

FULL/LONG TITLE OF THE STUDY	Systematic review & network meta-analysis of randomised controlled trials comparing antithrombotic drugs for cardiovascular risk reduction in patients with lower limb peripheral arterial disease.
SHORT STUDY TITLE / ACRONYM	NMA of Antithrombotic Drugs in PAD
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**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.

**For and on behalf of the Study Sponsor:**

Signature: **Not Required – Nonclinical Study**

Date:

.....

...../...../.....

**Chief Investigator:**

Signature:

Date:

.....

...../...../.....

Name: (please print):

**Iain Roy**

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LIST of CONTENTS	Page No.
PROTOCOL COMPLIANCE DECLARATION	1
TITLE PAGE	1
RESEARCH REFERENCE NUMBERS	1
SIGNATURE PAGE	2
LIST OF CONTENTS	3
KEY STUDY CONTACTS	4
STUDY SUMMARY	5
FUNDING	5
ROLE OF SPONSOR AND FUNDER	5
ROLES & RESPONSIBILITIES OF STUDY STEERING GROUPS AND INDIVIDUALS	5
STUDY FLOW CHART	Appendix 1
ABBREVIATIONS	7
1. BACKGROUND	8
2. RATIONALE	9
3. THEORETICAL FRAMEWORK	10
4. RESEARCH QUESTION/AIM(S)	11
5. STUDY DESIGN/METHODS	13
6. STUDY SETTING	19
7. SAMPLE AND RECRUITMENT	19
8. ETHICAL AND REGULATORY COMPLIANCE	20
9. DISSEMINATION	24
10. REFERENCES	27
11. APPENDICES	30

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Committees	Study Group

STUDY SUMMARY	
Study Title	Systematic review & network meta-analysis of randomised controlled trials comparing antithrombotic drugs for cardiovascular risk reduction in patients with lower limb peripheral arterial disease.
Internal ref. no. (or short title)	NMA of antithrombotics for PAD
Study Design	Systematic review & network meta-analysis of published randomised controlled trials
Study Participants	N/A
Planned Size of Sample (if applicable)	N/A
Follow up duration (if applicable)	N/A
Planned Study Period	November 2022 to October 2023
Research Question/Aim(s)	To objectively establish the relative efficacy/effects of the various antithrombotic drug/regimens in both the general and sub-populations of patients with lower limb peripheral arterial disease.

FUNDING

FUNDING AND SUPPORT	
FUNDER(S)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
National Institute for Health and Care Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number NIHR204123).	Iain Roy, Peter Holt, Daniel Carradice and Chao Huang – Salary Costs Patient and Public Involvement Costs Infrastructure and specific project costs

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

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Protocol contributors	
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David Sidebottom, Academic Foundation Doctor, St George’s, University of London	Drafting of protocol and writing of the protocol manuscript.
PPI group	As laid out in detailed PPI section below. The PPI group informed the development of this protocol including the importance of the research, its justification, outcomes that are important to patients, and dissemination. The PPI group will also be involved in the interpretation and dissemination phases as detailed below.
Funder	NIHR funding has been used to support preliminary PPI work. The team are also applying for an NIHR grant to support this research. This is pending and has not yet been approved. The funder is not expected to have any input on any stage in the research process and will not control any decision related to publication.
Sponsor	The sponsor will be St George’s, University of London. The sponsor will not control any decision related to publication.

**STUDY Schematic**

Please see appendix 1 for the study Gant chart as submitted as part of the NIHR grant application for this study.

ABBREVIATIONS	
AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CLTI	Chronic Limb-Threatening Ischaemia
CRF	Case Report Form
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
IC	Intermittent Claudication
ICF	Informed Consent Form
ISF	Investigator Site File
MACE	Major adverse cardiovascular event
MALE	Major adverse limb-related event
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network Meta-Analysis
PAD	Peripheral Arterial Disease
PI	Principal Investigator
PPI	Patient and Public Involvement
QOL	Quality of Life
RCT	Randomised Controlled Trial
RDS	Research Development Service
REC	Research Ethics Committee
SAE	Serious Adverse Event
SGUL	St Georges, University of London
SGHFT	St Georges, University Hospitals NHS Foundation Trust
JRES	(St Georges) Joint Research and Enterprise Services

## STUDY PROTOCOL

Systematic review & network meta-analysis of randomised controlled trials comparing antithrombotic drugs for cardiovascular risk reduction in patients with lower limb peripheral arterial disease.

### 1 BACKGROUND

Peripheral arterial disease (PAD) is the term used to describe a narrowing or occlusion of the peripheral arteries, typically affecting the lower limbs. PAD is most often caused by atherosclerosis or atherothrombosis, which narrows or occludes the affected arteries and limits blood flow to the affected limb [1]. This limitation of blood flow may be asymptomatic or cause symptoms such as intermittent claudication (IC), where diminished circulation leads to pain in the lower limb on exertion that is relieved by rest [2]. More severe PAD can present with or progress to chronic limb-threatening ischaemia (CLTI), a clinical pattern that represents threatened limb viability. CLTI is most often characterised by chronic, inadequate tissue perfusion at rest and is defined by ischaemic rest pain with or without tissue loss (for example ulcers, gangrene, or infection) [3,4]

Globally, over 230 million people have PAD [5]. PAD is uncommon in younger people, but the prevalence increases with age [2,6]. In the UK, around 2.2 million people have some degree of PAD, with the prevalence rising to 15% in those aged over 70 years [7]. While most individuals with PAD do not present to the healthcare service, between 10 and 30% experience IC (up to 660,000 people in the UK) [3]. CLTI has a reported prevalence of around 0.4 – 2% [3,4]. The prevalence of PAD is similar in both men and post-menopausal women [8], although the prevalence of more severe or symptomatic disease is higher in men [6]. Other risk factors for both the development and progression of PAD include smoking, hypertension, diabetes, dyslipidaemia, and obesity [3,5].

The direct effects of PAD include impairment of quality of life (QOL) [2,9], psychosocial consequences [10], tissue loss (ulceration and gangrene) in CLTI [3], an increased risk of amputation [11], as well as procedural complications resulting from invasive treatments for peripheral arterial disease [2]. In addition, atherosclerosis is often generalised and, if it is present at one site, there is an overall increased risk of cardiovascular events [2]. Patients with PAD are three times more likely to die of cardiovascular causes than someone without PAD [12]. They are also at higher risk of myocardial infarction, stroke, vascular dementia, renovascular disease, and mesenteric disease [1,13]. Symptomatic cardiovascular events are more likely in people with PAD, even if it is asymptomatic [9]. Of people presenting with claudication symptoms, 10–15% die of cardiovascular causes over the following five years, while 20% experience non-fatal cardiovascular events [9]. National and international guidelines therefore recommend the assessment of cardiovascular risk, and management of all key modifiable risk factors such as smoking, control of diabetes, hyperlipidaemia, hypertension, body weight, and exercise levels [3,14].

A number of randomised control trials (RCTs) have demonstrated the benefit of commencing or optimising antithrombotic pharmacological therapy, with the aim of preventing occlusive vascular events or their recurrence [15–23]. Antithrombotic therapy may include one or more antiplatelets and/or anticoagulation drugs. However, the optimal antithrombotic regimen for the medical management of PAD is contentious, both overall and in key sub-populations such as those with diabetes. Patients undergoing interventions in the form of surgical bypass or endovascular intervention have separate recommendations with more agreement. The National Institute for Health and Care Excellence (NICE) has previously published two antithrombotic guidelines relevant to PAD patients:

- NICE Technology appraisal guidance 210 (TA210) states “Clopidogrel is recommended as an option to prevent occlusive vascular events for people who have ... peripheral arterial disease or multivascular disease” [24].
- NICE Technology appraisal guidance 607 (TA607) states “Rivaroxaban plus aspirin is recommended ... as an option for preventing atherothrombotic events in adults with coronary artery disease or symptomatic peripheral artery disease who are at high risk of ischaemic events” [25]

Although NICE TA607 subsequently defines high-risk coronary heart disease (CHD), high-risk PAD is not defined [24]. Furthermore, TA607 was informed by the 'COMPASS' RCT, in which 90% of patients had coronary artery disease and only 27% of patients had PAD (which includes some patients with carotid artery disease) [15,16]. Patients were randomised to receive aspirin monotherapy, the current standard of care for stable CHD, or rivaroxaban plus aspirin combination therapy, despite clopidogrel being the preferred antiplatelet monotherapy for symptomatic PAD [3,24]. In contrast, the NICE TA210 recommendation for clopidogrel is based on the 'CAPRIE' RCT, which demonstrated the superior efficacy of clopidogrel monotherapy compared to aspirin monotherapy in patients with symptomatic PAD [17,24]. This discordance within NICE guidance means that clinicians and patients are asked to make their decisions regarding choice of antithrombotic therapy based upon incongruous recommendations.

## 2 RATIONALE

Incongruous guidance on the medical management of PAD generates confusion for both clinicians and patients, while variation in clinical practice is likely resulting in harm to patients. This network meta-analysis (NMA) aims to address a critical unanswered question in daily clinical practice which affects many patients. It aims to objectively inform PAD patients and clinicians regarding the relative efficacy and risks associated with each antithrombotic regimen in preventing cardiovascular events/death and limb loss in patients with PAD.

Previous large, randomised trials (CAPRIE, COMPASS, VOYAGER) compared the investigational product to aspirin monotherapy [15–17,20], which is not the preferred agent for the medical management of PAD [3,24]. No published RCT has directly compared clopidogrel to rivaroxaban plus aspirin in patients with PAD, while searches of ClinicalTrials.gov and 'The ISRCTN registry' on October 26, 2021 demonstrated that there is no RCT comparison of these antithrombotic medications in patients with PAD currently underway or being planned.

As detailed in Section 8.4, a PPI group has been involved in the development and improvement of this protocol, highlighting the timeliness and importance of this research to people living with PAD. These objectives align with recent research priority setting exercises conducted by the Vascular Society of Great Britain and Ireland, in conjunction with the James Lind Alliance and the Circulation Foundation, to identify the top research questions deemed most important to both patients and clinicians [26]. This research study aims to provide answers relevant to the number 1 priority research question in the clinical domains of both PAD and lower limb amputation. Furthermore, patients with PAD are mostly older people with multiple long-term conditions (multimorbidity) which is a current research priority for the NIHR, as laid out in the Strategic Framework for Multiple Long-Term Conditions [27].

Additional subgroup analyses have been developed in line with local PPI work to ascertain if there are any subgroups which may particularly benefit from a particular option. Optimal antithrombotic regimens have the potential to prevent or reduce events impacting upon QOL, limb loss and mortality, as well as reduce resultant NHS and social care spending. Therefore, the results are anticipated to directly inform clinical decision-making, as well as updates to both national and international guidelines, to reduce harms to patients and improve the management of PAD.

## 3 THEORETICAL FRAMEWORK

The preparation of this research proposal was informed and improved by assistance from the local NIHR Research Design Service (RDS). Patient and Public Involvement (PPI) was important in the development of this protocol and is detailed in subsequent sections. Subsequent PPI work was discussed at the focus group and has been developed based on the principles set out by Cochrane and other available resources [28].

NMAs permit the comparison of interventions for a specific condition within a network of interventions. This allows the indirect comparison of interventions that may never have been directly compared in a randomised controlled trial. This is important where clinical equipoise exists between two interventions that have both been compared directly against placebo or a standard of care, but never to one another. This is particularly relevant for this NMA when considering whether clopidogrel or rivaroxaban plus aspirin is superior for the medical management of PAD. As described above, both regimens have been directly compared to aspirin, the historical standard of care, but never to one another. A NMA will allow the indirect head-to-head comparison of these therapies. The underlying concepts behind NMAs are extensively laid out in the Cochrane handbook [28]

The proposed research will comply with the latest “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) statement, and conducted according to the processes set out in the “Cochrane Handbook for Systematic Reviews of Interventions” [28,29].

## 4 RESEARCH QUESTION/AIM(S)

To understand the relative efficacy and safety of previously investigated antithrombotic medications in preventing major cardiovascular events, limb loss, mortality and bleeding events in patients with lower limb PAD. A secondary aim is to investigate whether different patient groups have superior outcomes from different antithrombotic regimens.

### 4.1 Objectives

#### Primary objectives

1. Define the relative efficacy and hierarchy of efficacy of all antithrombotic medication regimens, previously investigated in RCTs, at reducing the risk of major adverse cardiovascular events (MACE), in patients with PAD.
2. Define the relative efficacy and hierarchy of efficacy of all antithrombotic medication regimens, previously investigated in RCTs, at reducing the risk of major adverse limb-related events (MALE), in patients with PAD.
3. Define the relative efficacy and hierarchy of efficacy of all antithrombotic medication regimens, previously investigated in RCTs, at reducing the risk of death from any cause, in patients with PAD.
4. Define the relative risk and hierarchy of risk of all antithrombotic medication regimens, previously investigated in RCTs, of serious adverse events (AEs) including fatal bleeding, gastrointestinal bleeding, intracranial bleeding, severe bleeding into any major organ, bleeding requiring blood transfusion and/or return to theatre, and bleeding requiring admission to hospital, in patients with PAD.

#### Secondary objectives

5. Define the relative risk and hierarchy of risk of all antithrombotic medication regimens, previously investigated in RCTs, of any other recorded adverse drug effects, in patients with PAD.
6. Define the relative compliance to differing antithrombotic medication regimens, previously investigated in RCTs, in patients with PAD.
7. Explore the available data for differential efficacy and/or risks of all antithrombotic medication regimens (objectives 1-4), previously investigated in RCTs, in different subgroups including by gender, age, ethnicity, disease status (asymptomatic/IC/CLTI), conservative versus interventional management, type of interventional management, co-morbidities (other disease states), in patients with PAD.
8. Explore whether any other subgroups of patient or disease characteristics are sufficiently well reported in the included RCTs to establish an analysis and, if so, conduct that subgroup analysis.

9. Establish whether the investigators of RCTs that form the judgement forming segments of the networks for the primary objectives are willing to collaborate and have sufficient data to undertake future individual patient network meta-analysis.

## 4.2 Outcomes

### Co-primary outcomes:

Co-primary efficacy outcome 1: composite of major adverse cardiovascular events, as defined in available literature, but to include acute coronary syndrome, ischaemic stroke, and cardiovascular death.

Co-primary efficacy outcome 2: composite of major adverse limb-related events, as defined in available literature, but to include acute limb ischaemia (and embolectomy/thrombectomy/thrombolysis), major amputation (at or above ankle), or need for peripheral revascularisation.

Co-primary efficacy outcome 3: all-cause mortality.

Co-primary safety outcome 4: major bleeding, as defined in available literature, but to include fatal bleeding, symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, bleeding causing a fall in haemoglobin level of 20 g/L or more, and/or bleeding requiring transfusion of red cells or whole blood.

### Secondary outcomes:

Secondary efficacy outcomes will include individual components of MACE and MALE outcomes; cardiovascular death, acute coronary syndrome, ischaemic stroke, major amputation, acute limb ischaemia, thrombectomy/thrombolysis, and need for a subsequent revascularisation procedure.

Secondary safety outcomes will include individual outcomes of fatal bleeding, gastrointestinal bleeding, intracranial bleeding, severe bleeding into any major organ, bleeding requiring blood transfusion and/or return to theatre, and bleeding requiring admission to hospital, venous thromboembolism, rash, discontinuation of assigned therapy for any reason, gastrointestinal symptoms resulting in discontinuation of assigned therapy. Additionally, any further drug-related AEs reported will be included to allow for the identification of unexpected AEs.

Adherence to therapy by any quantitative measure will be included, where reported.

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

This will be a systematic review and meta-analysis of antithrombotic agents for patients with peripheral vascular disease. The review will be pre-registered with the PROSPERO database and the authors aim to pre-publish the protocol, which will adhere to the PRISMA-P guidelines for systematic review protocols [30]. The study and all methods will be reported in line with the latest PRISMA guidelines and relevant extensions, including those for search strategies and NMAs [29,31,32].

### Types of studies

All published and unpublished RCT trial designs will be included. All other study designs, including cross-over study designs and non-randomised studies, will be excluded due to the high risk of bias.

### Types of participants

People with PAD will be eligible, defined as (1) symptoms and a diagnosis of PAD by a clinician with experience in PAD and/or (2) a previous procedure to treat PAD (re-vascularisation procedure or amputation) and/or (3) objective evidence of lower limb arterial malperfusion.

The ankle brachial pressure index (ABPI) is the most common objective measure of lower limb perfusion. Differing definitions of PAD exist using ABPI; for the avoidance of doubt an ABPI of  $\leq 0.9$  will be used as objective evidence of malperfusion.

No limits will be set on age, country, or previous therapy.

It is known that trials relevant to this review included patients with a variety of atherosclerotic disease phenotypes (e.g., coronary heart disease and/or ischaemic stroke in addition to PAD). Additionally, some trials are known to have included patients with carotid artery atherosclerotic disease within the PAD subgroup. These will be included provided that

- (1) a defined set of patients with symptomatic PAD was included,
- (2) one or more outcomes was specifically reported for the PAD subgroup, and
- (3) patients without lower limb PAD do not comprise greater than 25% of the PAD subgroup, but do have some other form of atherosclerotic pathology.

### Types of interventions

Trials comparing one antithrombotic regimen to another, or to placebo, will be eligible for inclusion. Antithrombotic medication regimen will be defined as any individual or combination of medications listed in the British National Formulary as an antiplatelet, anticoagulant, glycoprotein IIb/IIIa inhibitor (Appendix 1) and/or any other individual or combination of medications reporting to inhibit platelets or fibrin aggregation in thrombus formation [28]. No restriction will be placed on dose or route of administration. However, studies which combine medication regimens with non-medication-based co-interventions in a single arm will be excluded. Combinations of antithrombotic agents (for example clopidogrel with aspirin) will be analysed as separate groups to the individual agents.

Antithrombotic medications currently named in the British National Formulary are aspirin, clopidogrel, dipyridamole, prasugrel, ticagrelor, cangrelor, warfarin sodium, acenocoumarol, phenindione, apixaban, edoxaban, rivaroxaban, dabigatran etexilate, heparin (unfractionated), dalteparin sodium, enoxaparin sodium, tinzaparin sodium, danaparoid sodium, argatroban monohydrate, bivalirudin, epoprostenol, and fondaparinux [33].

### Types of outcome measures

#### Primary outcomes

## NMA of Antithrombotic Drugs in PAD

1. Major adverse cardiovascular events (MACE), composite outcome
  - Acute coronary syndrome and/or (binary)
  - Ischaemic stroke and/or (binary)
  - Major amputation and/or (binary)
  - Cardiovascular death (binary) and/or
  - Other MACE outcomes as defined in included literature (binary)
2. Major adverse limb-related events (LACE), composite outcome
  - Acute limb ischaemia and/or (binary)
  - Thrombectomy/thrombolysis and/or (binary)
  - Major amputation (at or above ankle) and/or (binary)
  - Need for peripheral revascularisation and/or (binary)
  - Other major adverse limb-related outcomes as defined in the included literature (binary)
3. All-cause mortality (binary)
4. Major bleeding, composite outcome
  - Fatal bleeding and/or (binary)
  - Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or (binary)
  - Bleeding causing a fall in the haemoglobin level of 20 g/L or more and/or (binary)
  - Bleeding leading to transfusion of two or more units of whole blood or red cells and/or (binary)
  - Other major bleeding outcomes as defined in included literature (binary).

Secondary outcomes (non-exhaustive, all available drug-related safety outcomes will be extracted).

- Cardiovascular death (binary)
- Acute coronary syndrome (binary)
- Ischaemic stroke (binary)
- Major amputation, defined as at or above ankle level (binary)
- Acute limb ischaemia (binary)
- Thrombolysis/thrombectomy (binary)
- Need for a subsequent revascularisation procedure (binary)
- Fatal bleeding (binary)
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome (binary)
- Bleeding requiring return to theatre (binary)
- Bleeding requiring admission to hospital (binary)
- Bleeding leading to a fall in the haemoglobin level of 20g/L or more
- Bleeding requiring transfusion of red cells or whole blood (binary)
- Intracranial haemorrhage (binary)
- Gastrointestinal haemorrhage (binary)
- Venous thromboembolism (binary)
- Rash (binary)

- Discontinuation of assigned therapy for any reason (binary)
- Gastrointestinal symptoms (binary)
- Adherence by any measure reported (continuous)
- Any further adverse cardiovascular outcomes reported in included literature (binary)
- Any further adverse limb-related outcomes reported in included literature (binary)
- Any further drug-related safety outcomes reported in included literature (binary).
- Understand the availability of individual patient datasets from included trials and assess feasibility of data transfer/acquisition for a future network meta-analysis at the individual patient level.

### Search methods

A search strategy was developed with an experienced information specialist and peer-reviewed by the information specialist of the Cochrane Vascular group.

The search strategy is available at <https://doi.org/10.24376/rd.sgul.21687866>.

### Selection of studies

The output of all searches will be imported into Covidence systematic review management software and screened for duplicates [34]. Once duplicates have been removed, two team members will independently screen the list of original papers by title and abstract to identify all RCTs of antithrombotic medication. For identified studies, all additional data sources will be sought utilising focussed searches for further published articles, published letters, trial registry entries, and requests for clinical study reports submitted to medical regulatory authorities. These documents will be bundled and screened in totality against the eligibility criteria by two independent, blinded reviewers. The reviewers will attempt to resolve any disagreements once unblinded and a third reviewer will act as a tie breaker where no resolution can be reached by discussion.

### Data extraction and management

The full data analysis plan is available at <https://doi.org/10.24376/rd.sgul.21688040>

Team members will extract the data from the full text and supplementary materials of included studies into a pre-piloted data collection form in Covidence developed in collaboration with the statistician. Data on RCT design, participant baseline characteristics, study interventions, methods, all reported study outcomes, results, and the authors' conclusions will be extracted and recorded as detailed in the Cochrane handbook.

Where PAD patients represent a subgroup of the overall study population, data will be collected for both the study population as a whole and the PAD patient subgroup where available. Details of the PAD subgroup including disease status and proportion of carotid artery disease patients will also be recorded. This will permit a sensitivity analysis of the likelihood that using whole-study data rather than subgroup-specific data would introduce bias within the analysis of AEs. Where multiple timepoints in follow-up are reported, the longest timepoint shall be used for all outcomes, with subsequent sensitivity analyses exploring the effect of the timepoint of outcome measurement.

For all binary outcomes, the preferred data to collect will be absolute numbers of events and numbers at risk. If the absolute number of events is not reported, risk or odds ratios with defined confidence intervals and/or standard error will be the first alternative. For continuous outcomes, the mean and standard deviation of the group will be the first choice of measure.

### Risk of bias assessment

Two study members will independently assess all included trials for risk of bias using the Cochrane-recommended Risk of Bias 2 (ROB 2) tool [35]. Risk of bias assessments will be undertaken by individuals with domain and meta-analysis experience. Areas of uncertainty in these assessments will look to be resolved by reference to collateral information sources as described above (trial registries and regulatory submissions) and contact with the primary investigators if necessary. A risk of bias assessment will be undertaken separately for primary outcome analyses and subgroup analyses.

### **Measures of treatment effects**

Risk ratios will be calculated for binary outcomes of included studies. If the absolute number of events is not available, risk or odds ratios with defined confidence intervals and/or standard error will be the first alternative. A time to event analysis is not anticipated to be a potential analysis due to the expected complexity of the network.

For continuous outcomes, the mean and standard deviation of the group will be the first choice of measure.

### **Unit of analysis issues**

Analyses will be conducted at the individual level. It is not anticipated that any trials will report data in another manner regarding this, however advice will be sought from the statistician should this occur.

### **Missing data**

Only published data will be analysed. Missing data will be considered within the risk of bias assessment.

### **Transitivity**

Recruitment criteria differ between the RCTs and as such the transitivity assumption may be threatened. This is particularly the case when considering trials of stable PAD compared with trials of peri-/post-procedural PAD. The validity of the transitivity assumption will be assessed quantitatively by considering the incoherence factor, which involves the comparison of direct and indirect effective estimates for each pair-wise comparison in the network, where they both exist); this will be evaluated using both the local and global strategies detailed in the Cochrane handbook [28].

### **Assessment of reporting**

Aspirin is expected to be a common comparator within RCTs in this NMA, which will facilitate exploration of publication bias using comparison-adjusted funnel plots [36]. The team has considered selective reporting within trials throughout the study design phase and will qualitatively consider the effect of this during subsequent phases.

### **Data synthesis**

Included studies will be summarised including the direct comparisons made, population characteristics, and characteristics of those patients with PAD. The medication regimen for both overall and PAD populations will be summarised separately.

Antithrombotic regimens will be grouped into common nodes based on the drugs used in that arm. A network diagram will be constructed for each outcome, where the size of each node is proportional to the number of patients assigned to that intervention, and the thickness of each line is based on the inverse of the variance of the direct comparison. Interventions that are absent from a particular network will be highlighted.

Analysis of primary and secondary outcomes will be undertaken on a whole network basis, subject to the checks of assumptions outlined above, wherever networks can be formed based on published data. All NMAs will create pairwise comparisons of medication regimens, and a ranking of all medication regimens will be produced with risk of bias estimates published alongside. Subgroup analyses are discussed further below.

We anticipate a complex NMA based upon prior knowledge. The analysis is planned by the statistician (CH) in R Statistical Software (v4.1) [37], primarily using the *netmeta* package [38]. It is possible that the transitivity assumption may be violated by RCT recruitment criteria, particularly when comparing trials of stable PAD and trials of peri-procedural PAD. If so, a separate network shall be established to allow meaningful analysis of these studies.

### Subgroup analysis

The PPI group highlighted the importance of being able to provide individualised recommendations to patients. Therefore, the intent is to extract all published results for subgroups and perform all NMAs that are possible. Anticipated subgroups are PAD disease state (such as IC & CTLI), sex, age, ethnicity, key co-morbidities, and peri-procedural status. We also intend to analyse any other subgroups that have sufficient data published but are not anticipated.

Subgroup analyses as described above, will be undertaken wherever sub-networks can be formed based on published data. The inclusion of these sub-analyses will likely be susceptible to non-reporting bias as they are less likely to have formed part of the original RCT per-protocol analysis plan. Candidate interventions that are absent due to non-publication of a particular subgroup analysis will be clearly identified.

### Sensitivity analysis

Pre-specified sensitivity analyses will include:

- Separate analysis of patients with stable and periprocedural PAD. This is to ascertain whether the optimal antithrombotic regimen differs for patients who have recently, or who have not recently, undergone a vascular procedure.
- Analysis of adverse event outcomes limited to reported trial subgroups of patients with PAD only. This is to ascertain whether adverse event rates in trials of mixed atherosclerotic disease e.g. CHD and stroke, as well as PAD, are applicable to the PAD population.
- Analysis of the primary outcomes restricted to studies at low risk of bias.
- Analysis by dose of antithrombotic agents, where these differed between trials. This is because we anticipate variable dosing strategies, particularly of aspirin, which may affect adverse event rates.
- Comparison of the primary outcomes at shorter and longer timepoints, where these were reported. This is to ascertain whether the optimal antithrombotic regimen may change over time for patients with PAD.

Further post-hoc sensitivity analyses may be developed and reported transparently in the final report.

### Confidence in cumulative evidence

A summary of findings table will be constructed for the key outcomes, including MACE, MALE, all-cause mortality, major amputation as an individualised outcome, and major bleeding. The underlying quality of evidence for each of these outcomes will be assessed according to the GRADE framework for NMAs, which classifies interventions by both the relative treatment effect size and certainty of evidence.

## **6 STUDY SETTING**

This is a systematic review and does not require any further primary data collection. Studies meeting eligibility criteria in all settings will be included, as described in Section 5.

## **7 SAMPLE AND RECRUITMENT**

### **7.1 Eligibility Criteria**

N/A

#### **7.1.1 Inclusion criteria**

Discussed in Section 5.

#### **7.1.2 Exclusion criteria**

Discussed in 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

### 7.3.3 Data collection tool

As discussed in Section 5, data will be extracted into a pre-piloted data-extraction form to be developed with the statistician.

### 7.3.4 Biological Sample Handling

N/A

## 8 ETHICAL AND REGULATORY CONSIDERATIONS

This is a systematic review and data will be collected from existing published literature. No additional ethical approval is required.

Some of the following standard text (as per the local SGUL/SGH NHS Foundation Trust protocol template) is not applicable to this study, which is a meta-analysis of secondary data. For clarity, we have added a strike-through to the sections that are not applicable.

### 8.1 Assessment and management of risk

This is a systematic review and so does not pose additional risk to any individual.

#### 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.

## **8.3 Peer review**

This systematic review has undergone multiple rounds of peer review as part of the NIHR grant application.

## **8.4 Patient & Public Involvement**

### **PPI to date**

As outlined in Section 2, Rationale, a focus group of people with lived experience of PAD was formed to gain insight and support the development of this research. Participants were keen to continue to be involved with this research. The main themes emerging were:

- In keeping with the general deficiency in national awareness and education regarding PAD, they were surprised to hear the high risks of other cardiovascular events associated with PAD.
- They felt that most patients would ask a doctor to recommend which antithrombotic to use, but would expect the doctor, if asked, to offer clear information regarding how each potential treatment compares in order to support patient decision making. All had heard of NICE and found the existence of their antithrombotic guidelines in PAD reassuring.
- They were shocked and disappointed that two NICE guidelines could produce recommendations for different antithrombotic medications for PAD without making it clear how one was to be selected over the other.

- They agreed that we should undertake research to inform which antithrombotic was best and the quantification of the difference in risks was important to allow patient/doctors to make informed choices now. If this is to be undertaken it made sense to do it for as many scenarios in a patient journey as possible at the same time.
- They felt that being alive without disabling complications including stroke, heart attack or amputation were the most important outcomes.
- They felt that any results of the research should be as personalised to individual patient characteristics if possible, favouring this over the simplicity of a single recommendation for all PAD patients.
- They advocated for targeted involvement of PAD patients in the research at key decision points and were willing to support the study in this way.

### Planned further PPI

Following data extraction, included studies will be assessed for the risk of bias, as described above, and a visual representation of the network for each outcome will be created. This, along with the risk of bias and difference in patient demographics of each included study will be discussed at a PPI group. This will allow the assessment of the perception of the PPI group about the quality of evidence included in the study. It will also allow public members to raise concerns about the quality/quantity of evidence that is potentially going to inform decision about treatment options recommended. This will occur prior to the analyses being run, thereby avoiding potential bias from the outcome of the NMA.

The results of the analysis are likely to be numerous and complex in their nature. Time has also been scheduled for a PPI focus group to discuss the outcome of the analysis and distil the results down to a meaningful level for patients and members of the public to interpret. This is intended to facilitate dissemination and ensure that patients with PAD can make an informed decision about the best management for them with their doctor. A summary of these PPI findings will be reported jointly with the analysis.

### 8.5 Protocol compliance

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

All protocol deviations must be adequately documented 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 sponsored research:**

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 data generated by this study will be an essential output. As detailed below, all data collected from screening, risk assessments, study results, and statistical coding to produce the published results will be made available, open access, on the lead applicant's institutional research data repository on completion. This will be important to facilitate the review of the NICE guidance that it is anticipated this study may trigger. A link to the data repository will be provided in the PROSPERO record for the systematic review. The authors also aim to make the search strategy available in full, open access, via the PROSPERO record.

## **9 DISSEMINATION**

### **9.1 Dissemination plan**

#### Publications

The work in this project is anticipated to represent at least two publications. A protocol paper will be submitted to an appropriate open access journal. This will be linked to the search strategy, which will either be published independently or made available via the lead applicants institutions' research data repository. Our research protocol will be prospectively published not only as a hallmark of a high-quality review, but to also clarify the prospective nature of the planned subgroup analyses.

The complex and detailed findings may warrant multiple papers. The authors anticipate that the primary will be published, open access, in a high impact cardiovascular journal. Further publications will also be submitted, open access, to other cardiovascular journals.

#### Data storage

The data generated from this research will be an essential output. The data collected from screening, risk assessments, study results, and statistical coding to produce the published results will be made available on the lead applicants institution research data repository to ensure ongoing future access. This will facilitate significant research efficiencies if/when future trials become available, and the analysis requires updating. ~~Any individual patient data obtained is likely to be subject to data sharing agreements and ethical considerations and as such is unlikely to be shareable at individual patient~~

~~level. We would seek to establish a~~ This resource will be able to be added-to, re-evaluated, or re-analysed with future trial data.

### Clinical Impact

The results will be presented to clinical domain specialists at UK vascular and endovascular conferences. Presentations will be made to key stakeholders including NICE, vascular and endovascular societies, the James Lind Alliance, the Circulation Foundation, and the all-party parliamentary group for vascular and venous disease. The lead applicants' institutions public relations team will be employed to maximise the visibility and availability of the results, both to patients and clinicians, through social and traditional media. The results will be disseminated through the UK national societies of vascular specialists and general practitioners to maximise the impact on clinical practice. The authors anticipate that the results of the research would be sufficient to trigger a review of the current NICE guidelines.

### Patient Impact

The patient accessible report will be submitted to UK vascular disease charities, such as the Circulation Foundation and the British Heart Foundation, for publication on their websites.

## **9.2 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.

### **9.3 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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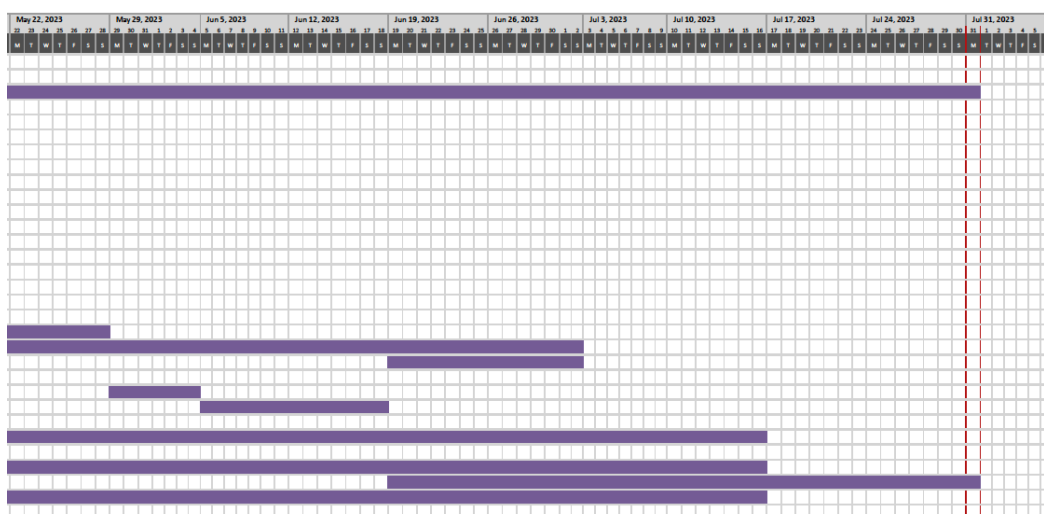
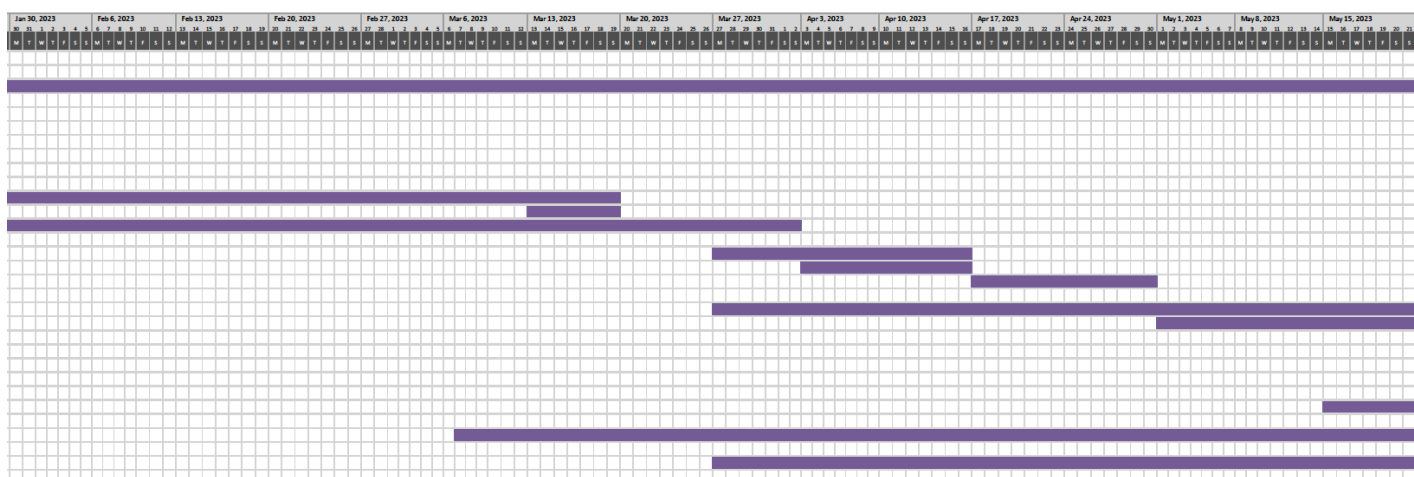
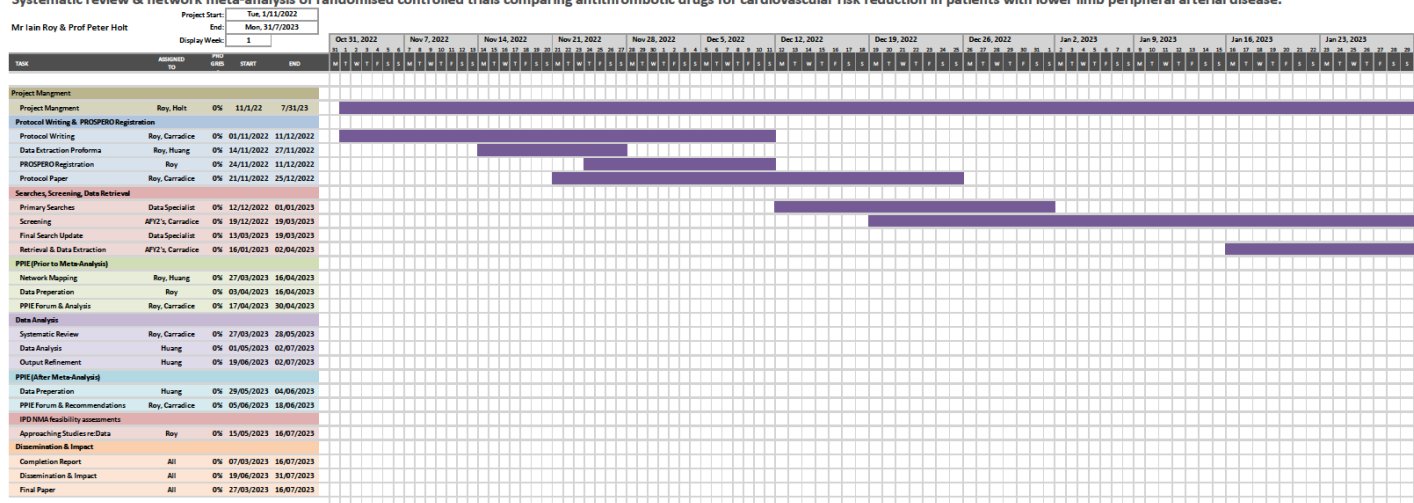
# NMA of Antithrombotic Drugs in PAD

## 11. APPENDICIES

### 11.1 Appendix 1: Gant chart for project

Systematic review & network meta-analysis of randomised controlled trials comparing antithrombotic drugs for cardiovascular risk reduction in patients with lower limb peripheral arterial disease.

Mr Iain Roy & Prof Peter Holt



## 11.2 Appendix 2

Amendment Log				
Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
0	1.0	2022-Nov-01	NA	Available at <a href="https://doi.org/10.24376/rd.sgul.21591216.v1">https://doi.org/10.24376/rd.sgul.21591216.v1</a>
1	2.0	2022-Jun-15	I.Roy	1. PROSPERO ID added to page 1 2. Research staff errors on page 4-6 updated. 3. Link to search strategy added page 14 4. Link to analysis plan added page 14

## 11.3 Appendix 3

Complete the form below. It will require review and sign-off by the Institute Director (SGUL) or the Care Group Lead (SGHFT).

## 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.

<b>Study Title/Acronym:</b>	NMA of Antithrombotic Drugs in PAD
<b>JRES Reference Number:</b>	RES2022-308
<b>Chief Investigator Name:</b>	Mr Iain N Roy
<b>Chief Investigator Email Address:</b>	iroy@sgul.ac.uk

PROJECT DETAILS
<b>Project / process description:</b> - 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.
No personal data nor special category personal data will be collected or processed during this systematic review, therefore a DPIA is not required.
<b>What personal data do you intend to use, and why? (List all categories)</b>
No personal data nor special category personal data will be collected or processed during this systematic review, therefore a DPIA is not required.
<b>Will the personal data be identifiable, pseudonymised or anonymised (if a mix tick accordingly)</b>

## NMA of Antithrombotic Drugs in PAD

Identifiable		
*Pseudonymised		
Anonymised	x	
<i>*Confirm that the key to this data is kept securely away from the used data with strict controlled access</i>		
<b>List all organisations / agencies which will have access to the personal data collection used for this project / process</b>		
No Personal Data		
<b>Length of the study – include an assessment of the necessity and proportionality of the processing in relation to the purpose. Also include who, internally &amp; externally, has been consulted in the preparation of this DPIA.</b>		
<b>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?</b>		
<b>RISK</b>		
<b>Can you achieve your objectives using anonymised data? – see ICO Code of Practice on Anonymisation</b>		
Yes		
No		Why not?
<b>What are the benefits to the individual of their personal data being used for this purpose?</b>		
<b>What are the organisational benefits of the individual's personal data being used for this purpose?</b>		
<b>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?</b>		
<b>How will you avoid causing unwarranted or substantial damage/distress to the individual when using their personal data for this purpose?</b>		
<b>Is the data already held by St George's?</b>		
Yes		
No		
<b>Is it held by one of the partner organisations / agencies involved in this process/project?</b>		
Yes		

No		Which agency will be collecting the data	
<b>Have you told the individuals whose personal data you want to use for this purpose, how and why you intend to use their data?</b>			
Yes			
No			
<b>If not, are you intending to tell them?</b>			
Yes			
No		Why not?	
<b>Do you already have the individual's consent to use their data for this purpose?</b>			
Yes			
No		Why not?	
<b>If not, are you going to ask for their permission?</b>			
Yes			
No		Why not?	
<b>Have individuals been given the opportunity to refuse us permission to use their data for this purpose?</b>			
Yes			
No			
<b>How will you make sure that the personal data you are using is kept accurate and up to date?</b>			
<b>What steps or controls are you taking to minimise risks to privacy?</b>			
<b>Please tick those which apply and provide details of how each is ensured</b>			
<ul style="list-style-type: none"> <li>• Risks to individual privacy are minimal</li> <li>• Personal data is pseudonymised</li> <li>• Encryption of data at rest, i.e. when stored</li> <li>• Encryption used in transfers</li> <li>• Information compliance training for staff has been completed - data protection, information security, FOI</li> <li>• Adherence to privacy by design principles</li> <li>• Special category personal data is not used</li> <li>• Participant opt out at any stage of the research</li> <li>• Personal data kept in the UK</li> <li>• Research is not used to make decisions directly affecting individuals</li> <li>• Short retention limits</li> <li>• Restricted access controls</li> <li>• Other (please specify)</li> </ul>			
<b>How long will you need to hold the personal data for after the study has completed?</b>			

How will you make sure that you are holding data for the appropriate length of time and no longer?		
How will the data be held /stored?		
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?		
Will personal data be transferred/shared between the organisations involved in this project? If so how?		
Will you be transferring personal data to a country or territory outside of the UK? <i>If yes, name countries and receiving parties.</i>		
Yes – within EEA	<input type="checkbox"/>	
Yes – outside of EEA	<input type="checkbox"/>	
No	<input type="checkbox"/>	
How will you ensure that third parties will comply with data protection obligations?		
What measures are in place to ensure only appropriate and authorised access to and use of, personal data?		
How will technical and organisational security be monitored/audited?		

## 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:

Signature:

Date:

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

Name:

Signature:

Date:

**JRES Reviewer**

Name:

Signature:

Date: