Study Title: PLatelet f**U**nction in patients undergoin**G** major, non-cardiac, vascular **S**urgery (PLUGS) – a prospective cohort study.

Internal Reference Number / Short title: Platelet function in major vascular surgery

Ethics Ref: 21/WM/0254

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Funder:	National Institute of Academic Anaesthesia & The Vascular Anaesthesia Society of Great Britain & Ireland
Chief Investigator Signature:	

Statistician Signature: N/A

The study group declare that there are no potential conflicts of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

TABLE OF CONTENTS

1. KEY CONTACTS

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Funder(s)	National Institute of Academic Anaesthesia & The Vascular Anaesthesia Society of Great Britain & Ireland
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Statistician	N/A
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2. LAY SUMMARY

Platelets are cells that help blood to clot. This process may become abnormal and the clots formed by platelets may block off important blood vessels, resulting in strokes and heart attacks. This is more common in patients who are older and who have high blood pressure or diabetes. As a result, many of these patients are prescribed antiplatelet medications, such as aspirin and clopidogrel. These drugs prevent formation of dangerous blood clots but may increase the risk of bleeding when a person undergoes an operation.

Many patients who require major operations of the blood vessels (vascular surgery) are taking antiplatelet medications. On the day of surgery, they may require an epidural for pain relief. An epidural is an injection in your back that blocks the nerves carrying pain from the area being operated on. It is generally a safe procedure which provides excellent pain relief. One rare risk is bleeding into the injection site, which can have potentially devastating complications such as paralysis. Bleeding into the epidural injection site is estimated to occur in 1 in every 150,000 cases. The risk is thought to be higher in patients who are on antiplatelet medications and therefore guidelines recommend stopping some antiplatelet medications for between 5 and 7 days before an epidural injection. However, this is not based on high-quality research and stopping these medications, even for a brief period, can result in patients being at higher risk of stroke or heart attack.

For patients in whom the risks of stopping antiplatelet medications before surgery are deemed too high, epidural analgesia may not be a safe option. However, little is known about how individual people respond to these medications. Some research suggests that antiplatelet medications may not work in a third of patients. Epidural analgesia may be a suitable option for these patients. Expert committees have called for more research on identifying these patients.

The aim of our study is to better understand the true effects that antiplatelet medication has on circulating platelets in the blood. We will use novel methods of analysing platelet function. We will aim to recruit 80 patient participants across four study groups who are scheduled to undergo major vascular surgery at the John Radcliffe Hospital, Oxford. We will require two to three teaspoons of blood from patients who have agreed to take part. This blood would be taken during routine pre-operative assessment clinic visits and again on the day of surgery. No drugs will be given as part of the study and the remainder of the study data will be collected from routine healthcare records.

This study will help us to design a larger study to see if we can change treatment plans for patients taking antiplatelet drugs so we can offer them epidural analgesia whilst also reducing the risk of bleeding and having a heart attack or stroke around the time of surgery.

3. SYNOPSIS

Study Title	**PL**atelet function in patients **U**ndergoin**G** major, non-cardiac, vascular **S**urgery (PLUGS) – a prospective cohort study.		
Internal ref. no. / short title	Platelet function in major vascular surgery (PLUGS)		
Study registration	We will register this study on ISRCTN following ethical approval and prior to recruitment of first participant.		
Sponsor	University of Oxford Boundary Brook House, Churchill Drive, Headington, Oxford, OX3 7GB		
Funder	NIAA / VASGBI		
Study Design	Prospective cohort study		
Study Participants	Age >18 years, scheduled to undergo elective, major non-cardiac, vascular surgery		
Sample Size	80 participants across four study groups (i) aspirin only; (ii) clopidogrel alone; (iii) dual antiplatelet therapy; and (iv) no antiplatelets (control group) (20 in each group)		
Planned Study Period	10 January 2022 – 31 May 2023		
Planned Recruitment period	10 January 2022 – 01 May 2023		
	Objectives	Outcome Measures	Timepoint(s)
Primary	To characterise platelet function,	1. Percentage of patients with antiplatelet drug	1. ‘Baseline’ (POAC visit)

	using the TEG6S assay	resistance at initial presentation to POAC. 2. Percentage of patients with platelet inhibition on the morning of surgery.	2. 'Timepoint 1' (day of surgery)
Secondary	To evaluate patient compliance with preoperative antiplatelet therapy. To investigate the association between perioperative platelet function and postoperative outcomes	Proportion of patients who self-report as being compliant with antiplatelet medications preoperatively. Compliance will be defined as taking >80% of prescribed doses as prescribed. Peri-operative blood loss, changes in haemoglobin concentration and transfusion requirements in the first 24 hours; return to theatre for bleeding in the first 24 hours and/or graft/stent thrombosis in the first 24 hours; peri-operative thrombotic events within 30 days of surgery; bleeding complications associated with regional anaesthesia; days-alive-and-out-of-hospital at 30 days (DAOH-30).	'Baseline' (POAC visit) 'Timepoint 2' (24-hour follow up) and 'Timepoint 3' (up to day-30 postoperatively)
Exploratory	To explore concentrations of von Willebrand factor (vWF)	Proportion of patients with low vWF antigen or vWF antigen in the normal range (0.5–1.50 iu/mL)	Blood sampling at 'Baseline' (POAC visit)
Intervention(s)	Non-interventional study		
Comparator	N/A		

4. ABBREVIATIONS

ASA	American Society of Anesthesiologists
CI	Chief Investigator
CRF	Case Report Form
DAOH	Days alive and out of hospital
FBC	Full Blood Count
GCP	Good Clinical Practice

HRA	Health Research Authority
ISRCTN	International Standard Randomised Controlled Trial Number
NHS	National Health Service
NIAA	National Institute of Academic Anaesthesia
OHTC	Oxford Haemophilia and Thrombosis Centre
OUHFT	Oxford University Hospitals NHS Foundation Trust
RES	Research Ethics Service
PI	Principal Investigator
POAC	Pre-operative Assessment Clinic
REC	Research Ethics Committee
SOP	Standard Operating Procedure
TEG	Thromboelastography
UE	Urea and Electrolytes
VASGBI	The Vascular Anaesthesia Society of Great Britain & Ireland
vWF	von Willebrand factor

5. BACKGROUND AND RATIONALE

Most patients presenting for vascular surgery are prescribed antiplatelet medication for the primary or secondary prevention of cardiovascular disease. These medications, in particular clopidogrel, represent a frequent challenge to anaesthetists, particularly when regional anaesthesia is being considered.

The problem of antiplatelet therapy and regional anaesthesia

An epidural haematoma is a potentially devastating complication of neuraxial anaesthesia. However, it is also a rare complication, with an estimated incidence (95%CI) of 1.6 (1.0–3.7) events per 100,000 cases (1). Guidelines currently recommend a one-size-fits-all discontinuation of clopidogrel 5–7 days prior to surgery to reduce the risk of bleeding, but also before attempting to insert an epidural catheter in order to mitigate the risk of developing an epidural haematoma (2, 3). These recommendations are based on low quality (Level C) evidence consisting mainly of case series and do not take into consideration the individual variability in pharmacodynamic responsiveness or different platelet recovery profiles following discontinuation of clopidogrel (4). Furthermore, approximately 32% of patients on clopidogrel may be non-responders because of their impaired ability to metabolise the pro-drug clopidogrel to its active metabolite (5).

Withholding antiplatelet medications may result in catastrophic stent thrombosis. Withholding peri-operative regional anaesthesia may increase postoperative complications and compromise postoperative analgesia and early mobilisation (6, 7). Patients undergoing major vascular surgery are likely to have extensive co-morbidities, and in certain patients, particularly those with underlying lung disease, the benefits of offering epidural anaesthesia/analgesia may outweigh the rare risk of an epidural haematoma (8). This may be a viable option as one retrospective, single-centre study from the USA reported no cases

of postoperative neurological symptoms from the use of epidural analgesia in 306 patients undergoing major vascular surgery in whom clopidogrel was not withheld pre-operatively (9).

Measurement of platelet function may help guide decision making
There is a growing body of evidence evaluating the relationship between measured platelet function and bleeding in patients on clopidogrel, or similar agents undergoing non-cardiac surgery (10–12). However, patient compliance with antiplatelet therapy was not reported in these studies. The gold standard method of assessing platelet function is light transmission aggregometry, but this is a time-consuming, labour-intensive method and requires a large volume of blood in comparison with other methods. Thromboelastography 6S (TEG6S) provides near patient, real-time information on the viscoelastic properties of clot formation, along with information on platelet mapping and percentage inhibition, and has been approved for clinical use (13).

The glycoprotein, von Willebrand factor (vWF), is essential for platelet adhesion. Increasing vWF levels may compensate for platelet dysfunction (15) and is under investigation for reversal of antiplatelet drugs in intracerebral haemorrhage (16). A better understanding of the relationship between vWF levels and platelet function may identify patients who could benefit from therapeutic interventions such as desmopressin.

Rationale for this study
Previous studies have included heterogenous surgical patients. Data on the relationship between platelet function and implications for regional, in particular epidural, anaesthesia are lacking. The study by Orla et al. (9) is a useful starting point but has drawn criticism, especially as no evaluation of platelet function was performed. Current practice on the provision of regional anaesthesia in patients on antiplatelet therapy who are undergoing major vascular surgery in the United Kingdom is also not known. There is ample evidence to suggest that clinicians may not always adhere to clinical guidelines (17, 18).

In view of these uncertainties, the leading question in a research priority setting exercise conducted by The Vascular Anaesthesia Society of Great Britain & Ireland (VASGBI), was – “Can regional anaesthesia safely be performed on patients taking clopidogrel and similar antiplatelet agents”. Our study will provide the first step towards answering this question.

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To characterise platelet function, using the TEG6S assay, in patients scheduled to undergo elective major, non-cardiac vascular surgery.	1. Percentage of patients with antiplatelet drug resistance at initial presentation to POAC. 2. Percentage of patients with platelet inhibition on the morning of surgery.	1. ‘Baseline’ (POAC visit) 2. ‘Timepoint 1’ (day of surgery)

Secondary Objectives		
To evaluate patient compliance with preoperative antiplatelet therapy.	Proportion of patients who self-report as being compliant with antiplatelet medications preoperatively. Compliance will be defined as taking >80% of prescribed doses as prescribed.	'Baseline' (POAC visit)
To investigate the association between perioperative platelet function and postoperative outcomes.	Peri-operative blood loss, changes in haemoglobin concentration and transfusion requirements in the first 24 hours; return to theatre for bleeding in the first 24 hours and/or graft/stent thrombosis in the first 24 hours; bleeding complications associated with regional anaesthesia; perioperative thrombotic events within 30 days of surgery; days-alive-and-out-of-hospital at 30 days (DAOH-30).	'Timepoint 2' (24-hour follow up) and 'Timepoint 3' (up to day-30 postoperatively)
Exploratory Objectives To explore concentrations of von Willebrand factor (vWF).	Proportion of patients with low vWF antigen or vWF antigen in the normal range (0.5–1.50 iu/mL).	Blood sampling at 'Baseline' (POAC visit)

7. STUDY DESIGN

This is a prospective, non-interventional, cohort, pilot study that will be undertaken at the John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust. We aim to recruit 80 participants across four groups who are scheduled to undergo elective, major non-cardiac, vascular surgery. This includes participants who are prescribed antiplatelet medication and will be split into the following groups: (i) aspirin alone, (ii) clopidogrel alone or (iii) dual antiplatelet therapy for primary/secondary prevention of cardiovascular disease as well as a control group of participants (iv) who are not on any antiplatelet therapy.

As part of routine care, patients who are on aspirin – group (i) - are advised to continue it until the day before surgery. Patients on clopidogrel are advised to stop taking it 7 days prior to surgery and switch to aspirin instead – group (ii). Patients who are on clopidogrel and aspirin – group (iii) - and who have experienced a stroke or myocardial infarction requiring stenting within the preceding 6 months are advised to continue clopidogrel until surgery and the case is discussed a senior anaesthetist. This information will be collected from participants and/or their medical notes for the study.

Participants will be enrolled at the 'Baseline' pre-operative assessment clinic (POAC). We will collect peripheral blood samples for research purposes at enrolment ('Baseline' visit). In addition, we will also collect blood samples on the day of surgery ('Timepoint 1'). Clinical data will be collected at enrolment

('Baseline'), day of surgery ('Timepoint 1'), 24 hours after surgery ('Time point 2') and at 30 days after surgery ('Time point 3'). A study flow chart is shown in **Appendix A**.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Participants (age >18 years old) who are scheduled to undergo elective, major non-cardiac, vascular surgery.

8.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Aged 18 years or above.
- Scheduled to undergo major non-cardiac vascular surgery (including, but not restricted to, abdominal aortic aneurysm (open or endovascular), carotid endarterectomy, lower limb arterial revascularisation)
- For participants taking antiplatelet therapy: (i) aspirin alone, (ii) clopidogrel alone or (iii) dual antiplatelet therapy groups, at least 7 days of prescribed antiplatelet therapy prior to study recruitment. Patients who are on other antiplatelet therapy, but from the same therapeutic class as either aspirin or clopidogrel, will be allocated to that particular group.
- Participants in a control group (iv) should not have been on any antiplatelet therapy

8.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Congenital / inherited bleeding disorders
- Haemodialysis-dependent chronic kidney disease
- Enrolled into a study where an intervention may affect platelet function – this would be discussed on a case-by-case basis between the study Chief Investigators

9. PROTOCOL PROCEDURES

A schedule of study procedures is shown in **Appendix B**.

9.1. Recruitment

This study will be carried out at the John Radcliffe Hospital, which is the central hub for the Thames Valley Vascular Surgery Network.

Delegated clinical care staff, including POAC nurses, will screen for potential participants during clinics and MDT meetings, and check relevant medical records to identify eligible participants. Potential participants will then be sent a study invitation letter prior to their attendance at the POAC or at POAC in

cases where clinical timelines do not allow for earlier contact (as in the case of the patients scheduled to undergo carotid endarterectomy within 2 weeks for a transient ischaemic attack (NICE Guidance NG128).

9.2. Screening and Eligibility Assessment

All identified patients will be allocated a screening number and entered into the screening log, which will be kept in the Investigator Site File (ISF). The screening log will contain reasons for exclusion and the reasons why those that were eligible were not approached for consent.

Demographics, medical history, planned surgical procedures and concomitant medications, in particular any antiplatelet therapy, will be screened to identify eligible participants. Each participant must satisfy all the approved inclusion and exclusion criteria of the protocol.

9.3. Informed Consent

Potential participants should have received a study invitation letter prior to their attendance at POAC. This will ensure that potential participants will have had sufficient time to read about the study and consider taking part. The participant will have the opportunity to question the Investigator or other independent parties to decide whether they will participate in the study.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

This a non-interventional study without any changes to routine care. The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Chief/Principal Investigator. One copy of the signed Informed Consent will be given to the participant and another copy will be added to the participant's medical notes. The original signed form will be retained at the study site.

9.4. Randomisation

This is not a randomised study. Enrolled participants will be allocated a unique study identification number.

9.5. Blinding and code-breaking

There is no blinding in this study.

9.6. Description of study intervention(s), comparators and study procedures (clinical)

9.6.1. Description of study intervention(s)

There are no interventions as part of this study.

9.6.2. Description of study procedure(s)

After informed consent, venous blood sampling will be performed at time points listed in Appendix A. further information is given in sections 9.7-9.9.

9.7. Baseline Assessments

Baseline clinical data:

- Confirmation with inclusion and exclusion criteria
- Participant demographics
- ASA status
- Pre-existing comorbidities, including reasons for antiplatelet therapy
- Planned surgical procedure
- Adherence to any antiplatelet therapy (self-reported) – study groups (i) – (iii)

Baseline laboratory data:

- FBC, UEs, Coagulation screen – these will be available as part of routine care

Research blood samples:

- TEG6S (CE marked) assay – to determine platelet inhibition rate
- vWF antigen levels

9.8. Subsequent Visits

Timepoint 1 – Day of surgery

Clinical data:

- Changes to any antiplatelet therapy from Baseline (POAC) visit for groups (i) to (iii)
- Time (days) between POAC visit and surgery
- Details of anaesthesia including mode of anaesthesia, including any regional techniques.
- Relevant surgical details including approach (e.g. open versus endovascular), cross-clamp time, total surgical time

Research blood samples:

- TEG6S assay

Timepoint 2 – 24-hours postoperatively

Clinical data:

- Perioperative blood loss (ml) as estimated by surgical team and total of any drain outputs

- Return to theatre for bleeding
- Graft/stent thrombosis defined as complete radiological occlusion and/or requiring re-operation
- Blood and blood product transfusion requirements – defined as need for a transfusion (i.e. Yes or No) and number of units transfused (incl. red cells, platelets, fresh frozen plasma etc)

Laboratory data

- Changes in haemoglobin from baseline visit to first laboratory measured Hb in 24 hours post-op – these will be available as part of routine care

Timepoint 3 – 30-days postoperatively

Clinical data:

- Peri-operative thrombotic events – see **Appendix C** for definitions
- Acute limb ischaemia – sudden decrease in limb perfusion that threatens limb viability
- Bleeding complications associated with regional anaesthesia, defined as haematoma causing neurovascular compromise and/or bleeding requiring intervention (e.g. compression or radiological intervention)
- Days-alive-and-out-of-hospital at 30 days (DAOH-30)

9.9. Sample Handling

Study specific blood samples will be taken at the POAC visit (Baseline), and on the day of surgery (Timepoint 1) by an appropriately trained member of the research team. None have to be drawn under fasting conditions. The total volume of blood will be approximately 10 mls (5ml taken at each visit). In order to minimise patient discomfort, blood sampling will occur during aspects of routine care where possible e.g. whilst obtaining blood samples for routine POAC bloods, after cannulation prior to induction of anaesthesia.

9.9.1 Sample handling for study purposes

TEG6 assays will be run in accordance with the manufacturer's guidelines by a trained member of the research team in the operating theatres of the John Radcliffe Hospital, OUHFT. These will be run within 20-40 minutes of being taken. Plasma samples for vWF will be frozen at -80C and stored in the Oxford Haemophilia and Thrombosis Centre (OHTC), OUHFT. They will be analysed in batches at the end of the study at OHTC.

Any surplus plasma samples will be stored for any potential future ethically approved studies in the UK at the end of the study if the participant consented to this. The study team and other delegated members specified in the investigator site file will have access to the samples. A dedicated SOP for sample handling and processing will be followed.

9.10. Early Discontinuation/Withdrawal of Participants

During the course of the study a participant may choose to withdraw early from the study treatment at any time. This may happen for several reasons, including but not limited to:

- Inability to comply with study procedures
- Participant decision

Participants may choose to stop treatment and/or study assessments but may remain on study follow-up.

Participants may withdraw from active follow-up and further communication but allow the study team to continue to access their medical records and any relevant hospital data that is recorded as part of routine standard of care (e.g. clinical outcome data, laboratory results). This will be explained in the participant information sheet and consent form.

In addition, the Investigator may discontinue a participant from the study treatment at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Clinical decision

The type of withdrawal and reason for withdrawal will be recorded in the CRF. Withdrawn participants will not be replaced. Data and samples collected up to the point of withdrawal will be retained. The type of withdrawal and reason for withdrawal will be recorded in the CRF.

9.11. Definition of End of Study

The end of study will be when the 30-day follow-up for the last recruited participant has taken place.

10. SAFETY REPORTING

Safety reporting is not applicable to this study as it is a non-interventional study, without any changes to routine care.

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

The plan for the statistical analysis of the study are outlined below. There is not a separate SAP document in use for the trial.

11.2. Description of the Statistical Methods

The primary outcome is the percentage of patients with antiplatelet drug resistance pre-operatively at POAC attendance and on the morning of surgery. For aspirin – group (i), drug resistance will be defined as an arachidonic acid (AA)-induced platelet-fibrin clot strength (MA_{AA}) > 47 mm plus an AA-induced platelet inhibition rate < 50% (18). For $P2Y_{12}$ inhibitors (clopidogrel) – group (ii), drug resistance will be defined as an adenosine diphosphate (ADP)-induced platelet-fibrin clot strength (MA_{ADP}) > 47 mm plus an ADP-induced platelet inhibition rate < 50%.

11.3. Sample Size Determination

Our centre performs more than 300 major vascular cases per year. In this pilot study, we will aim to recruit 80 participants over 52 weeks (1–2 participants per week on average) and compare platelet inhibition across each of the following study groups: (i) aspirin only; (ii) clopidogrel alone (iii) dual antiplatelets; and (iv) no antiplatelets (which will act as a control group). Based on previous work (10), we will include 20 participants in each group. The information obtained from this study will be used to inform the sample size calculations for a future, multicentre study.

Categorical data will be presented as absolute and relative frequencies, whereas continuous data will be presented either as mean (standard deviation) or as median (interquartile range) as appropriate. Fisher's exact test, the independent samples t-test or the Mann–Whitney U test will be used to determine differences in percentage platelet inhibition across the study groups. Repeated measures ANOVA will be used to compare platelet inhibition in participants who required sampling to two timepoints. Analyses will be stratified on patient compliance and whether antiplatelet therapy was continued or stopped.

11.4. Analysis populations

Analyses will be conducted on the intention-to-treat and per-protocol populations. As this is a small study, effect estimates are likely to have wide confidence intervals and consequently inferences will be tentative and reported as such.

11.5. Decision points

After 40 participants, we will undertake an interim analysis to ensure that we are enrolling participants in each of our prespecified study groups detailed in Section 11.3.

11.6. Stopping rules

There are no formal stopping rules for this study.

11.7. The Level of Statistical Significance

Tests will be two-sided and considered to provide evidence for a significant difference if p-values are less than 0.05.

11.8. Procedure for Accounting for Missing, Unused, and Spurious Data.

Reasons for missing data, loss to follow-up and participant withdrawals will be carefully considered, reported and assessment for that type of random ‘missingness’ will be made. Missing data will be minimised by collecting the minimum amount of data required and collecting data from routine healthcare records. All data queries will be resolved prior to analysis.

11.9. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Deviations are not anticipated. The analysis outline in this protocol will be followed. Any deviations from this will be reported in the final study report.

11.10. Health Economics Analysis

There are no planned health economic analyses.

12. DATA MANAGEMENT

The plan for the data management of the study are outlined below. There is not a separate Data Management document in use for the study.

12.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), and clinical and laboratory records.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

12.3. Data Recording and Record Keeping

All study data will be entered on a research database platform – 'RedCAP', an internationally recognised standard for study database management. This will be hosted on servers managed by the University of Oxford. The participants will be only be identified by a unique study ID code in the database.

The CI will be data custodian for a separate master list that will link the study ID and participant personal data. This master list will be kept and maintained securely on a protected server. Four patient identifiers will be used – patient name, date of birth, NHS number and hospital number. These identifiers will be used to enable data collection for the 30-day postoperative timepoint.

Personal data will be held for a maximum of 12 months after the study has ended. All research data will be anonymised and will be stored for up to 5 years.

13. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13.1. Risk assessment

No formal risk assessment will be undertaken as this a non-interventional study without any changes to routine clinical care.

13.2. Study monitoring

Not applicable.

13.3. Study Committees

The Study Management Group will be responsible for the day to day running and the management of the study. The team will aim to meet at least every two weeks during the planning and initial start-up stages of the study and less frequently when the study is running.

14. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

15. SERIOUS BREACHES

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3. Approvals

Following Sponsor approval the protocol, informed consent form, and participant information sheet will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4. Other Ethical Considerations

The risks of our invasive procedure (blood sampling) are minimal. Patients attending POAC usually have blood samples collected as part of their routine care and this study requires the collection of a small volume of additional without detriment to their medical condition. We will also aim aspirate blood during cannulation or from central / arterial lines if required on the day of surgery. Venepuncture attempts will only be performed by appropriately trained staff.

Time for consent is another ethical consideration. We will send potential participants an invitation letter prior to their attendance at POAC to allow them to have sufficient time to consider participation in the study.

16.5. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

16.6. Transparency in Research

Prior to the recruitment of the first participant, this study will have been registered on a publicly accessible database (ISRCTN).

16.7. Participant Confidentiality

The study will comply with the UK General Data Protection Regulation (UK GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.8. Expenses and Benefits

Not applicable.

17. FINANCE AND INSURANCE

17.1. Funding

Funding for this study has been obtained from the National Institute of Academic Anaesthesia & The Vascular Anaesthesia Society of Great Britain & Ireland (WKR0-2020-0017).

17.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the National Institute of Academic Anaesthesia & The Vascular Anaesthesia Society of Great Britain & Ireland. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Not applicable

19. ARCHIVING

Data will be stored in a secure server after the study has ended. Paper data will the stored in the Trial Master File in secure locker access in the Nuffield Department of Anaesthesia, John Radcliffe Hospital. Anonymised research data will be kept for a minimum of 5 years.

20. REFERENCES

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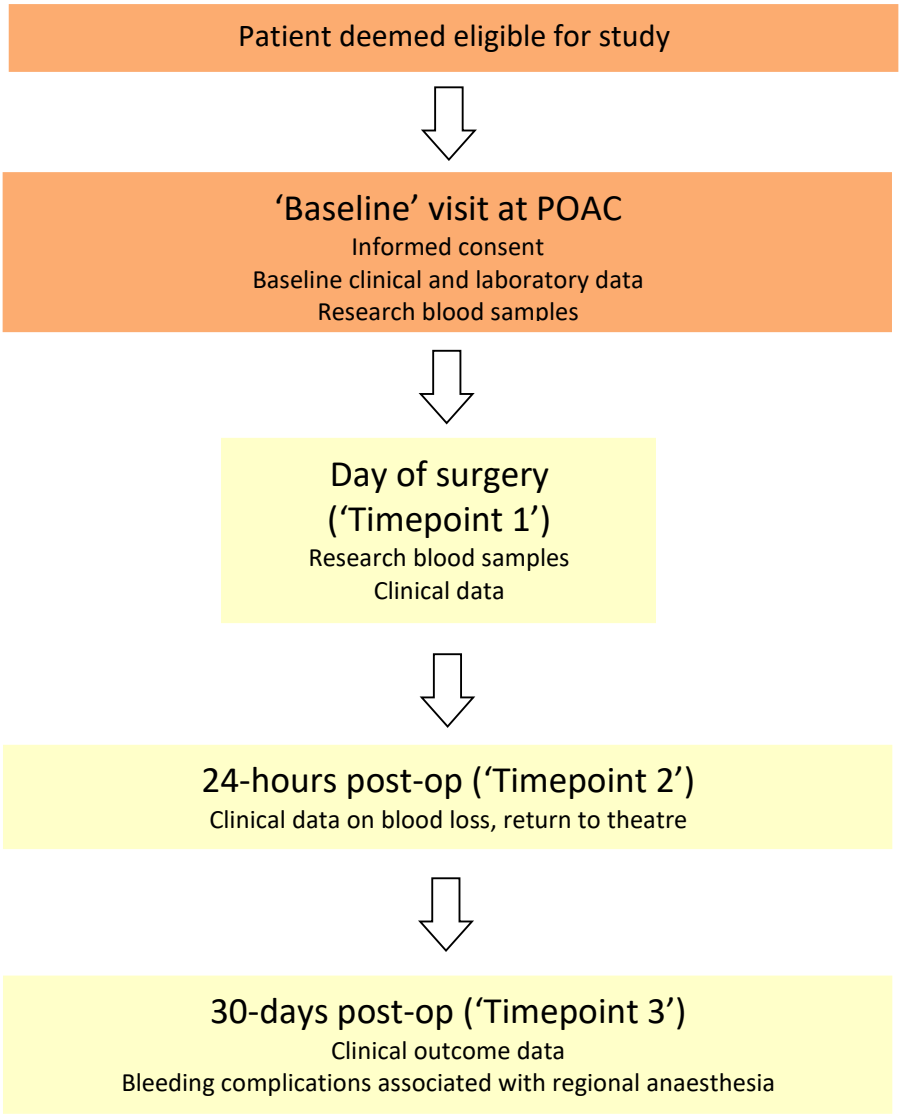
21. APPENDIX A: STUDY FLOW CHART



22. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Procedures	**Visit timing POAC**	**Timepoint 1**	**Timepoint 2**	**Time point 3**
	Baseline	**Day of surgery**	**24-hours post-op**	**Day 30 post-op**
Informed consent	X			
Demographics	X			
Medical history	X			
Research blood samples	X	X		
Clinical data	X	X	X	X

23. APPENDIX C: DEFINITIONS OF PERI-OPERATIVE THROMBOTIC EVENTS

Myocardial infarction will be defined as detection of an elevated cardiac troponin with at least one value above the upper reference limit in the context of myocardial ischemia and at least one of the following:

- Symptoms of myocardial ischaemia;
- New ECG changes indicative of ischaemia (for example ST segments changes or new left bundle branch block) or development of new T wave inversion or pathological Q waves
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Ischaemic stroke will be defined as evidence of a new infarction on a CT scan of the head and new neurologic deficit lasting at least 24 hours

Venous thromboembolism will be defined as deep venous thrombosis confirmed by compression ultrasound, CT venogram or MR venogram; Pulmonary embolism confirmed by high probability ventilation perfusion scan or CT pulmonary angiogram' splanchnic vein thrombosis confirmed by CT abdomen or MRI of abdomen; or cerebral venous sinus thrombosis confirmed by CT venogram.

24. APPENDIX D: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1.	2.0	12 Sep 2022	Akshay Shah (CI)	Minor change to Section 9.1 Recruitment on potential participants in whom clinical timelines do not allow sending of an invitation letter.
2.	3.0		Akshay Shah (CI)	Change to study end date

List details of all protocol amendments here whenever a new version of the protocol is produced. This is not necessary prior to initial REC / HRA submission. Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee and HRA (where required).

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