Non-CTIMP Study Protocol

NON-INVASIVE CORONARY THROMBUS IMAGING TO DEFINE THE CAUSE OF ACUTE MYOCARDIAL INFARCTION

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CONTENTS

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
^{18}F-GP1	Fluoride-18 labelled glycoprotein-1
PI	Principal Investigator
QA	Quality Assurance
REC	Research Ethics Committee
SOP	Standard Operating Procedure
PET	Positron Emission Tomography
CT	Computed Tomography

1 INTRODUCTION

1.1 BACKGROUND

1.1.1 Background of coronary artery disease and acute myocardial infarction

Coronary artery disease remains the leading cause of death worldwide, with more than 23 million annual deaths estimated to occur by 2030 (1). The introduction of high-sensitivity cardiac troponin measurement has revolutionised the identification and management of patients presenting with acute chest pain and myocardial infarction. However, elevated cardiac troponin concentrations can result from both ischaemic (myocardial infarction) or non-ischaemic (myocardial injury) causes. Moreover, the further subclassification of myocardial infarction relies on the underlying aetiology of infarction which is often not readily apparent and remains a diagnostic challenge.

1.1.2 Universal definition of myocardial infarction

Acute myocardial infarction is defined as cardiomyocyte injury and necrosis in a clinical setting consistent with acute myocardial ischaemia. The fourth universal definition of myocardial infarction describes five subtypes of acute infarction (2). Type 1 myocardial infarction is characterised by underlying atherosclerotic plaque disruption (rupture, ulceration, fissuring, erosion, or calcific nodules) resulting in intraluminal thrombosis, distal coronary embolisation and intraplaque haemorrhage that ultimately cause myocyte necrosis (3, 4). In contrast, type 2 myocardial infarction is classified as an ischaemic myocardial injury secondary to oxygen supply and demand mismatch, and importantly is not a consequence of atherosclerotic plaque rupture and coronary atherothrombosis. However, some causes of type 2 myocardial infarction do involve intracoronary thrombus including coronary thromboembolism and spontaneous coronary artery dissection. Currently, invasive coronary angiography remains the primary modality to identify patients presenting with plaque related disruption and coronary thrombosis, ultimately providing the distinction between type 1 and type 2 myocardial infarction. However, it is not always definitive (5) and only 10-20% of patients presenting with type 2 myocardial infarction undergo further investigations to identify the presence of underlying coronary artery disease or to exclude coronary atherothrombosis (6). Indeed, we recently demonstrated comprehensive cardiac imaging and coronary angiography that identified two thirds of patients had previously unrecognised underlying coronary artery disease, and this resulted in diagnostic reclassification of many patients (7). These standard techniques were however unable to determine whether this plaque was implicated in the presentation or simply a bystander finding. A non-invasive imaging technique to reliably detect intracoronary thrombus and facilitate this distinction would therefore be of major clinical value.

1.1.3 Imaging intracoronary thrombosis

At present, invasive coronary angiography is the primary modality used to detect the presence of intracoronary thrombus in patients presenting with acute myocardial infarction, through an abrupt occlusion of the coronary artery or a filling defect in partially occluded vessels. This approach has high specificity but low sensitivity for detection of intracoronary thrombus, necessitating the introduction of adjunctive invasive coronary intravascular imaging including angioscopy, intravascular ultrasound and optical coherence tomography to improve rates of identification of

coronary thrombosis and atherothrombosis (8). Intravascular ultrasound-based studies have indicated an incidence of plaque disruption of 30-40% in patients with myocardial infarction and non-obstructive coronary arteries (9, 10), although this imaging technique cannot differentiate between echo-lucent plaques and acute thrombus (8, 11). Optical coherence tomography has replaced intravascular ultrasound as the gold standard in high-resolution cross-sectional imaging of the arterial intima, providing a more detailed assessment of coronary artery dissection and thrombus formation (12). However, these invasive techniques are not always available, have limitations in respect to assessing smaller or stenosed vessels, and only provide circumstantial evidence of the presence of a thrombus based on the characteristic appearances of the images (13-15). As such, atherothrombotic events may be missed, resulting in misdiagnosis and, importantly, a missed opportunity to establish patients on appropriate treatment and secondary prevention.

1.1.4 Uncertain role of coronary thrombosis in myocardial infarction

An accurate diagnosis is imperative for establishing subsequent appropriate therapeutic intervention in patients with myocardial infarction. Patients presenting with type 1 myocardial infarction require short-term anticoagulation as well as medium-term dual antiplatelet therapy, in conjunction with other secondary prevention therapies. For most patients with type 2 myocardial infarction, the above strategy would be both ineffective and potentially harmful, such as in patients with bleeding associated anaemia. However, intracoronary thrombus formation underpins certain causes of type 2 myocardial infarction including coronary thromboembolism and spontaneous coronary artery dissection. Accurate identification of intracoronary thrombus is a central tenet in both the diagnosis of type 1 myocardial infarction, and in the differentiation of the various aetiologies underlying type 2 myocardial infarction.

1.1.4.1 Myocardial infarction with non-obstructive coronary arteries

Co-existing coronary artery disease is common in patients with myocardial infarction and non-obstructive coronary arteries, with plaque disruption being the key trigger of acute myocardial infarction in many cases (3, 4, 9). Myocardial infarction and non-obstructive coronary arteries was first documented over 75 years ago when pathological studies reported evidence of myocardial necrosis in the absence of coronary atherosclerosis (16, 17). Its recognition in clinical practice remains more recent, and it comprises a heterogenous group of vascular or myocardial disorders, occurring in 5-15% of patients presenting with acute myocardial infarction (18-20). Compared to patients with obstructive coronary artery disease, patients with myocardial infarction and non-obstructive coronary arteries are younger (21, 22), more likely to be female, and have specific genetic and ethnic predispositions (23-25). Interestingly, the prevalence of traditional coronary artery risk factors including dyslipidaemia, hypertension and diabetes mellitus is lower in patients with myocardial infarction and non-obstructive coronary arteries (12, 14-16).

Myocardial infarction and non-obstructive coronary arteries has defined criteria as outlined by the European Society of Cardiology in 2017 (26) and the American Heart Association/American College of Cardiology in 2019 (19). To fulfil the diagnosis, patients must present with (i) acute myocardial infarction as defined by the fourth universal definition of myocardial infarction (2), (ii) non-obstructive coronary arteries on angiography (no coronary artery stenosis ≥ 50%), and (iii) no specific alternative diagnosis for the clinical presentation. Only ischaemic causes of acute myocardial infarction are now included in the underlying aetiology of myocardial infarction and

non-obstructive coronary arteries. This includes patients presenting with either type 1 or type 2 myocardial infarction but excludes those with takotsubo cardiomyopathy and myocarditis. Although this has simplified the diagnostic work-up of this patient cohort, there remains a high degree of variability in the way patients with suspected myocardial infarction and non-obstructive coronary arteries are investigated and treated, because it is a diagnosis of exclusion. The identification and management of these patients will depend on local practice and resources, where there may be limited access to more advanced diagnostic testing. This is likely one of the contributory factors underlying a recent analysis demonstrating that patients with myocardial infarction and non-obstructive coronary arteries had a higher one-year adjusted mortality than patients with myocardial infarction and obstructive coronary artery disease (20). As such, there is a clinical need to improve the accuracy in the identification, investigation, and management of this patient population.

1.1.4.2 Coronary thromboembolism

Coronary thromboembolism results in myocardial infarction and non-obstructive coronary arteries if it involves the microcirculation or if the epicardial coronary thrombus is not associated with atherosclerotic coronary artery disease (19). Underlying aetiologies can range from atrial fibrillation, hypercoagulable states, inherited thrombophilia, paradoxical embolism, valvular vegetations, valvular calcifications and cardiac tumours (19, 27). As this subtype of event typically involves smaller calibre coronary vessels, their identification using catheter-based techniques is limited by the inability to access smaller vessels due to the size and physical limitations of the intravascular probes. A more sensitive novel and non-invasive imaging modality that can more accurately assess small calibre coronary vessel thrombosis would be of great clinical value to identify coronary thrombosis events resulting in type 2 myocardial infarction.

1.1.4.3 Spontaneous coronary artery dissection

Spontaneous coronary artery dissection is an uncommon cause of acute myocardial infarction, with a predominance in younger (<50 years) women (28, 29). Myocardial ischaemia is driven by obstruction to coronary blood flow, secondary to separation of medial and adventitial coronary vascular walls, with associated intramural haematoma resulting in protrusion into the coronary arterial lumen. The coronary arteries can appear normal or near normal on coronary angiography, due to gradual tapering of the vessel, and this is commonly a missed diagnosis. Moreover, the prevalence of iatrogenic catheter-induced coronary artery dissection is reported to be increased in patients with spontaneous coronary artery dissection, meaning that many clinicians are reluctant to perform intravascular imaging in patients with this suspected diagnosis (30). Consequently, the true incidence of spontaneous coronary artery dissection is likely to be underestimated (19, 29).

1.1.5 Non-invasive imaging of coronary thrombus - Pilot data

We have recently used positron emission tomography (PET) with computed tomography (CT) coronary angiography to identify intracoronary thrombus using a novel radiotracer, ^{18}F-GP1. This radiotracer is highly selective and specific for the activated glycoprotein IIb/IIIa receptor on activated platelets (31-33). As part of a previous BHF-funded Clinical Research Training Fellowship (Dr Evangelos Tzolos; FS/CRTF/20/24086) and Project Grant (PG/19/40/34422), we have demonstrated that ^{18}F-GP1 has specificity for the detection of intravascular thrombosis in a range of

cardiovascular conditions (34, 35). We have recently undertaken studies in patients with coronary atherothrombosis in acute type 1 myocardial infarction (35). This was the first demonstration that non-invasive imaging can identify *in vivo* intracoronary thrombus in patients presenting with acute myocardial infarction, and for this work, Dr Tzolos was awarded the European Society of Cardiology Young Investigator Award in 2021. We have confirmed the high selectivity and specificity of ^{18}F-GP1 binding to activated platelets within fresh human thrombus and coronary thrombectomy specimens, and importantly we have observed ^{18}F-GP1 uptake only occurs within the culprit coronary arteries of those with acute myocardial infarction (35). For example, in patients with triple vessel disease, coronary ^{18}F-GP1 uptake was only seen at the site of the culprit lesion. We have also demonstrated preliminary findings of focal ^{18}F-GP1 uptake at the site of spontaneous coronary artery dissection, coronary thromboembolism (36) and extra-coronary thrombus including unrecognized left ventricular and atrial thrombus, as well as infarct-related intramyocardial ^{18}F-GP1 uptake. This changed both the diagnosis (type 1 reclassified as type 2 myocardial infarction) and the treatment (initiation of anticoagulation) of patients presenting with acute myocardial infarction. These data demonstrate the feasibility of identifying patients with intracoronary thrombus and type 1 myocardial infarction, and those with type 2 myocardial infarction caused by spontaneous coronary artery dissection and coronary thromboembolism. Importantly the pattern of ^{18}F-GP1 distribution differs among these three conditions, allowing their differentiation. This technique holds major promise in aiding the classification of myocardial infarction, especially in patients with myocardial infarction and non-obstructive coronary arteries or where the presence of coronary thrombosis is unclear.

1.2 RATIONALE FOR STUDY

With the evolving complexity in modern diagnostic criteria and treatments, it has become increasingly important to determine the aetiology of acute myocardial infarction and specifically determine the presence of intracoronary thrombosis. This has major implications for treatment decisions and patient outcome. However, there are currently no techniques that can reliably determine the presence of intracoronary thrombus throughout the coronary circulation. Here, we will assess a promising highly sensitive and accurate technique to determine the contribution of coronary thrombosis in patients presenting with uncertain or difficult to diagnose causes of myocardial infarction. This will potentially provide a completely novel approach that could provide major insights into the diagnosis, investigation and treatment of these patients.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

The primary objective of this study is to establish the origin, frequency and distribution of activated platelets and thus thrombotic causes of myocardial infarction in patients presenting with myocardial infarction with non-obstructive coronary arteries

2.1.2 Secondary Objectives

To inform the pathophysiology and understanding of acute myocardial subtypes, by providing additional mechanistic information regarding the presence of intracoronary activated platelets and thrombosis.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

The primary endpoint will be the degree and location of platelet activation as determined by the target to background ratio of ^{18}F-GP1.

2.2.2 Secondary Endpoints

The secondary endpoints will include measuring the presence of platelet activation in acute myocardial infarction with non-obstructive coronary arteries and identifying the presence and site of platelet activation in thrombosis-related coronary causes of type 2 myocardial infarction.

3 STUDY DESIGN

This will be a prospective observational case-control cohort study

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

We will recruit two patient populations after invasive coronary angiography has been completed. We have established comparator control populations including 50 patients with stable coronary artery disease (no angina or recent myocardial infarction) and valvular heart disease who underwent ^{18}F-GP1 cardiac PET-CT as part of a concurrent study (NCT04073875) (34).

4.1.1 Cohort 1: Patients with myocardial infarction with non-obstructive coronary arteries

We will recruit 50 patients with myocardial infarction and non-obstructive coronary arteries on coronary angiography

4.1.2 Cohort 2: Patients with coronary causes of type 2 myocardial infarction

We will recruit 10 patients with coronary artery thromboembolism and 10 patients with spontaneous coronary artery dissection. Finally, we will include 10 subjects who have had iatrogenic coronary artery dissection or intramural haematoma as a complication of their percutaneous coronary intervention.

4.2 INCLUSION CRITERIA

- Males and females ≥ 18 years of age

- Clinical presentation of chest pain, ST-segment deviation within a coronary artery territory on the electrocardiogram, raised cardiac troponin and non-obstructive coronary arteries on invasive coronary angiography as per international societal diagnostic criteria (19, 26).

4.3 EXCLUSION CRITERIA

- <18 years of age
- Takatsubo cardiomyopathy
- Myocarditis
- Renal failure (estimated glomerular filtration rate <30 mL/min/1.73 m^2)
- Woman of child-bearing potential who are pregnant or breastfeeding
- Known allergy or contraindication to iodinated contrast or radiotracer
- Patients unable to tolerate the supine position
- Patients unable to provide informed consent

4.4 CO-ENROLMENT

Co-enrolment with other studies may be considered in line with ACCORD co-enrolment policy. Co-enrolment between studies will be agreed by the respective PIs prior to beginning of the study. Individual patients who are eligible for co-enrolment will be discussed between research fellows and Pis as necessary. This will ensure co-enrolment:

1. Is appropriate (i.e. there are no contra-indications)
2. Would not jeopardise the integrity of either study
3. Would not compromise patient care, safety, or result in an undue burden on the patient, including exposure to too much radiation.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Potential participants for all the cohorts will be identified by their usual care team whilst in the Royal Infirmary of Edinburgh. A member of the study team will provide an information sheet if the participant is interested in taking part in the study.

5.2 CONSENTING PARTICIPANTS

Participants will be enrolled following an opportunity to read the patient information sheet and once written informed consent is obtained, screening for eligibility can begin. Consent will be confirmed at the beginning of any study activities.

5.2.1 Withdrawal of Study Participants

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form if possible. The participant will have the option of withdrawal from:

(i) all aspects of the study but continued use of data collected up to that point. To safeguard rights, the minimum personally identifiable information possible will be collected.

6 STUDY ASSESSMENTS

6.1 STUDY ASSESSMENTS

All patient's eligible for the study will have informed consent taken. This will as well as a standardised clinical assessment will be performed either whilst still an inpatient or as soon as practical possible from symptom onset. The clinical assessment will be carried out in the Clinical Research Facility or on participants' inpatient ward.

6.2 Study Screening

Eligible participants in will be approached as described in section 5. We will also assess capacity to ensure adequate understanding of the study procedures and their ability to provide informed written consent.

6.3 Baseline Visit

All patient's eligible for the study will have informed consent taken. This will as well as a standardised clinical assessment will be performed either whilst still an inpatient or as soon as practical possible from symptom onset. The clinical assessment will be carried out in the Clinical Research Facility or on participants' inpatient ward.

The assessment will include:

- Demographic details
    - Name, initials, age, sex, height, weight, CHI number, telephone number, address, postcode and email address if available
- Past medical and surgical history
- Medications
- Allergies
- Clinical examination
    - Blood pressure assessment and heart rate
    - Physical examination by clinically qualified study researcher including cardiovascular examination
- Electrocardiography (assessing for evidence of myocardial infarction and arrhythmia)
- Clinical haematology and biochemistry will be recorded as part of standard of care.
- A urinary pregnancy test in women of childbearing potential

6.4 Echocardiography

Transthoracic echocardiography will be performed by a British Society of Echocardiography-accredited research ultra-sonographer according to American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines. Patients will be studied with a standard 3 MHz transducer and 2- dimensional, M-mode, Doppler and colour Doppler measurements taken. Ejection fraction will be quantified using the modified Simpson's technique and regional wall motion abnormalities assessed. Agitated saline and ultrasound contrast will be performed to assess for intracardiac shunts and left ventricular thrombus as appropriate. If not performed as part of standard of care, we will organise a study specific

transthoracic echocardiogram to be performed at baseline visit or as soon as possible as when is convenient for the participant.

6.5 Invasive coronary angiography and intravascular imaging

Invasive coronary angiography will be performed in all patients. Adjunctive imaging with optical coherence tomography (or intravascular ultrasound) will be encouraged as part of standard of care.

6.6 Cardiac magnetic resonance imaging

All patients will undergo cardiac magnetic resonance imaging as standard of care for the investigation of patients with myocardial infarction and non-obstructive coronary arteries or myocardial infarction of uncertain aetiology. This will be performed prior to ^{18}F-GP1 PET/CT coronary angiography to exclude patients without myocardial infarction, such as those with myocarditis or takotsubo cardiomyopathy.

6.7 Hybrid ^{18}F-GP1 positron emission tomography and coronary computed tomography coronary angiography

^{18}F-GP1 will be synthesized by our radiochemistry facility, the Edinburgh Imaging Facility Radiochemistry (EIFR), which is co-located within our Edinburgh Imaging Facility, Queens Medical Research Institute (EIF QMRI) using our well-established protocols. Each patient will undergo ^{18}F-GP1 PET/CT coronary angiography imaging on our hybrid scanner (Biograph mCT, Siemens) as soon as practical after their index event and within a maximum of 7 days from symptom onset. In our previous studies the 18F-GP1 signal diminished after this time point (35). Patients will initially be injected with 250 MBq ^{18}F-GP1, before resting in a quiet environment for 60 min. A low-dose attenuation correction CT scan (120 kV, 50 mAs, 5/3 mm) will be followed by acquisition of PET data in list mode using a two 20-min bed position centred on the thoracic aorta and heart. A contrast-enhanced CT coronary angiogram will then be performed. After optimal co-registration of the CT and PET data, regions of interest will be drawn for PET quantification around areas of uptake in the coronary arteries, ascending and arch of the aorta as well as the atria and ventricles of the heart. Mean and maximum standardised uptake values (SUV) for ^{18}F-GP1uptake will be measured. Tissue to background ratio (TBR) will also be calculated after correcting thrombus uptake for tracer activity in the blood pool of the right atrium as described previously (37).

6.8 Myocardial infarction classification

Following the completion of all standard of care investigations the participants investigations will be presented to a panel of cardiology experts from the cardiology consultant body at the Royal Infirmary of Edinburgh who will be asked to classify the myocardial subtype using the Universal definition of myocardial infarction (2). This will help to ensure, with addition of the usual care team myocardial infarction classification, a robust classification of the myocardial infarction subtype for each patient.

6.9 Schedule of study assessments

Assessment	Screening	Day 1 – 7	6 – 12 months post PET-CT scan
Assessment of Eligibility Criteria	☒		
Written informed consent	☒		
Demographic data, contact details	☒		
Blood samples as per standard clinical care and study protocol	☒		
12-lead ECG as per standard clinical care	☒		
Coronary angiogram as per standard clinical care	☒		
Transthoracic Echocardiogram as per standard clinical care		☒	
Urinary pregnancy test	☒		
18F-GP1 injection and waiting period		☒	
PET-CT scan of heart		☒	
CT Coronary angiogram		☒	
Review of clinical notes looking for recurrent myocardial infarction, stroke or transient ischaemic attack, pulmonary embolism, all haemorrhage, current medications and death			☒
A standardized study questionnaire will be posted or sent via email			☒

6.10 LONG TERM FOLLOW UP ASSESSMENTS

We will then follow participants up following their PET-CT scan. This will be performed once between 6 and 12 months following their myocardial infarction, with subsequent follow up used to obtain as much data as possible. We will collect data on recurrent myocardial infarction, stroke or transient issue attack (TIA), pulmonary embolism, all haemorrhage, current medications and death. A standardized questionnaire will be posted or sent via email to the participants and a review of electronic medical notes will be undertaken between 6 and 12 months to collect this data. A telephone call to patients will be considered if patients do not return the questionnaire or further clarification is needed. Prior to contacting participants, we will check case notes to ensure the participants are not deceased and contact would distress relatives.

6.11 STORAGE AND ANALYSIS OF SAMPLES

Blood samples for storage will be frozen and kept for a minimum of five years. It will be stored in a locked freezer in appropriately secured premises in the Laboratory at Edinburgh Royal Infirmary. The retained blood samples and participants data (including CT/PET and MRI images) will be used for secondary studies separate to this study as hypothesis arise. Anonymised blood samples may be sent to other academic institutions or commercial companies for analysis.

7 DATA COLLECTION

Clinical Assessment
Any changes in medication, any hospital admission or any clinical symptoms will be assessed at the study visit by the investigator.

Blood Sampling
Blood samples will be collected as per standard clinical care. The results will be uploaded onto the patients electronic NSH Lothian medical record.

Electrocardiogram
Electrocardiograms will be collected as per standard clinical care and uploaded onto the patient's electronic NHS Lothian medical record.

Echocardiography
Echocardiography will be performed according to standard clinical care. Echocardiograms will be uploaded to the EchoPAC data storage system as part of the patient's electronic NHS Lothian medical record.

Computed Tomography Positron Emission Tomography
Imaging datasets will be stored on the servers at the Edinburgh Imaging Facility for subsequent analysis. Summary imaging DICOM files will be uploaded to the PACS system as part of the patient's electronic NHS Lothian medical record.

7.1 Source Data Documentation

The study database will be used to document all data collection in a NHSL computer. All patient-related data will be recorded in an anonymized way. Each patient will be unequivocally identified by a trial subject number, attributed at recruitment into the study. Key data from blood results, echocardiography, CT, MRI and PET-CT/PET-MR reports will be documented in the case record form of the study database. The original reports and images will be retained by the imaging core laboratory for future reference.

8 DATA MANAGEMENT

Patient NHS electronic records will be accessed following formal and explicit patient consent. Anonymised data will be made available for other researchers to use where appropriate.

All identifiable participant information (Name, age, sex, address and postcode, CHI number, telephone number, email address, height, weight, clinical condition, date of study enrolment and date of PET-CT scan.) will be stored in a secure manner accessible only to members of the research team. CHI number is required to review participants relevant medical history, medications, medical imaging and standard of care intervention results. This will be stored on an NHS password protected onedrive excel file.

All computers will be encrypted and password protected. Electronic data will be stored on (2-step) password-protected computers (University laptop and NHS computers) and only accessible to the study investigators. No personal identifiable information including CHI numbers will be accessed by members outside the research team or NHS Lothian.

All University of Edinburgh employed researchers and study staff will complete the Data Protection Training through Learn.

All University of Edinburgh employed researchers, students and study staff will complete the Information Security Essentials modules through Learn and will have read the minimum and required reading setting out ground rules to be complied with.

Only study subject number will be transferred to the password protected University laptop.

The study will be guided by the principles of Good Clinical Practice and Data Protection Act in ensuring the confidentiality of personal data. Participant consent forms will contain personal data and a linked participant identification number. Hard copies of consent forms will be stored in a secure filing cabinet in a locked University Office (Room SU 305, Chancellor's Building). Study data will be kept on University password protected computers as linked anonymised data. This will enable the identification of each participant's data during the study, in order for any participant to withdraw and have personal data destroyed if they wish. All data will be anonymised after the study period.

8.1 Personal Data

The following personal data will be collected as part of the research:

- Name, age, sex, address and postcode, CHI number, height, weight, clinical condition, date of study enrolment and date of PET-CT scan
- Personal data will be stored or accessed for a period of 6 to 12 months after the study has ended on a NHSL password protected onedrive excel file to allow participants to be identified so we can follow up on their management and clinical course. Thereafter, anonymised data may be stored for a period of up to five years. No peronsal identifiable data will be transferred to the University of Edinburgh.

8.2 Data Information Flow

All data collected or generated by the study (including personal data) will not be transferred to any external individuals or organisations outside of the Sponsoring organisation(s).

8.3 External Transfer of Data

All data collected or generated by the study (including personal data) will not be transferred to any external individuals or organisations outside of the Sponsoring organisation(s).

8.4 Data Controller

The data controller is the University for Edinburgh and NHS Lothian. The data controller is the organisation who determines the purposes for which, and the manner in which, any personal data are processed.

8.5 Data Breaches

Any data breaches will be reported to the University of Edinburgh (dpo@ed.ac.uk) and NHS Lothian (Lothian.DPO@nhslothian.scot.nhs.uk) Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

9 STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

We have found that ^{18}F-GP1 is markedly discriminatory for the presence of thrombus with an accuracy of 96% with 100% specificity and false negatives predominantly seen in patients imaged beyond 7 days from presentation (37). The prevalence of coronary thrombosis in patients with myocardial infarction and non-obstructive coronary arteries is unknown but estimates suggest that plaque disruption may be as high as one third of cases although it is unclear if this is bystander disease or the cause of the infarction (19). We have estimated that routine clinical evaluation may suggest thrombus in 10-20% of patients with myocardial infarction and non-obstructive coronary arteries. For 80-90% power at two-sided $p<0.05$, we will require a study population of 36-50 to detect an incidence of thrombosis of 25-40%. Population sizes for coronary thromboembolism and spontaneous coronary dissection are based on the proof-of-principle of the detection of coronary thrombosis and have greater than 95% power to detect a prevalence of coronary thrombus in over two thirds of patients.

9.2 PROPOSED ANALYSES

As with our previous studies, image analysis will be performed on bespoke PET analysis software from our long-standing collaborators (FusionQuant, Cedars Sinai Hospital, Los Angeles) that provides automated motion correction and advanced cardiovascular PET quantification (31, 32, 38). After accurate co-registration of the PET and CT data sets, ^{18}F-GP1 uptake will be quantified within regions of interest around areas of thrombus on the CT images.

Descriptive statistics will incorporate numbers and proportions, means and standard deviations or median and interquartile ranges. Proportions will be compared with Chi-squared test and continuous variables will be compared with regression analysis, Student's *t*-test or analysis of variance with repeated measures for longitudinal assessments. Statistical significance will be taken as two-sided $p<0.05$.

10 ADVERSE EVENTS

The Investigator, or a delegated researcher, is responsible for the detection and documentation of adverse events that may be related to participating in the study and that meet the criteria and definitions detailed below.

10.1 Definitions

An **adverse event** (AE) is an untoward medical occurrence in a study participant.
An **adverse reaction** (AR), in the context of this study, is any untoward and unintended response which is related to any dose of iodinated contrast agent or PET tracer administered to that participant.

A **serious adverse reaction** (SAR) is any AR that:

- results in death of the clinical trial participant; is life threatening*;
- requires in-patient hospitalisation or prolongation of existing hospitalisation;

- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

A **suspected unexpected serious adverse reaction** (SUSAR) is any AR that is classified as serious and is suspected to be caused by the iodinated contrast agent, that it is not consistent with the information in PET tracer Investigator Brochure.

*Life-threatening in the definition of an SAE or SAR refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

10.2 Identifiying AEs and ARs

All AEs and ARs related to the imaging procedures will be identified from the time a PET/CT scan related procedure commences until 7 days after PET/CT scan completion.

10.3 Recording AEs and ARs

AEs will be recorded in the study CRF. There is no requirement to complete an additional AE form.

When an AE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. To the extent the CRF permits, the Investigator will record relevant safety information in the CRF.

Any adverse reaction (AR) to iodinated contrast or PET tracer that meets seriousness criteria (see section 10.1) will be recorded and reported in the study CRF and will also be recorded on an ACCORD SAE form, which will then be sent to the Sponsor via email (safety@accord.scot).

Pre-existing medical conditions (i.e. existed prior to informed consent) should be recorded as medical history and only recorded as AEs/ARs if medically judged to have unexpectedly worsened during the study. Events that are consistent with the expected progression of underlying disease should not be recorded as adverse events.

10.4 Assessment of AEs, SAEs, ARs, SARs and SUSARs

Seriousness, causality, severity and expectedness will be assessed by the PI. The Investigator is responsible for assessing each adverse event. The CI may not downgrade an event that has been assessed by an Investigator as a SAR or SUSAR, but can upgrade an AR, SAR or SUSAR if appropriate.

10.4.1 Assessment of causality

The Investigator will make an assessment of whether an AE is likely to be related to the administration of iodinated contrast or PET tracer (and therefore be considered an AR) according to the definitions below.

- Unrelated: Where an event is not considered to be related to the administration of iodinated contrast or PET tracer.
- Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the administration of iodinated contrast or PET tracer in this study.

10.4.2 Assessment of seriousness

Subsequent to the assessment causality, the Investigator will make an assessment of seriousness as defined in Section 10.1

10.4.3 Assessment of severity

The Investigator will make an assessment of severity for each SAR, and record this on the ACCORD SAE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.
Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.
Severe: an event that prevents normal everyday activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

10.4.4 Assessment of expectedness of SARs

10.5 No SARs are considered expected by the sponsor for the purpose of expedited reporting of SUSARs based upon the reference safety information available in the most current version of the PET tracer Investigator Brochure. Reporting of SARs/SUSARs

As this trial is a non-CTIMP and involves procedures and interventions that are very well established in the medical community, with extensive information available regarding risks, only serious adverse reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) related to iodinated contrast administration, will be onward reported to the Sponsor.

Once the Investigator becomes aware that a contrast or PET tracer related SAR/SUSAR, has occurred in a study participant, the information will be reported to the ACCORD Research Governance & QA Office within 24 hours. If the Investigator does not have all information regarding an event, they should not wait for this additional information before notifying

ACCORD. The ACCORD SAE report form will be used to submit the event report, and can be updated when the additional information is received. SAR/SUSARs relating to the PET tracer will also be forwarded onto Life Molecular Imaging SA as stipulated in exhibit D of the legal material transfer agreement. This stipulates that within two business days all cases concerning Serious Adverse Events independent of their causal relationship to the GP1 tracer will be reported to Life Molecular Imaging SA using the email address GRA@life-mi.com by the study lead.

The SAE form will be sent via email to safety@accord.scot within 24 hours Only forms in a pdf format will be accepted by ACCORD via email.

Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the investigator and request the missing information.

All reports sent to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File.

10.6 Reporting requirements

The ACCORD Research Governance & QA Office is responsible for pharmacovigilance reporting on behalf of the co-sponsors (Edinburgh University and NHS Lothian).

10.7 FOLLOW-UP PROCEDURES

After initially reporting a radiotracer related SAR/SUSAR, the Investigator will follow each participant until resolution or the completion of study follow-up. Follow-up information will be reported to the ACCORD office.

11 OVERSIGHT ARRANGEMENTS

11.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit study related monitoring and audits on behalf of the Sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the Sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

11.2 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if a study specific risk assessment is required.

If required, a study specific risk assessment will be performed by representatives of the Sponsor(s), ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs. Input will be sought from the Chief Investigator or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans.

If considered necessary, ACCORD clinical trial monitors, or designees, will perform monitoring activities in accordance with the study monitoring plan. This will involve on-site visits and remote monitoring activities as necessary. ACCORD QA personnel, or designees, will perform study audits in accordance with the study audit plan. This will involve investigator site audits, study management audits and facility (including 3rd parties) audits as necessary (delete where not required).

12 GOOD CLINICAL PRACTICE

12.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all necessary approvals will be obtained and any conditions of approvals will be met.

12.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

12.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any study specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the Sponsor(s).

The Investigator or delegated member of the study team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The original will be signed in the Investigator Site File (ISF). The participant will receive a copy of the signed consent form and a copy will be filed in the participant's medical notes.

12.2.2 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their study related duties.

12.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

12.2.4 Investigator Documentation

The Principal Investigator will ensure that the required documentation is available in local Investigator Site files (ISFs).

12.2.5 GCP Training

For non-CTIMP (i.e. non-drug) studies all researchers are encouraged to undertake GCP training in order to understand the principles of GCP. This is not a mandatory requirement unless deemed so by the Sponsor. GCP training status for all investigators should be indicated in their respective CVs.

12.2.6 Data Protection Training

All University of Edinburgh employed researchers and study staff will complete the Data Protection Training through Learn.

NHS Lothian employed researchers and study staff will comply with NHS Lothian mandatory Information Governance Data Protection training through LearnPro.

Non-NHS Lothian staff that have access to NHS Lothian systems will familiarise themselves and abide by all NHS Lothian IT policies, as well as employer policies

12.2.7 Information Security Training

All University of Edinburgh employed researchers, students and study staff will complete the Information Security Essentials modules through Learn and will have read the minimum and required reading setting out ground rules to be complied with.

NHS Lothian employed researchers and study staff will comply with NHS Lothian mandatory Information Governance IT Security training through LearnPro.

Non-NHS Lothian staff that have access to NHS Lothian systems will familiarise themselves and abide by all NHS Lothian IT policies, as well as employer policies

12.2.8 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

12.2.9 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

13 STUDY CONDUCT RESPONSIBILITIES

13.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Proposed amendments will be submitted to the Sponsor for classification, review and authorisation.

Amendments to the protocol must be submitted in writing to the appropriate REC and local R&D for approval prior to implementation and prior to participants being enrolled into the amended protocol.

13.2 MANAGEMENT OF PROTOCOL NON COMPLIANCE

13.2.1 Protocol Waivers

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the Sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC and local R&D for review and approval if appropriate.

13.2.2 Management of Deviations and Violations

Deviations and violations are non-compliance events discovered after the event has occurred. Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the Sponsors every 3 months. Each protocol violation will be reported to the Sponsor within 3 days of becoming aware of the violation.

Deviation logs will be maintained for each site in multi-centre studies.

Deviation logs/violation forms will be transmitted via email to QA@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

13.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the study; or

(b) the scientific value of the study.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the Sponsor(s) (qa@accord.scot) must be notified within 24 hours. It is the responsibility of the Sponsor(s) to assess the impact of the breach on the scientific value of the study, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

13.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 3 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will be destroyed with permission from the Sponsor.

13.5 END OF STUDY

The end of study is defined as the last participant's last visit.

The Investigators and/or the Sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R&D Office(s) and Sponsor(s) within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the Sponsor(s) via email to researchgovernance@ed.ac.uk.

A summary report of the study will be provided to the REC within 1 year of the end of the study.

13.6 CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

The end of study is defined as the last participant's last visit. The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R&D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot.

A summary report of the study will be provided to the REC within 1 year of the end of the study.

13.7 INSURANCE AND INDEMNITY

The Sponsor(s) are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the Sponsor(s)' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The Sponsor(s) require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

14 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team.

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