | | |
| **What are the benefits to the individual of their personal data being used for this purpose?** | | | | | |
| N/A | | | | | |
| **What are the organisational benefits of the individual’s personal data being used for this purpose?** | | | | | |
| N/A | | | | | |
| **What are potential negative impacts to the individual of their personal data being used for this purpose in the event of a Data Breach occurring?** | | | | | |
| N/A | | | | | |
| **How will you avoid causing unwarranted or substantial damage/distress to the individual when using their personal data for this purpose?** | | | | | |
| N/A | | | | | |
| **Is the data already held by St George’s?** | | | | | |
| Yes |  |  | | | |
| No | X |  | | | |
| **Is it held by one of the partner organisations / agencies involved in this process/project?** | | | | | |
| Yes |  |  | | | |
| No | X | Which agency will be collecting the data | | |  |
| **Have you told the individuals whose personal data you want to use for this purpose, how and why you intend to use their data?** | | | | | |
| Yes |  | N/A | | | |
| No |  |  | | | |
| **If not, are you intending to tell them?** | | | | | |
| Yes |  |  | | | |
| No |  | Why not? |  | | |
| **Do you already have the individual’s consent to use their data for this purpose?** | | | | | |
| Yes |  | N/A | | | |
| No |  | Why not? |  | | |
| **If not, are you going to ask for their permission?** | | | | | |
| Yes |  | N/A | | | |
| No |  | Why not? |  | | |
| **Have individuals been given the opportunity to refuse us permission to use their data for this purpose?** | | | | | |
| Yes |  | N/A | | | |
| No |  |  | | | |
| **How will you make sure that the personal data you are using is kept accurate and up to date?** | | | | | |
| N/A | | | | | |
| **What steps or controls are you taking to minimise risks to privacy?**  **Please tick those which apply and provide details of how each is ensured** | | | | | |
| * Risks to individual privacy are minimal * No personal data is being generated. All data is already published. | | | |  | |
| **How long will you need to hold the personal data for after the study has completed?** | | | | | |
| N/A | | | | | |
| **How will you make sure that you are holding data for the appropriate length of time and no longer?** | | | | | |
| N/A | | | | | |
| **How will the data be held /stored?** | | | | | |
| N/A | | | | | |
| **Will you be using any electronic and/or paper Case Report Forms (CRFs) to collect data? If so what are these and how will they be held securely and managed at the end of the project?** | | | | | |
| N/A | | | | | |
| **Will personal data be transferred/shared between the organisations involved in this project? If so how?** | | | | | |
| N/A | | | | | |
| **Will you be transferring personal data to a country or territory outside of the UK?** *If yes, name countries and receiving parties*. | | | | | |
| Yes – within EEA |  |  | | | |
| Yes – outside of EEA |  |  | | | |
| No | X |  | | | |
| **How will you ensure that third parties will comply with data protection obligations?** | | | | | |
| N/A | | | | | |
| **What measures are in place to ensure only appropriate and authorised access to and use of, personal data?** | | | | | |
| N/A | | | | | |
| **How will technical and organisational security be monitored/audited?** | | | | | |
| N/A | | | | | |

**Declaration**

I confirm that the information recorded on this form is, to the best of my knowledge, an accurate and complete assessment of the potential privacy impacts of this study.

Name: R Leatherby

Signature:A close-up of a signature

Description automatically generated

Date: 15/3/24

**Institute Director (SGUL) or Care Group Lead (SGHFT)**

Name: P Holt

Signature:A close-up of a logo

Description automatically generated

Date: 15/3/24