**FULL/LONG TITLE OF THE STUDY**

Multi-parameter analysis of platelet function: the impact of cardiometabolic disease: The **RE**adin**G** plat**E**let fun**C**tion stud**Y** - REGENCY

**PROTOCOL VERSION NUMBER AND DATE**

Version 2.1 (14-12-2020) – Protocol Version and Date listed in IRAS A5-1

**RESEARCH REFERENCE NUMBERS**

|  |  |
| --- | --- |
| **IRAS Number: 285583** |  |
| **SPONSORS Number:** |  |
| **FUNDERS Number:** |  |

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

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| **For and on behalf of the Study Sponsor:** | | |
| Signature:  .............................................................................................. |  | Date: ....../....../...... |
| Name (please print):  .............................................................................................. |  |  |
| Position: .............................................................................................. |  |  |
| **Chief Investigator:** | | |
| Signature: .............................................................................................. |  | Date: ....../....../...... |
| Name: (please print):  .............................................................................................. |  |  |

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# KEY STUDY CONTACTS

|  |  |
| --- | --- |
| Chief Investigator | Professor Jonathan Gibbins  Institute for Cardiovascular and Metabolic Research, School of Biological Sciences, University of Reading, Harborne Building, Whiteknights, Reading RG6 6AS.  Tel. +44  (0)118 3787082 (Direct) Fax: +44 (0) 118 9310180 |
| Study Co-ordinator | Mark Brunton (Senior Research Nurse Royal Berkshire Hospital) |
| Sponsor | University of Reading,  Whiteknights Campus, Reading, Berkshire  RG6 6AS |
| Joint-sponsor(s)/co-sponsor(s) | N/A |
| Funder | The British Heart Foundation |
| Protocol Author (s) | Professor Jon Gibbins, University of Reading  Abigail Whyte, Royal Berkshire NHS Foundation Trust |
| Key Protocol Contributors | Professor Jon Gibbins, University of Reading  Dr Neil Ruparelia, Royal Berkshire NHS Foundation Trust  Dr Charlie McKenna, Royal Berkshire NHS Foundation Trust  Abigail Whyte, Royal Berkshire NHS Foundation Trust  Jessica McKean, Royal Berkshire NHS Foundation Trust  Alex Bye, University of Reading |
| Committees | TVCTU |

**STUDY SUMMARY**

|  |  |
| --- | --- |
| Study Title | Multi-parameter analysis of platelet function: the impact of cardiometabolic disease |
| Internal ref. no. (or short title) | Multi-parameter analysis of platelet function |
| Study Design | Lab, Single Centred Study |
| Study Participants | Patients will be under investigation for stable ischaemic heart disease, which, as part of their clinical care are scheduled for diagnostic or CT coronary angiography; with or without Ischaemic Heart Disease; and with or without Diabetes Mellitus. |
| Planned Size of Sample (if applicable) | 400 – 100 in each cohort  Cohort 1: Control Group without DM  Cohort 2: Control Group with DM  Cohort 3: IHD without DM  Cohort 4: IHD with DM |
| Follow up duration (if applicable) | N/A |
| Planned Study Period | 5 years |
| Research Question/Aim(s) | To establish whether IHD, and further to this, T2DM, are associated with changes in platelet function.  To determine whether phenotype profiles are altered in cardiometabolic diseases and may be exploited in personalised/stratified medicine |

**FUNDING AND SUPPORT IN KIND**

|  |
| --- |
| **FUNDER** |
| The British Heart Foundation |

**ROLE OF STUDY SPONSOR AND FUNDER**

The sponsor of this study is the University of Reading. The responsibilities of the sponsor are: overseeing the implementation of the study throughout its process. They do not control the final decision regarding any of the aspects of the study individually; this is a collaborative project between the University of Reading and Royal Berkshire NHS Foundation Trust, so final decisions will be made between the two institutes.

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

Prior to the recruiting process, public facing documents (patient information sheet, informed consent form and any other relevant documents), will be shown to members of the public. This will allow identification of any changes that need to be made to the documents if necessary, and whether they are patient friendly.

Further to this, within the patient information sheet, it will state that results can be disseminated at the end of the study if the patient requests so.

**PROTOCOL AUTHORS**

Professor Jon Gibbins, Professor of Cell Biology at University of Reading

**Necessary** Abigail Whyte, Research Assistant at Royal Berkshire Hospital

**PROTOCOL CONTRIBUTORS**

Dr Neil Ruparella, Consultant Cardiolgist at Royal Berkshire Hospital

Dr Charlie McKenna, Consultant Cardiologist at Royal Berkshire Hospital

Abigail Whyte, Research Assistant at Royal Berkshire Hospital

Jessica McKean, Clinical Research Facilitator at Royal Berkshire NHS Foundation Trust

Dr Alex Bye, University of Reading

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**STUDY PROTOCOL**

Multi-Parameter Analysis of Platelet Function: The Impact of Cardiometabolic Disease

# 1 BACKGROUND

Drugs that target platelets to suppress their functions are clinically proven to reduce the risk of thrombotic disease in many patients, and have made a considerable contribution to the 75% decline in the death rate from heart and circulatory disease since the creation of the British Heart Foundation in 1961. Anti-platelet medications, however, are without benefit in many patients, and this is reflected in high UK mortality rates from thrombotic disease. For example in 2017 coronary heart disease and ischaemic stroke were responsible for approximately 66,000 and 36,000 deaths, respectively. Notably, anti-platelet medications are also associated with serious side effects such as bleeding.

Platelets isolated from different people display variability in responsiveness to physiological activators such as collagen, ADP and thrombin although how this correlates to efficacy of anti-platelet medication is not understood. At present a ‘one size fits all’ approach is used to target platelets with drugs, without considering whether treatment strategies can be tailored to suit patients more specifically. To more effectively target and treat patients at high risk of thrombosis, we need to understand the nature of variability in platelet function in the population, how this may change with underlying cardiometabolic disease, and the molecular basis of these differences so that personalised therapy may be applied using existing or future medication.

In our current BHF Programme Grant we have established methodology for detailed high throughput deep platelet function analysis, and incorporated machine-learning techniques to scrutinise multi-parameter data to phenotypically cluster healthy blood donors into distinctive groups. In this renewal application we propose to exploit this knowledge and new tools to determine whether phenotype profiles are altered in cardiometabolic diseases and may be exploited in personalised/stratified medicine.

# 2 RATIONALE

Patients with diabetes mellitus have a higher risk of developing cardiovascular disease and also have poorer clinical outcomes following acute events (e.g. acute myocardial infarction). The aims are to increase understanding of the impact and mechanisms of platelet function that lead to worse outcomes associated with metabolic dysfunction which is common in this patient group. This is expected to benefit patient care in a number of ways: (1) the establishment of personalised care pathways for specific patients, allowing patient stratification and therefore more effective therapy, (2) use of knowledge of how platelet function and regulation in obesity-related metabolic dysfunction to identify specific defects that may be targeted with new pharmacological strategies, and (3) the identification of new drug targets for these patients. It is not anticipated that this study will benefit the patients that volunteer to take part, but the study will provide a legacy that will improve the treatment of future patients.

**3 THEORETICAL FRAMEWORK**

a) Metabolic dysfunction is associated with an increase in platelet function.

b) The impact of metabolic dysfunction or platelet function in cardiovascular disease patients has not been studied.

c) Sensitive assays have been developed to study platelet function in patients that have not previously been done.

# 4 RESEARCH QUESTION/AIM(S)

An over-arching aim of the proposed study is to develop new ways to assess the potential need for anti-platelet therapy and to use this for targeted approaches in specific patients, to enable greater efficacy of currently available medication, while also facilitating the development, testing and use of new anti-platelet agents

**4.1** **Objectives**

(i) to establish the impact of cardiometabolic disease on platelet phenotypic group profile and determine whether healthy and cardiometabolic disease patients differentiate into discrete sub-populations based on phenotypic profile and responses to specific anti-platelet medication,

(ii) to determine the impact of phenotypic groups on thrombus formation and experimentally induced thrombosis, and

(iii) to establish the molecular bases of differential platelet reactivity within healthy and diseased individuals.

**4.2 Outcome**

Provide important understanding of how variation in platelet function in the population impacts on the occurrence of thrombotic disease and responsiveness to anti-platelet medication

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

This is a lab based observational, single centred study, in patients with coronary artery disease and diabetes mellitus. Blood samples will be collected in the Cardiology or Radiology department, and immediately transported to the laboratory within the Harborne Building the University of Reading, where a member of Professor Gibbins’ team will begin analysing the sample. Below describes the analysis techniques that will be carried out in the laboratory.

All samples will bear an anonymisation code that will prevent data from being attributed to a specific participant. The research coordinators will possess the coding system which will be stored securely in paper form. Data will be stored in anonymised form at the University of Reading on dedicated computers with secure non-network-accessible backup. Data will not be communicated by email, and will not be stored on cloud-based storage platforms. Computer storage will be in encrypted form.

# 6 STUDY SETTING

***Analysis of platelet function and blood components:***

**Platelet aggregation:** Platelet aggregation will be measured using isolated washed platelets and platelet-rich plasma from the cohorts by optical aggregometry to enable the kinetics and extent of aggregation to be observed. A range of agonists (ADP, collagen, collagen-related peptide, thrombin, U46619) and agonist concentrations will be used. Analysis of the initial kinetics of aggregation will be performed in addition to analysis of aggregation levels/stability over extended periods (up to 10 minutes) to assess early and late phases of aggregation. A newly developed high-throughput application of optical aggregometry [14](#_ENREF_14) that is established at Reading will also be used to maximise possible data from small blood samples to enable thorough functional profiling from patient cohorts.

**Platelet surface receptor expression levels:** In order to analyse the effects of IHD on platelet function, it will be necessary to establish whether this affects normal platelet function. The expression levels of key platelet receptors will be assessed by flow cytometry and compared with that of our normal control cohort. Standard haematological parameters including platelet number and mean platelet volume will be obtained from the patients’ full blood count (FBC) performed during their routine hospital visit. The erythrocyte sedimentation rate (ESR) will also be determined to monitor inflammation. Both the FBC and ESR will be performed using the same blood sample (EDTA vac-container).

**Platelet procoagulant activity:** activated platelets may exteriorise phosphatidyl serine (PS) that provides a surface for the assembly of the prothrombinase complex, and therefore the localised generation of thrombin and fibrin generation. Annexin V binding to platelets (which itself binds to PS) will be assessed by flow cytometry.

**Fibrinogen binding:** Platelet aggregation and thrombus formation is supported through up-regulation in affinity of integrin αIIbβ3 on platelets. Here, integrin αIIbβ3 affinity modulation will be assessed through the measurement of fibrinogen binding to platelets by flow cytometry.

**Platelet alpha-granule secretion (**P-selectin exposure**):** Secretion from α-granules will be measured by quantification of the exposure of P-selectin, the cell adhesion molecule, which resides in α-granules and is released to the platelet surface during platelet activation. An established flow cytometry assay will be used.

**Platelet adhesion to collagen:** Platelet adhesion to collagen may be monitored under static conditions in a 96-well plate, following the labelling of platelets with calcein and measured by spectrofluorimetry.

**Thrombus formation (*in vitro*):** Thrombus formation may be examined using whole blood from patient cohorts including controls to assess the impact of IHD on platelet thrombus formation studied *in-vitro* under arterial flow conditions. This will establish whether aspect\aspects of thrombus formation (e.g. platelet adhesion, activation, thrombus growth and stability) are modified in IHD. Whole blood will be labelled with the lipophilic fluorescent dye DiOC6 and perfused over collagen coated within Cellix Vena8 microfluidic flow cells. During perfusion, various parameters of thrombus formation will be measured by confocal microscopy to assess the rate, size, structure and stability of thrombi formed.

***Analysis of platelet cell signalling***

Following the stimulation of platelets with activators of platelet function, cells will be lysed, cleared of any cellular debris, and protein extracts stored frozen. Should changes in platelet function be observed associated with IHD, this will allow later detailed analysis of the molecular mechanisms that control platelet function. The following measurements, guided by the outcomes of functional analysis of platelets may be included in these analyses.

**Protein tyrosine phosphorylation:** Platelets will be stimulated in the presence of eptifibatide to prevent aggregation, lysates prepared and total levels of tyrosine phosphorylation assessed following stimulation with collagen, collagen-related peptide (CRP), thrombin, ADP and U46619 by immunoblot analysis. Comparisons will be made between levels of tyrosine phosphorylation in each of the patient groups.

**Platelet signalling pathway analysis:** The levels of activation of key proteins within the GPVI signalling pathways will be assessed by immunoblot analysis following stimulation with collagen, thrombin or ADP. The specifics of which proteins will be measured will be dependent on the outcomes of experiments and agonist but will be likely that the tyrosine phosphorylation of the FcR γ-chain, Syk, LAT and PLCγ2 will be assessed. In addition AKT phosphorylation (Ser473), a measure of phosphoinositide 3-kinase (PI3K) signalling, and levels of PKC activity will be assessed using phospho-substrate-specific antibody. These represent integration points with signalling pathways stimulated by secondary agonists, and therefore these and intracellular Ca2+ mobilisation will be measured following stimulation with platelet agonists. It is possible that inhibitory cyclic nucleotide-dependent (cAMP, cGMP) inhibitory platelet signalling is affected. This will be determined through analysis of the protein VASP using immunoblotting and phosphospecific antibodies. Integrin αIIbβ3 affinity modulation will be measured by flow cytometry using the activation-selective antibody PAC-1.

**Analysis of coagulation factors and plasma constituents:** Coagulation factors and other plasma constituents will be measured in plasma samples prepared and stored following collection of blood from patient cohorts, including controls, to assess the impact of IHD and diabetes on expression levels. Coagulation factors will be measured using a multiparameter haemostasis analyser. The specifics of which plasma constituents will be measured will be dependent on the outcomes of experiments, but will include biomarkers of cardiovascular health and molecules known to influence platelet function such as soluble GPVI, oxidised LDL and thromboxane B2,

**Long term storage of samples**

Platelet analysis will begin using fresh blood samples within 2 hours of donation. Cells will not be stored beyond these experiments. Platelet protein extracts, containing no cellular debris may be stored frozen for later analysis of cell signalling mechanisms. While sample documentation, booking in and out and inventory will conform to HTA standards, this type of storage does not require use of an approved HTA storage facility.

**Data Analysis**

All data will be stored and analysed in anonymised form.

Analysis of data will depend on the form of data to be analysed and whether this is normally distributed and whether parametric or non-parametric tests should be applied. Statistical advice from the CTU will be gained on appropriate methodologies as required, although in most cases, methods such as ANOVA and student’s t-test would be appropriate.

**7 SAMPLE AND RECRUITMENT**

**7.1 Eligibility Criteria**

**7.1.1 Inclusion criteria**

* Patients will be under investigation for stable ischaemic heart disease, which, as part of their clinical care are scheduled for diagnostic or CT coronary angiography.

**7.1.2 Exclusion criteria**

* Patients who have had ACS in the past 12 months
* Patients on P2Y12 inhibitors (including Clopidogrel, Ticagrelor and Prasugrel)
* Patients on treatment dose anti-coagulation, including warfarin or novel anti-coagulant drugs (NOACS).
* Patients with other metabolic dysfunction
* Evidence of alcohol or drug misuse.
* Patients unable to give informed consent
* Patients under 18 years of age
* Pregnancy
* Active or recent malignancy (<1 years) or on active treatment
* Any underlying haematological pathologies
* Renal disease (EGFR <30)
* Liver Cirrhosis

**7.2 Sampling**

Blood samples will be taken from participants during their visit to the cardiology or radiology department. Up to 50mL of blood will be taken on each occasion (no overnight fast will be required). A blood sample will be attained by the patient’s clinical team during their angiogram appointment through venous access. Around 10 participants in each cohort will be invited to return for repeat blood sampling either at the Royal Berkshire Hospital or the University of Reading. Body composition measurements may also be taken.

**7.2.1 Size of sample**

Previous studies in healthy donors (150 participants in Reading, 550 in Cambridge) identified 8 stable (pvclust, n=50,000, P<0.001) subpopulations (each containing 10% to 18% of the total study population) including one with a low platelet function phenotype that was associated with metabolic disease markers. Using this group to estimate power and effect sizes (in this case for BMI) for comparing disease markers between phenotype groups within a single study arm (effect size 0.996, α err. prob. 0.05, power 90%) 84 individuals would be required for each arm of the study.  We therefore propose to recruit up to 100 participants in each arm, to ensure sufficient power to identify differences between phenotypic subpopulations.

**7.2.2 Sampling technique**

All patients having an angiogram as part of routine care within the Royal Berkshire Hospital will be screened for the study to find if they are eligible for the study (see exclusion criteria 7.1.2). This will be completed by the Cardiology Research team at the hospital, which currently consists of: Consultant Cardiologists, Charge Nurse and Research Assistant.

**7.3 Recruitment**

The study visit will be carried out during the patient’s planned clinical visit to the Royal Berkshire Hospital for their angiogram. The investigation will be carried out by the Cardiology team and the research participation will not alter the normal clinical progress of the participant’s investigation. Patients recruited will be having an angiogram as part of their standard care.

The additional components to the angiogram, including asking potential participants, with their consent, to take blood samples at their visit and to record the details of the clinical procedure, will be performed by trained study investigators, identified on the delegation log. With the informed consent of the participant, the researchers will also collect medical information relevant to the research from the referral letter and medical records regarding the relevant medical history of the participant, such as history of high blood pressure, current relevant medication, height and weight, smoking status, diabetes history, age and evidence of coronary artery disease from previous investigations.

Participants will first be approached about the study via telephone contact and subsequently by sending a participant information sheet in the post, to be received up to a fortnight and no less than the day before their angiogram taking place. A member of the research team will then go to speak to the patient on the day of their procedure to answer any questions that the patient may have and receive their informed consent prior to the procedure.

Participants will be provided with a copy of the relevant Participant Information Sheet in advance and the signed consent form for their information and records, copies of each will be added to their medical records.

The study team will also recruit a small number of volunteers who will be available throughout the length of the study, in order to test the continued quality of the chemicals and equipment used.

**7.3.1 Sample identification**

The research programme will be led by Professor Jonathan Gibbins at the University of Reading (chief investigator). Participants will be recruited from the Cardiology Department at the Royal Berkshire Hospital in Reading by the delegated research team members. Patients will be identified in advance by reviewing elective angiogram lists.

A research team member based at the Royal Berkshire hospital will assist with recruitment and organisation of appointments and sample dates. Samples will be processed by a member of the research team based in Professor Gibbins’ laboratory at the University of Reading. Professor Gibbins’ research group has expertise in the study of platelet function and its regulation in health and disease.

The research team will have access to medical records in order to record any other medication used by subjects during the study, adverse events, disease progression and blood test results, including HbA1C values.

**7.3.2 Consent**

Prior to the patient being approached for the study, an assessment of capacity will be carried out by a member of the study team. For consent to be ethical and valid in law, participants must be capable of giving consent for themselves for this study. A capable person will: understand the purpose and nature of the research; understand what the research involves, its benefits (or lack of benefits), risks and burdens; understand the alternatives to taking part; be able to retain the information long enough to make an effective decision; be able to make a free choice; be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity); where participants are capable of consenting for themselves but are particularly susceptible to coercion, it is important to explain how their interests will be protected. Capacity will be reassessed prior to any recall visits.

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, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. 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 will be suitably qualified and experienced, and have been authorised to do so by the Chief Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

# 8 ETHICAL AND REGULATORY CONSIDERATIONS

## **Declaration of Helsinki**

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

## **Guidelines for Good Clinical Practice**

The Investigator will ensure that this study is conducted in full conformity with relevant regulations.

## **Approvals**

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), the Health Research Authority (HRA) and host institution(s) for written approval.

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

Approval will be sought for NIHR portfolio adoption.

## **Reporting**

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

## **Participant Confidentiality**

The study staff will ensure that the participants’ anonymity is maintained. The participants will be identified only by initials and a participants ID number on any electronic database. Documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with General Data Protection Regulation (GDPR) and Data Protection Act 2018, which requires data to be anonymised as soon as it is practical to do so. Personal identifying information of participants will be destroyed as soon as it is practicable to do so.

## **Expenses and Benefits**

Around 10% of each cohort will be asked to attend for additional blood tests at the hospital or University, as preferred by the patient; in this circumstance recalled patients will be reimbursed for travel expenses. Those who only have blood samples taken at their angiogram appointment will not have their expenses covered by the study team.

## **Language provisions**

Some investigators speak additional languages, and can translate where appropriate. It will not be feasible to provide other translation services, and so where a potential participant cannot adequately understand the study information they will not be included in the study.

## **Storage of Blood Samples**

It will be made clear to participants in the PIS and as part of the informed consent process how blood samples they provide will be used for this study and stored.

**QUALITY ASSURANCE PROCEDURES**

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

**8.1 Assessment and management of risk**

Patients who are recalled will have a small increased venepuncture risk. Risk will be managed as the procedure will be undertaken by trained staff.

If it becomes apparent that while collecting sensitive data from the patient, there is potential risk/ harm to them, it will be raised to the suitable body for safeguarding. This is to mitigate harm to the patient. To mitigate harm, information would be shared with the safe guarding champion at the Royal Berkshire Hospital.

*Risk to Researchers/Other Staff:* Taking blood carries a risk of needle stick injury to the phlebotomist, which in turn carries a risk of exposure to blood borne infections. This risk will be minimised by a) ensuring staff are adequately trained, b) ensuring staff have been vaccinated against, and show immunity to Hepatitis B, and c) having a local policy for needle stick injury which describes the process of being assessed for and receiving post exposure prophylaxis.

**8.2 Research Ethics Committee (REC), Health Research Authority (HRA) and other Regulatory review & reports**

A favourable opinion will be sought from REC for the study protocol, informed consent forms, participant information sheets, GP letters and other relevant study documents.

HRA and Health Care Research Wales (HCRW) approval will be sought for the study on the basis described in the application form, protocol and supporting documentation.

* Substantial amendments that require review by REC/HRA will not be implemented until that review is in place and other mechanisms are in place to implement at site.
* All correspondence with the REC/HRA will be retained.
* It is the Chief Investigator’s responsibility to produce the annual reports as required.
* The Chief Investigator will notify the REC of the end of the study.
* 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 and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.
* Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

**Regulatory Review & Compliance**

The Chief Investigator/Sponsor has ensured 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.

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.

Amendments

If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor’s responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

If applicable, other specialist review bodies (e.g. Confidentiality Advisory Group (CAG)) need to be notified about substantial amendments in case the amendment affects their opinion of the study.

Amendments will also be notified to the [national coordinating function of the UK](http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/preparing-amendments/) country where the lead NHS R&D office is based and communicated to the participating organisations (R&D office and local research team) departments of participating sites to assess whether the amendment affects the NHS permission for that site. Note that some amendments that may be considered to be non-substantial for the purposes of REC still need to be notified to NHS R&D (e.g. a change to the funding arrangements).

**8.3 Peer review**

This project has been reviewed and approved by the Chairs and Programme Grants Committee of the British Heart Foundation

**8.4 Patient & Public Involvement**

Patients will be involved in the design of the participant information sheet and any other patient facing documents to ensure that it is easy to understand and user friendly.

**8.5 Protocol compliance**

**Protocol violation:**

A protocol violation can be defined as: Any accidental or unintentional change to, or non-compliance with the protocol that does increase risk or decrease benefit, or has a significant effect on the participant’s rights, safety, or welfare, or on the integrity of the data.

Examples of a violation include, but are not restricted to:

* Failure to obtain valid informed consent
* Breaches of eligibility criteria

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

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

**8.6 Data protection and patient confidentiality**

All personal data will be regarded as strictly confidential. The study will comply with the Data Protection Act, 1998. All study records and Investigator Site Files will be kept at site in a locked filing cabinet with restricted access.

8.7 Indemnity

The University of Reading is the Sponsor and through the Sponsor, University indemnity is provided in respect of potential liability and negligent harm arising from study management. Indemnity in respect of potential liability arising from negligent harm related to study design is provided by the substantive employers of protocol authors (HEIs/NHS).

All study sites are NHS organisations and indemnity in respect of potential liability arising from negligent harm related to study conduct at individual sites will be provided via NHS schemes.

**8.8 Access to the final study dataset**

All investigators within the study will have access to the final dataset.

### 9 DISSEMINIATION POLICY

### 9.1 Dissemination policy

The outcomes from this study will be published in leading research journals such as Blood, Circulation, JACC and Nature Medicine, and will be presented at national and international research conferences such as the European Society of Cardiology,  American Heart Association, and the International Society on Thrombosis and Haemostasis.

There are no plans to notify participants of the results. However, they are able to contact us, as stated in the participant information sheet, for a summary of the key outcomes from this study.

The data arising from the study will be owned by University of Reading and Royal Berkshire NHS Foundation Trust. The data is accessible to researchers at the University of Reading and Royal Berkshire NHS Foundation Trust.

**9.2 Authorship eligibility guidelines and any intended use of professional writers**

### All study team members will be involved in writing reports/ manuscripts.

11. APPENDICIES

**11.1 Appendix 1- Required documentation**

* Participant Information Sheet on headed paper
* Participant Informed Consent Form on headed paper
* Volunteer information Sheet on headed paper
* Volunteer Informed Consent Form on headed paper
* GP letter on headed paper
* CVs of the research team
* GCP certificates of the research team

**11.2** **Appendix 2 – Schedule of Procedures**

|  |  |  |
| --- | --- | --- |
| **Procedures** | **Visits** | |
| **Baseline** | **Recall visits (Optional)** |
| Informed consent | x |  |
| Blood sampling | x | x |
| Demographics | x |  |
| Medical history | x | x |
| Observation of condition | x | x |