



Study Protocol

The RAPID-CTCA Trial

(Rapid Assessment of Potential Ischaemic Heart Disease with CTCA)

The role of early CT Coronary Angiography in the evaluation, intervention and outcome of patients presenting to the Emergency Department with suspected or confirmed Acute Coronary Syndrome

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CONTENTS

LIST OF ABBREVIATIONS.....	4
PROFESSIONAL SUMMARY.....	6
LAY SUMMARY.....	7
1 INTRODUCTION	8
1.1 BACKGROUND AND RATIONALE	8
2 STUDY OBJECTIVES.....	11
2.1 OBJECTIVES.....	11
2.1.1 Primary Objective	11
2.1.2 Secondary Objectives.....	11
2.2 ENDPOINTS	11
2.2.1 Primary Endpoint	11
2.2.2 Secondary Endpoints.....	11
3 STUDY DESIGN	12
4 STUDY POPULATION	12
4.1 NUMBER OF PARTICIPANTS	12
4.2 INCLUSION CRITERIA.....	12
4.3 EXCLUSION CRITERIA	12
4.4 CO-ENROLMENT	13
5 PARTICIPANT SELECTION AND ENROLMENT	13
5.1 IDENTIFYING PARTICIPANTS.....	13
5.2 CONSENTING PARTICIPANTS.....	13
5.3 SCREENING FOR ELIGIBILITY.....	14
5.4 RANDOMISATION	
5.4.1 Randomisation Procedures	
5.4.2 Intervention Allocation	15
5.4.3 Compliance and withdrawal of Study Participants	15
6. STUDY ASSESSMENTS	16
7. DATA COLLECTION	17
8. STATISTICS AND DATA ANALYSIS.....	18
9. ADVERSE EVENTS.....	19
9.1. DEFINITIONS	19
9.2. IDENTIFYING AEs AND SAEs.....	19
9.2.1 Adverse Events relating to CT Scanning.....	19
9.2.2 Exemptions from Reporting.....	19
9.3. Recording AEs and SAEs.....	20
9.4 ASSESSMENT OF AEs AND SAEs	20
9.4.1. Assessment of Causality	20
9.4.2 Assessment of expectedness.....	20
9.4.3. Assessment of Severity	20
9.5 REPORTING OF SAEs/SARs/SUSARs	21
9.6 FOLLOW UP PROCEDURES	21
10 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS.....	21
10.1 TRIAL MANAGEMENT COMMITTEE	21
10.2 TRIAL STEERING COMMITTEE	21
10.3 DATA MONITORING COMMITTEE	21
10.4 INSPECTION OF RECORDS.....	22

11. GOOD CLINICAL PRACTICE.....	22
11.1 ETHICAL CONDUCT	22
11.2 INVESTIGATOR RESPONSIBILITIES	22
11.2.1 Informed Consent	22
11.2.2 Study Site Staff	22
11.2.3 Data Recording.....	22
11.2.4 Investigator Documentation	22
11.2.5 GCP Training	22
11.2.6 Confidentiality	23
11.2.7 Data Protection	23
12. STUDY CONDUCT RESPONSIBILITIES	23
12.1 PROTOCOL AMENDMENTS	23
12.2 PROTOCOL VIOLATIONS AND DEVIATIONS.....	23
12.3 STUDY RECORD RETENTION	23
12.4 END OF STUDY	24
12.5 INSURANCE AND INDEMNITY	24
13. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS.....	24
13.1 AUTHORSHIP POLICY	24
13.2 PUBLICATION	24
13.3 PEER REVIEW	25
14. REFERENCES	25
15. APPENDIX 1	29

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian
ACS	Acute Coronary Syndrome
AE	Adverse Event
AHA	American Heart Association
AKI	Acute Kidney Injury
AR	Adverse Reaction
CAD	Coronary Artery Disease
CHB	Complete Heart Block
CI	Chief Investigator
CKD	Chronic Kidney Disease
CT	Computerised Tomography
CTCA	Computerised Tomography Coronary Angiography
CTU	Clinical Trials Unit
CRF	Case Report Form
CV	Curriculum Vitae
ECTU	Edinburgh Clinical Trials Unit
ECG	Electrocardiogram
ED	Emergency Department

LIST OF ABBREVIATIONS (continued)

GCP	Good Clinical Practice
GTN	Glyceryl Trinitrate
HTA	Health Technology Assessment
ICA	Invasive Coronary Angiography
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IHD	Ischaemic Heart Disease
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MACE	Major Adverse Cardiac Event
MAU	Medical Assessment Unit
MI	Myocardial Infarction
PACS	Picture Archiving and Communication System
PI	Principal Investigator
PMG	Project Management Group
QA	Quality Assurance
QALY	Quality-adjusted life year
REC	Research Ethics Committee
R&D	Research and Development
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVT	Supra ventricular tachycardia
TSC	Trial Steering Committee
TMF	Trial Master File
UAR	Unexpected Adverse Reaction
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

SUMMARY

Professional Summary

Design: Open parallel group randomised controlled trial of early computed tomography coronary angiography (CTCA) in patients presenting with suspected/confirmed acute coronary syndrome (ACS) to Emergency Departments (ED), Cardiology Departments, and Medical Assessment Units (MAU).

Setting: ~35 EDs, acute medical services, radiology, and cardiology departments in tertiary and district general hospitals in the UK.

Target population: Inclusion criteria are patients ≥ 18 years with symptoms mandating investigation for suspected or confirmed ACS with at least one of: 1. ECG abnormalities e.g. ST segment depression >0.5 mm; 2. History of ischaemic heart disease (where the clinician assessing patient confirms history based on patient history or available records); 3. Troponin elevation above the 99th centile of the normal reference range or increase in high sensitivity troponin meeting European Society of Cardiology criteria for 'rule-in' of myocardial infarction. Exclusion criteria: 1. Signs, symptoms, or investigations supporting high-risk ACS: ST elevation MI; ACS with signs or symptoms of acute heart failure or circulatory shock; Crescendo episodes of typical anginal pain; Marked or dynamic ECG changes e.g. ST depression of >3 mm; Clinical team have scheduled early invasive coronary angiography on day of trial eligibility assessment. 2. Patient inability to undergo CT: Severe renal failure (serum creatinine >250 $\mu\text{mol/L}$ or estimated glomerular filtration rate <30 mL/min); Contrast allergy; Beta blocker intolerance (if no alternative heart rate limiting agent available/suitable) or allergy; Inability to breath hold; Atrial fibrillation (where mean heart rate is anticipated to be greater than 75 beats per minute after beta blockade). 3. Patient has had invasive coronary angiography or CTCA within last 2 years and the previous investigation revealed obstructive coronary artery disease, or patient had either investigation within the last 5 years and the result was normal. 4. Previous recruitment to the trial; 5. Known pregnancy or currently breast feeding; 6. Inability to consent; 7. Further investigation for ACS would not be in the patient's interest, due to limited life expectancy, quality of life or functional status; 8. Prisoners

Health technologies being assessed: Early use of ≥ 64 -slice CTCA as part of routine assessment compared to standard care.

Measurement of costs/outcomes: Primary end-point will be one-year all-cause death or recurrent type 1 or type 4b MI at one year, measured as time to such event. Secondary endpoints: 1. Hospital length of stay, coronary care length of stay; 2. Proportion of patients receiving invasive coronary angiography during index hospitalisation; 3. Proportion of patients receiving coronary revascularisation during index hospitalisation; 4. Proportion of patients receiving subsequent unplanned coronary revascularisation after index hospitalisation; 5. Proportion of patients receiving invasive coronary angiography despite no significant lesion on CTCA; 6. Proportion of patients assigned to CTCA with obstructive or non-obstructive disease; 7. Proportion of patients prescribed ACS therapies during index hospitalisation; 8. Proportion of patients discharged on prevention treatment or have alteration in dosage of prevention treatment during index hospitalisation; 9. Rehospitalisation/presentation with chest pain within 12 months; 10. Patient symptoms and quality of life up to 12 months; 11. NHS resource utilisation; 12. Patient satisfaction; 13. Clinician certainty of presenting diagnosis after CTCA. Safety: 1. Proportion of patients with allergy/anaphylaxis/acute kidney injury; 2. Proportion of patients with alternative diagnoses that relates to presentation on CTCA e.g. aortic dissection or pulmonary embolus; 3. Proportion of patients with incidental finding but potentially concerning on CTCA e.g. malignancy or pulmonary nodules; 4. Total average radiation exposure from CTCA in the intervention arm during index hospitalisation. Cost effectiveness: Estimated in terms of the lifetime incremental cost per quality-adjusted life year (QALY) gained.

Sample size: one-year death or recurrent MI for this patient group is ~20% (Mills et al, 2011). The aim is to recruit 2424 evaluable patients (1212 per arm) to have 90% power to detect a 20% vs.15% difference in one-year death or recurrent type 1 MI or type 4b MI rate, 2-sided $P < 0.05$. With a ~3% drop out rate, the sample size will be 2,500 patients.

Lay Summary

Coronary artery disease (CAD) occurs when narrowing develops in the blood vessels supplying the heart. If the blood vessels become blocked, the patient may develop a critical lack of blood and oxygen getting to the heart muscle or an acute coronary syndrome (ACS) and be at risk of a heart attack, heart failure and death. Around 700,000 people attend hospital emergency (also known as A&E) departments (EDs) each year with chest pain mainly for assessment for suspected ACS.

Standard assessment involves using a tracing of the heart (electrocardiogram, ECG) and a blood test to measure the level of a protein released from heart cells called troponin. If both tests are normal then the patient is at low risk of a bad outcome and can often be discharged home. If either test is positive, the patient is at intermediate (medium) or high risk and requires admission to hospital. While in hospital, patients may require invasive coronary angiography. This test accurately identifies blockage in the coronary blood vessels that can then be treated, but involves passing a tube or catheter into the heart and therefore carries significant risks.

High-risk patients are usually investigated with invasive coronary angiography while they are in hospital because there is a substantial chance of finding a blocked artery that can then be unblocked and kept open. Medium-risk patients are sometimes investigated with invasive coronary angiography but may not undergo this investigation because the risks may not justify the potential benefits. However, medium-risk patients have a 20%-risk of developing a serious heart problem over the following months. This could be reduced if their heart disease was more accurately investigated and appropriate treatment including long term medicines provided. Also, troponin testing is becoming more sensitive, increasing the amount of patients who are given a diagnosis of ACS but small rises in this blood test may not reflect CAD or a blocked heart artery. If this results in more invasive coronary angiograms and more use of powerful anti-clotting medication, this may increase the risk to patients and costs for the NHS without significant benefit.

Computerised Tomography coronary angiography (CTCA) involves using a CT scan to identify blockages in the coronary arteries. It is slightly less accurate at identifying obstruction than invasive coronary angiography but has much fewer risks. It could therefore be used to improve the investigation of medium-risk patients. It could be used to identify patients with significant blockage who require invasive coronary angiography, allowing treatment of the obstruction and reducing the risk of serious heart problems. It could also identify patients without significant obstruction who don't have a blockage and could therefore be discharged home, avoiding unnecessary tests and medication. However, although the ability of CTCA to detect obstruction is well known, it is unclear whether using CTCA leads to more appropriate use of coronary angiography and medication, a reduced risk of serious heart problems and improved patient outcomes.

The aim is to undertake a research study of CTCA in patients admitted to hospital with suspected or confirmed ACS in the group of patients who are at medium risk, excluding high-risk patients needing immediate coronary angiography and very low-risk patients who can be discharged home without further investigation.

Patients who are suitable will be given information about the study and asked to sign a consent form. Patients will be allocated to either receive CTCA as part of their assessment or receive standard assessment without this test. We will then follow up patients for one year to determine the rate of bad outcomes (such as heart attack or death), quality of life, patient satisfaction, the use of diagnostic tests or treatments, and health care costs. The study will be undertaken by an experienced team of UK researchers involved in previous successful trials in patients with chest pain. The team includes experts in emergency medicine, cardiology, radiology, acute medicine, statistics, and economics.

1 INTRODUCTION

1.1 BACKGROUND AND RATIONALE

Scale of the problem

Ischaemic heart disease (IHD) including myocardial infarction (MI) continues to be a major cause of mortality in the UK. In 2011, 5% of deaths in England were as a consequence of acute MI and 13% were directly related to IHD [Office for National Statistics, 2012]. Approximately 700,000 patients present annually to Emergency Departments (ED) with chest pain in England and Wales, resulting in around 350,000 emergency chest pain admissions [Goodacre S, 2005]. The vast majority of these patients present and are subsequently admitted for evaluation of suspected ACS. Chest pain admissions have doubled in the last decade accounting for approximately 5% of all emergency admissions (the commonest reason for acute hospital admission), whilst those for angina or ACS have fallen, see figure 1, [Health and Social Care Information Centre (HSCIC), 2012; Hospital Episode Statistics, 2012]. Therefore, the majority of patients admitted for suspect ACS are discharged with the condition not being diagnosed. However, confirmed ACS remains a common diagnosis and associated with major adverse outcomes. One fifth of patients with ACS are re-hospitalised for suspected recurrent ACS or heart failure within 6 months of index admission [Goldberg R et al, 2004]. Mortality remains high with a 6-month mortality of around 20% [Das R et al, 2006]. These events may be the consequence of their index event or due to further myocardial ischaemia. They can be reduced by pharmacological and coronary revascularisation interventions [Fox K et al, 2007; Wallentin L et al, 2009]. The prompt diagnosis and treatment of ACS is therefore critically important.

Current diagnostic pathways for suspected ACS

Due to the consequences of inadvertent discharge of a patient with ACS and the limitations of initial clinical assessment, most patients with suspected ACS will require diagnostic investigation and a short hospital admission. This assessment and evaluation period in the United Kingdom is based on national guidelines [NICE, 2012; SIGN, 2013] and includes serial cardiac biomarkers, typically troponin I or T, and 12-lead ECGs. Current troponin assays do not reach maximal sensitivity until 12 hours after chest pain onset. Patients with an elevated troponin who present with a suspected ACS will have sustained an acute MI according to the Universal Definition of MI [Thygesen K, 2012]. Subsequent assessment, to further delineate IHD especially if troponin testing is negative, is inconsistent in the UK, resulting in many patients being discharged from hospital with “troponin negative” chest pain and no clear alternative diagnosis. This leads to many patients and clinicians being unclear what to do in the event of the patient having recurrent symptoms since coronary artery disease has not been unequivocally excluded.

The role of additional investigations

Exercise ECG testing is not widely used for the further delineation of CAD in UK emergency care settings [Dunham M et al, 2010]. When used it is typically in the context of a standardised assessment alongside biomarker testing on a chest pain unit. These units are widespread in the United States but have only been established in a few centres in the UK in the light of a cluster-randomised trial that failed to show evidence of benefit [Goodacre S et al, 2007]. European Society of Cardiology guidelines recommend using a stress test (typically exercise ECG) to select patients for further investigation with coronary angiography [Hamm C et al, 2011], while NICE guidance does not recommend using exercise ECG in the context of suspected ACS [NICE, 2012]. However, a systematic review of 54 observational studies incorporating 19,874 patients with clinical MI indicates that pre-discharge stress testing provides limited additional prognostic information to guide patient management [Shaw L et al, 1996]. All forms of non-invasive stress testing demonstrate similar sensitivities and specificities for the prediction of future cardiac events. Although the negative predictive value is high (~94%), the positive predictive value is low (<10% for cardiac death and <20% for cardiac death or MI).

Invasive coronary angiography (ICA) is recommended by the European Society of Cardiology [Hamm C et al, 2011] in confirmed ACS or those patients believed to be at high risk of obstructive coronary disease but is costly and associated with a small but significant major complication rate, including death [British Cardiovascular Intervention Society, 2012]. It often requires the transfer of patients between hospitals in the UK as only around 35% of acute hospitals have on-site revascularisation facilities [British Cardiovascular Intervention Society, 2012]. It is unknown how many patients receive unnecessary ICA but it is likely to be significant and a potentially increasing number, if all patients with a raised troponin and chest pain receive coronary angiography. Some patients with confirmed ACS do not receive ICA due to limited availability, belief that troponin elevation is due to an alternative condition or other reasons for a decision to pursue non-invasive management. In the RITA-3 trial of patients presenting with a non-

ST elevation ACS [Fox K et al, 2002], those undergoing invasive investigation were managed with medical therapy in 43%, percutaneous coronary intervention in 35% or coronary artery bypass graft surgery in 22%. On this basis, patients with an ACS could be investigated by CTCA with onward referral for percutaneous coronary intervention or coronary artery bypass graft surgery limited to patients with clear treatable coronary obstruction. Indeed, CTCA has similar discriminatory value in determining the need for coronary revascularization as ICA [Miller J et al 2008].

The potential impact of improved diagnosis

A recent large observational study [Mills N et al, 2011; Mills N et al, 2012] revealed that changing the diagnostic threshold of troponin reported to treating clinicians had a significant effect on patients with suspected ACS whose troponin level was in the range between old and new reported diagnostic thresholds: 3-month (27% to 11%) and 12-month (39% to 21%) death or recurrent MI rates were dramatically improved. Associated changes in coronary interventions and preventative medication confirm a causal pathway between increased diagnosis and improved outcomes. Coronary angiography and revascularisation rates went from 20% to 46% and 16% to 20% respectively. Primary and secondary prevention drug prescription rate also increased e.g. dual antiplatelet therapy administration increased from 27 to 58%. We, therefore, believe that there remains the potential for further significant incremental improvement in outcome if CTCA is widely adopted as part of the early assessment of ACS.

CT Coronary Angiography in chest pain assessment

Without doubt there is a need for novel interventions as part of the evaluation of suspected or confirmed ACS that enable the following: 1. better identification of ACS; 2. better risk stratification of ACS; 3. better case selection for ICA in patients with ACS; 4. provide information to tailor subsequent management and improve outcomes. CTCA could potentially fulfil all of these requirements.

CTCA is quicker, simpler, substantially cheaper and more readily delivered than ICA and should translate into a highly effective and safe imaging strategy. A recent systematic review of 21 diagnostic accuracy studies of CTCA reported a pooled sensitivity of 99% and specificity of 89% for detection of CAD [Mowatt G et al, 2008]. A recent HTA-funded meta-analysis of eight diagnostic cohort studies of CTCA in suspected ACS [Goodacre S, 2013] reported sensitivity of 94% (95% predictive interval 61–99%) and specificity of 87% (95% predictive interval 16–100%), but decision-analysis modelling was unable to draw reliable conclusions about effectiveness and cost-effectiveness of CTCA in suspected ACS. Three recent US trials investigating CTCA in patients with chest pain presenting to the ED promote its use and widespread adoption [Goldstein J, 2011; Hoffman U, 2012; Litt H et al, 2012]. Meta-analyses of 4 trials [D'Ascenzo F et al, 2012; Hulten E et al, 2013] conclude that CTCA is safe, cost effective and reduces length of stay in the US health care system. However, the event rates in these studies are low with no difference between trial arms. Moreover, the participants had relatively long hospital stays, and many additional tests compared with UK practice. CTCA enables non-invasive anatomical quantification of CAD. This allows accurate identification of patients that may benefit from coronary revascularisation [Miller J et al, 2008] and more accurately target patients for primary or secondary therapies, thus improving clinical outcomes. In those patients without disease, it may reduce hospital stay, recurrent hospitalisation and improve patient satisfaction due to clarity around the absence of CAD. However, if CTCA use results in an increase in ICA as a result of false positive or equivocal results in low-risk patients, it may increase the cost and risk without clinical benefit. This risk-benefit dilemma needs evaluation so that benefit can be proven or refuted before widespread adoption across the NHS.

The rationale for this trial

This research is likely to have a significant impact on this large and important group of patients presenting with suspected or confirmed ACS to NHS hospitals. If the trial is positive, those patients with CAD will receive an early and accurate anatomical characterisation of coronary arteries by CTCA allowing targeting of ICA to those patients that are most likely to require revascularisation and facilitating early optimisation of primary and secondary preventive medicines. These interventions will save lives and reduce the burden of undiagnosed ischaemic heart disease. In patients with non-obstructive CAD or normal coronary arteries, it is likely to facilitate earlier discharge and prevent unnecessary ICA with the attendant risks. In terms of NHS benefit, this research is likely to lead to more optimal use of scarce expensive resources, reduced duration of hospital stay at the time of index presentation, and subsequent reduced hospitalisation. The early effective use of primary and secondary prevention will lead to lower long-term cardiovascular events.

If the trial is negative, the results will prevent widespread NHS adoption of an ineffective technology that, if implemented unnecessarily without significant patient outcome benefit, would substantially increase NHS costs and expose patients to unnecessary investigation with radiation exposure and potential anxiety related to a false positive diagnosis.

Additionally, the increasing use of high sensitivity troponin will result in many more patients who have elevated troponin measurements; some of these patients will not have ACS. CTCA will enable local screening of these patients and only select patients for ICA that will directly benefit from this intervention.

To reiterate, it is imperative that CTCA is proven to improve clinical and cost outcomes before widespread adoption in the NHS. A positive or indeed a negative trial is equally important and valuable to the NHS.

Evidence explaining why this research is needed now

HTA evidence synthesis

A Health Technology Assessment (HTA) comprehensive systematic review in 2008 assessed the role of 64-slice multidetector computed tomography as an alternative to ICA [Mowatt G et al, 2008]. In keeping with previous analyses [Schroeder S et al, 2008], it confirmed the excellent accuracy of multidetector computed tomography in the identification of CAD. However, this systemic review highlighted several areas that need further research and highlighted, amongst other things, the need to evaluate the usefulness of multidetector CTCA in patients with suspected CAD.

A recent evidence synthesis [Goodacre S et al, 2013] evaluated the diagnostic and prognostic accuracy, and cost-effectiveness of CTCA in suspected ACS. This evidence review showed that CTCA has good diagnostic accuracy for coronary artery obstruction: sensitivity, 94% (95% predictive intervals 61-99%); specificity, 87% (95% predictive intervals 16-100). Coronary artery obstruction on CTCA predicted MACE with a relative risk of 3.1 (0.3-18.7) or 5.8 (0.6-24.5) depending upon how indeterminate scans were classified. Economic analysis was subject to substantial uncertainty but CTCA was likely to be cost-effective if subsequent MACE was >2% (£30,000/QALY threshold) or >2.9% (£20,000/QALY threshold). The review suggests further research regarding the effect of testing and treatment on MACE is needed.

National Institute of Clinical Excellence

The NICE guidelines [NICE, 2012] identified areas of evidence uncertainty including the investigation of the cost-effectiveness of CTCA as a first-line test in patients with troponin-negative ACS. A subsequent NICE commissioned review suggests that CTCA is cost effective [NICE, 2013]

Recent randomised controlled trials and meta-analysis

Three recent US trials investigating CTCA in patients with chest pain presenting to the ED promote its use and widespread adoption [Goldstein J et al, 2011; Hoffman U et al, 2012; Litt H et al, 2012]. Meta-analyses of 4 trials [D'Ascenzo F et al, 2012; Hulten E et al, 2013] conclude that CTCA is safe, cost effective and reduces length of stay in low-risk patients in the US health care system. The event rates in these studies are low, with long hospital stays, and many additional tests compared with UK practice. The event rate in troponin negative patients is likely to fall further, with sensitive troponin use, negating any small benefit of additional investigation in this negligible risk group.

Early CTCA needs investigation in intermediate-risk ACS patients where improved and optimal targeting of interventions, including coronary revascularisation, and primary and secondary preventive therapy is likely to improve diagnosis and longer term outcome. The clinical and cost effectiveness of early CTCA in suspected or confirmed ACS must be clearly demonstrated before adoption of the technology into routine NHS practice given its cost, risk and uncertainty of benefit. A positive or negative trial is equally important to the NHS.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

This study aims to investigate the effect of early CTCA in patients with suspected or confirmed ACS presenting to the ED, MAU, or cardiology, upon interventions, event rates and health care costs in a pragmatic clinical trial and economic evaluation up to 1 year after the trial intervention. The primary objective will be to investigate the effect of the intervention by comparing all-cause death or recurrent non-fatal type 1 or type 4b MI at one year.

2.1.2 Secondary Objectives

1. The proportion of patients receiving coronary angiography and revascularisation at index hospitalisation and during 12-month follow up.
2. The proportion of patients representing or readmitted to hospital with suspected ACS/recurrent chest pain up to one year after index presentation.
3. The use of cardiovascular treatment and preventative therapies during index hospitalisation and after discharge.
4. Length of stay at index hospitalisation.
5. The use of NHS resource including hospitalisation and other investigations and interventions.
6. The proportion of patients with symptoms, morbidity and mortality up to one year.
7. Quality of life.
8. The incremental cost per QALY gained by providing CTCA compared to current standard practice.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

The **primary end-point** will be all-cause death or recurrent non-fatal type 1 or type 4b MI at one year, measured as time to first such event. MI will be defined according to the most recent Universal Definition [Thygesen K, 2012] and will be adjudicated by two independent cardiologists blinded to the intervention.

2.2.2 Secondary Endpoints

1. Hospital length of stay, coronary care length of stay.
2. Proportion of patients receiving invasive coronary angiography during index hospitalisation;
3. Proportion of patients receiving coronary revascularisation during index hospitalisation;
4. Proportion of patients receiving subsequent unplanned coronary revascularisation after index hospitalisation within 12 months;
5. Proportion of patients in CTCA arm receiving invasive coronary angiography despite <50% stenosis on CTCA;
6. Proportion of patients assigned to CTCA with normal or mild non-obstructive disease.
7. Proportion of patients prescribed ACS therapies during index hospitalisation;
8. Proportion of patients discharged on prevention treatment or have alteration in dosage of prevention treatment during index hospitalisation;
9. Representation or rehospitalisation with suspected ACS/recurrent chest pain within 12 months;
10. Patient symptoms and quality of life up to 12 months;
11. NHS resource utilisation;
12. Patient satisfaction.
13. Clinician certainty of presenting diagnosis after CTCA.

Safety:

1. Proportion of patients with allergy/anaphylaxis/acute kidney injury;
2. Proportion of patients with alternative diagnoses that relates to presentation on CTCA e.g. aortic dissection or pulmonary embolus
3. Proportion of patients with incidental finding but potentially concerning on CTCA e.g. malignancy or pulmonary nodules
4. Total average radiation exposure from CTCA in the intervention arm during index hospitalisation.

Cost effectiveness: Estimated in terms of the lifetime incremental cost per quality-adjusted life year (QALY) gained.

3 STUDY DESIGN

RAPID-CTCA is an open prospective parallel group randomised controlled trial of CTCA and standard care or standard care only in patients presenting to the ED, MAU, or cardiology with suspected or confirmed ACS. Recruitment will take place in ~35 NHS tertiary and district hospitals (with and without on-site coronary angiography facilities) with emergency departments, acute medical, radiology and cardiology services. Participants will be randomised to CTCA and standard care, or standard care only. Participants allocated CTCA will receive the scan during the initial admission or if discharged, as an ambulatory patient within 72 hours of randomisation (see section 5.4.2). All participants will be followed up for one year and be asked to complete questionnaires at baseline, 1, 6 and 12 months to assess quality of life, angina symptoms and NHS services usage.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

One-year death or recurrent MI rate for this patient group is ~20% [Mills N *et al*, 2011]. 2424 evaluable patients are required (1212 per arm) to have 90% power to detect a 20% vs.15% difference in one-year death or recurrent MI rate, 2-sided $P < 0.05$. With a 3% drop out rate, the sample size will be 2,500 patients.

4.2 INCLUSION CRITERIA

Patient ≥ 18 years with symptoms mandating investigation for suspected or confirmed ACS with at least one of:

- ECG abnormalities e.g. ST segment depression > 0.5 mm;
- History of ischaemic heart disease (where the clinician assessing patient confirms history based on patient history or available records);
- Troponin elevation above the 99th centile of the normal reference range or increase in high sensitivity troponin meeting European Society of Cardiology criteria for 'rule-in' of myocardial infarction (NB troponin assays will vary from site to site; local laboratory reference standards will be used).

4.3 EXCLUSION CRITERIA

1. Signs, symptoms, or investigations supporting high-risk ACS:
 - ST elevation MI;
 - ACS with signs or symptoms of acute heart failure or circulatory shock;
 - Crescendo episodes of typical anginal pain;
 - Marked or dynamic ECG changes e.g. ST depression of > 3 mm
 - Clinical team have scheduled early invasive coronary angiography on day of trial eligibility assessment.
2. Patient inability to undergo CT:
 - Severe renal failure (serum creatinine > 250 $\mu\text{mol/L}$ or estimated glomerular filtration rate < 30 mL/min);
 - Contrast allergy;
 - Beta blocker intolerance (if no alternative heart rate limiting agent available/suitable) or allergy ;
 - Inability to breath hold;
 - Atrial fibrillation (where mean heart rate is anticipated to be greater than 75 beats per minute after beta blockade).

3. Patient has had invasive coronary angiography or CTCA within last 2 years and the previous investigation revealed obstructive coronary artery disease, or patient had either investigation within the last 5 years and the result was normal.
4. Previous recruitment to the trial;
5. Known pregnancy or currently breast feeding;
6. Inability to consent;
7. Further investigation for ACS would not in the patient's interest, due to limited life expectancy, quality of life or functional status;
8. Prisoners

4.4 CO-ENROLMENT

Co-enrolment will be permitted with non-interventional studies that involve data collection only. Co-enrolment with another interventional trial may be allowed provided this is not expected to place an undue burden upon participants and their families, and will not compromise the primary end-point of either trial. Consideration will also be given to the total exposure to ionising radiation should additional studies require further exposure. Co-enrolment will only be permitted with agreement of the Chief Investigators of both studies.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

The research nurses, where it is locally agreed that they are part of the clinical care team, will identify patients using triage information and clinical or electronic records in the Emergency Department, Cardiology Department or the Medical Assessment Unit. In this case, it is anticipated they would identify patients and make the first approach. Any member of the clinical team who has received general and trial specific training and is on the delegation log may also identify patients in this way.

If research nurses are not considered to be part of the direct care team locally, activities carried out prior to consent (including identification) will be carried out by a member of the direct care team.

Where research nurses are not considered to be part of the care team, the research nurse should ask a member of the direct care team to identify suitable patients and ask permission from the patient to be approached by the research nurse to discuss participation.

There will be no additional trial specific screening tests performed. The patient will receive routine acute clinical assessment including, as a minimum, a 12-lead ECG, vital signs measurement (pulse rate, non-invasive blood pressure, respiratory rate, conscious level, oxygen saturations and skin prick blood sugar) and admission routine blood tests including troponin and renal function. The results of these will inform trial eligibility and the patient may be approached as soon as these are available (normally in the first 2 hours after presentation). Patients may be approached up to 24 hours after presentation. This time period has been chosen as it allows the longest period for recruitment where the patient could be deemed to be receiving acute assessment i.e. up to the point where a 12-hour troponin result is being used by routine clinicians for acute decision making. Patient and clinician will be unaware of treatment allocation until after screening, consent and randomisation.

5.2 CONSENTING PARTICIPANTS

Potentially eligible participants who are willing to take part in the study will be asked to provide written informed consent. Consent will be obtained by trained members of the clinical team or members of the research team who have been delegated this responsibility. The Investigator is responsible for the

delivery of processes to ensure informed consent is obtained before any protocol specific procedures are carried out. The decision of a patient to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

The patient (and if present and appropriate their accompanying relative) will be given a Patient Information Sheet, which will explain the aims of the trial and the potential risks and benefits of the study treatments. If necessary a summary sheet will be provided first to provide a brief outline of the study and allow potential participants to decide whether or not they wish to proceed and before the full Patient Information Sheet is provided.

The patient (and if appropriate the accompanying relative) will be given enough time to consider the trial and ask questions regarding their participation in the trial. At most this could be an hour but may be only 10-15 minutes. Potential participants must receive adequate oral and written information. The oral explanation to the patient will be performed by the clinical research nurse or a trained and delegated member of the clinical team, and must cover all the elements specified in the Participant Information Sheet and Consent Form. The patient must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The patient must be given sufficient time to consider all the information provided. It should be emphasised that the patient 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 representatives of the sponsor(s).

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

Capacity will be assessed by the Principal Investigator (PI) or a clinician responsible for the treatment of the participant. This assessment of capacity will be documented in the participant's medical records. The trial excludes patients who have "life threatening features" and therefore this will effectively exclude patients who lack temporary capacity due to their current illness. Patients with permanent incapacity will not be recruited.

5.3 SCREENING FOR ELIGIBILITY

All patients aged ≥ 18 years of age with suspected or confirmed ACS will be screened for eligibility. Ineligible and non-recruited patients will receive standard medical care.

Female patients of child bearing potential i.e. women who have experienced menarche, are pre-menopausal, have not been sterilised should be asked if they are pregnant prior to entry into the trial. If the patient is unsure, they should be given an hCG pregnancy test to confirm before randomisation.

An anonymised log will be kept for patients who were screened for the study and those who were subsequently found to be ineligible or who were not recruited. This data should be entered onto the e-CRF for central monitoring purposes. Further guidance about screening can be found in the RAPID-CTCA Screening guidelines.

5.4 RANDOMISATION

5.4.1. Randomisation Procedures

After assessment for eligibility and consent, the clinical research nurse or a delegated member of the clinical team will collect the baseline data necessary to complete the pre-randomisation information on RAPID-CTCA Admission CRF. Randomisation will be carried out using a web-based randomisation service (managed by the Edinburgh Clinical Trials Unit) that ensures allocation concealment. Randomisation will be carried out within 24 hours of arrival at the hospital. Once a patient is randomised, s/he will remain in the study and have all outcomes recorded regardless of compliance with randomised pathway allocation, unless s/he specifically withdraws consent to have data stored. Consented patients

will be randomised on a 1:1 basis to CTCA in addition to standard care or standard care alone and will be stratified by study site.

5.4.2. Intervention Allocation

CTCA results will be available to the clinical team to support acute clinical decision making. It is anticipated that the provision of immediate CTCA with early reporting is likely to be variable across the centres. The intervention will be delivered by routine clinical staff. It is anticipated that 60-70% of patients will be recruited between 8.00 am and 6.00 pm and would be eligible for immediate CTCA [Goodacre S et al, 2011]. Patients recruited to the study and randomised to CTCA should receive a CTCA as soon as feasible, and normally on the day of, or day following randomisation providing this does not significantly delay routine processes of care including discharge. Where a clinical decision is made to discharge the participant before the scan takes place, they should be asked to return for ambulatory CTCA within 72 hours. The patient should receive clinical review in the ED, MAU or cardiology after the CTCA, and the CTCA result should be available to support this clinical decision making. Discharged patients will receive an appointment card detailing study contact details, the date, time, and location of their CTCA.

The results of the CTCA are likely to direct subsequent management. A guideline has been developed which will be available to clinicians to guide subsequent management dependent on the CTCA result. [Appendix 1]. A template GP letter is available to clinicians if they wish to use this to inform the GP about non-obstructive disease identified by the CTCA which may require secondary prevention being implemented by the GP.

Other interventions

All other management and admission or discharge decisions will be at the discretion of the treating clinicians. Sites will be requested not to use CTCA as part of the routine investigation of ACS and this will be closely monitored.

Blinding

This is an open trial. The patient, recruiting and treating clinicians and radiologist will not be blinded to the intervention including results. Outcome assessors, however, will be blinded to the intervention.

Follow up

Patients will be followed up using routine clinical notes and research contact with the patient by phone, email or post. A 3% loss to follow up (patient withdrawal and inability to retrieve data for the primary outcome from routine NHS records) is built into the sample size calculation for the primary outcome; all patients will be analysed for the primary outcome on an intention-to-treat basis. At Trusts where it is not possible to routinely get this data from the NHS records, the research team at site will attempt to contact the participant and/or their GP by telephone to gather the 12-month follow up data. All patients will be followed for 1 year.

5.4.3. Compliance and withdrawal of Study Participants

Study participants are free to withdraw from the trial at any time. Reasons, if given, will be recorded and data collected up to that time point may be used in the final analyses, unless the patient specifically requests that their data are not used. If the patient withdraws consent to have their data stored, then this will be documented on the trial CONSORT flow diagram as 'withdrawn' and their data will not be used in the final analyses. Patients may withdraw from participation in active follow up but data will continue to be collected unless the patient requests otherwise. The patient may be willing to give a reason for withdrawal but this is not obligatory.

Crossover

Any patient in the control group that has a CTCA as part of routine care within 30 days of randomisation will be defined as a crossover and does not need to be recorded as a deviation.

Non-adherence

This will be defined as to have occurred in any participant not receiving a reported CTCA if randomised to it within 72 hours of the randomisation and this would be recorded as a deviation. This allows

ambulatory CTCA to be delivered when appropriate.

Individual site retention, crossover and non-adherence will be monitored and reviewed at the Project Management Group and Trial Steering Committees meetings.

6. STUDY ASSESSMENTS

Patients will be screened, consented, recruited and randomised in the ED, Cardiology or MAU of participating centres within 24 hours of arrival to the hospital. All patients will receive standard acute clinical assessment including a presentation 12-lead ECG and troponin measurement.

CTCA will be delivered and reported by a trained radiologist or cardiologist within an established radiology service as soon as possible, ideally within 2 hours of procedure and reported and communicated immediately to the treating clinician.

Patients randomised to standard care will receive the standard management for patients with suspected or confirmed ACS at that NHS hospital site. The only difference will be the early use of CTCA in the intervention arm and the subsequent impact on patient care after the result is provided to the clinician for clinical decision making. Local chest pain management guidelines will be collected or confirmation obtained from PI that CTCA is not currently in routine use for eligible patients (including change in practice, during the period of the trial).

CTCA delivery

The technology being assessed is 64 slice or greater multidetector CT scanners enabled to perform ECG-gated cardiac studies. The examination may include a non-contrast ECG-triggered acquisition for calcium scoring (if part of local protocol) and a post-contrast ECG-gated acquisition covering the whole of the heart and the root of the aorta.

Patients must be able to hold their breath for >20 seconds. The intervention will be for no longer than 30 minutes and the patient will be observed for a period of 30 minutes afterwards.

Radiation reduction techniques will be employed and, where appropriate, intravenous or oral beta blockade (or alternative heart rate limiting agent) will be used to reduce heart rate (target of <70 /min) enabling significant radiation dose saving protocols.

Due to the variation in conversion factors used by sites to convert dose-length product (DLP) to effective dose in mSv, radiation dose will be routinely reported for the trial as DLP. A DLP to mSv conversion factor of 0.014 mSv/mGy/cm will be used for trial reporting in line with recent publications in this area of research.

A typical participant with a heart rate below 70 beats per minute in sinus rhythm and a BMI <25 should have a DLP ≤ 686 mGy.cm and cases exceeding this will be considered to be a protocol deviation. Deviations will be reviewed by a Radiologist/Cardiologist in the central trials team and any cases which have an impact on patient safety or study outcomes will instead be reported as a protocol violation. For other participants, without the typical characteristics stated above, DLP values ≥ 686 mGy.cm are anticipated as part of routine clinical practice (for example, due to the need for continuous retrospectively gated scanning in some participants with arrhythmia). For such participants, any DLP which exceeds 1500 mGy.cm will be considered to be a protocol deviation. Deviations will be reviewed by a Radiologist/Cardiologist in the central trials team and any cases which have an impact on patient safety or study outcomes will instead be reported as a protocol violation.

All participating centres will be required to verify that their CTCA imaging protocol complies with the doses outlined in the research protocol prior to recruitment and patient doses will be recorded and monitored as part of the study. Iodine based contrast agent will be administered intravenously using the standard local procedure at each site. The use of GTN for coronary artery dilatation will be used at the discretion of individual centres.

Further guidance can be found in the trial CT coronary angiography guidance document.

CTCA result reporting

CTCA will be usually reported by a trained radiologist or cardiologist at recruiting centres as soon as possible, ideally within 2 hours and communicated immediately to the treating clinician.

The clinical report detailing the results should be reported according to the Society of Cardiovascular CT guidelines, with the use of the AHA coronary artery segment model and will include both the calcium score if calculated and the presence of cardiac and non-cardiac findings. Stenoses will be quantified as: no significant coronary artery disease (estimated stenosis <10%), mild non-obstructive disease (estimated stenosis of 10-49%), moderate non-obstructive disease (estimated stenosis of 50-70%), or obstructive coronary artery disease (estimated stenosis of >70%).

The research Scan Report should also be completed by the radiologist/cardiologist and will record scanner technology, acquisition protocol, dose length product and patient characteristics.

A proportion of CTCA reporting may be delivered remotely using remote access technology by a core group of readers. Transfer of image data is simple and a well-established process within the UK for out-of-hours reporting. Secure electronic transfer via the national PACS system (with required permissions) will allow reporting using voice recognition dictation either direct to the host radiology information system or via e-mail direct to the referring centre.

QA reporting of CTCA scans

A proportion of scans will be re-reported by experts independent to the trial site and blinded to the initial report to measure inter-observer reliability. The first 10 scans carried out at each site will undergo this process as well as a 5% random sample of the remaining scans, as detailed in the working practice document 'Dual Quality Assurance Reporting of CTCA Scans'.

Impact of technology on care pathway

A trial guideline on the management of trial participants depending on CTCA result is listed in appendix 1. This will, however, not be mandated as this is a pragmatic trial investigating the impact of the diagnostic intervention on practice and clinical outcomes.

Current alternative investigation strategies and standard care arm

Investigation guidelines and strategies for each centre will be collected and the use of CTCA will be monitored during the trial. Each centre will be requested not to use CTCA in the routine assessment of suspected or confirmed ACS during trial recruitment and should inform the trials team about any changes to local practice.

7. DATA COLLECTION

Data collection for primary, secondary and safety clinical outcomes

Data will be collected by the research team from routinely available NHS hospital records or trial specific documentation and will include the following categories: eligibility criteria, consent and baseline demographics, comorbidities, regular treatment, ECG results, vital signs, blood results, admission and discharge diagnoses, cardiology and other relevant investigations or interventions, length of stay, repeat hospitalisations and adverse events. Detail will also be collected on the trial intervention including timing, details of the procedure including dose, reporting clinician, report including incidental findings, and any adverse events as a result of the intervention.

Collection of cost and health outcome data

Length of stay and major adverse cardiac events will be recorded from telephone contact of patients, hospital and primary care records, and deaths from the Central Registry Office or equivalent. At baseline, 1, 6 and 12 months, quality of life and angina symptoms will be measured using the EQ-5D-5L and ROSE questionnaires by direct patient interview, postal or email survey with telephone follow up for non-responders after two mailings two weeks apart.

8. STATISTICS AND DATA ANALYSIS

Statistical Analysis

The trial will be reported on an intention-to-treat basis. The primary outcome is defined as first event of all cause death or recurrent non-fatal MI type 1 or 4b. Time to primary outcome is defined as time from randomisation to primary outcome. Patients discontinuing the study (for any reason) prior to reaching primary outcome will have their time to primary outcome censored at the last contact date. The relationship between intervention and the primary outcome will be analysed using Cox proportional hazard regression adjusted for study site (used to stratify the randomisation), age, baseline GRACE score, previous CAD, and baseline troponin level. The results will be expressed as a hazard ratio with the corresponding 95% confidence intervals and p-value. The individual elements of the composite primary outcome will be reported separately. Subgroup analysis on the primary outcome is planned for age, baseline GRACE score, previous CAD and baseline troponin concentration. These will be assessed by examining the effect of entering the treatment by subgroup interaction into the Cox regression model. Secondary outcomes will be analysed using appropriate methods: logistic regression for binary outcomes and linear regression for normally distributed continuous outcomes, adjusted as described above. Continuous outcomes that are not normally distributed will be analysed using appropriate nonparametric techniques. The primary analysis will be intention-to-treat. Every effort will be made to minimise missing data, and our primary analysis will be a complete case analysis. If there is a sufficient level of missing data for it to affect our conclusions, a multiple imputation analysis will be undertaken, using clinically appropriate variables, as a sensitivity analysis. A full statistical analysis plan will be written during the trial, and finalised prior to database lock.

Economic analysis

Economic evaluation will assist policy makers to decide whether multidetector computed tomography scanning represents a cost-effective use of NHS resources. Cost-effectiveness analysis will be used to estimate the incremental costs and quality adjusted life years (QALYs). The economic analysis will include a) within-trial cost effectiveness analysis (i.e comparing the observed costs and QALYs of the intervention and control groups during the trial period), and b) analysis of the long-term cost effectiveness of CTCA, by adapting an existing decision analytic model [Goodacre S et al, 2013; Thokala P et al, 2012],

In the within trial cost-effectiveness analysis, incremental cost per QALY gained by using CTCA compared to standard care will be estimated by calculating the area under the curve for health utility using the EQ-5D-5L and health service costs up to one year. Quality of life and symptoms will be measured using the EQ-5D-5L and ROSE questionnaires (see above) at baseline and 1, 6 and 12 months after index admission. All health care consumption and costs will be estimated from a societal perspective using patient self-reported questionnaires, and from hospital records. Costs will be attributed to the need for (i) continued hospitalisation, (ii) additional invasive or non-invasive imaging, (iii) drug therapy, and (iv) rehospitalisation for myocardial ischaemia. Costs of hospital admission will be measured using a top-down costing strategy. These costs will be measured for each patient in the trial and multiplied by national average costs to provide the estimated cost per patient. Local unit costs for staff and consumables will be obtained from each hospital finance department.

Long term cost-effectiveness will be estimated by adapting an existing model, developed for as part of a previous HTA evidence synthesis project [Goodacre S et al, 2013; Thokala P et al, 2012]. The model used published sources to capture the life expectancy, annual costs and corresponding annual utilities, based on whether they had MI at initial hospital attendance and whether they suffered reinfarction. The data from the trial will be input into the model which estimates the lifetime QALYs and costs of surviving patients. The results will be reported as the incremental cost effectiveness ratio (ICER) of CTCA arm compared to usual care.

Sensitivity analyses will explore the potential impact of parameters upon costs, QALYs and ICERs. Parameter uncertainty will be included in probabilistic sensitivity analysis based on Monte Carlo simulation. Cost effectiveness acceptability curves (CEACs) will be plotted to identify the probability of the CTCA arm being cost effective compared to standard care for a range of threshold values for an additional QALY.

9. ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

All adverse events (AE) meeting the criteria outlined in section 9.2.1 must be reported in detail on the Adverse Events CRF. Participants undergoing CTCA will be instructed to contact their Investigator after consenting to join the trial if any symptoms develop from consent until 10 days after joining the study. Participants in the standard care arm that go on to receive a scan should also have any relevant AEs recorded.

In the case of an AE, the Investigator should initiate the appropriate management according to their medical judgment. Participants with AEs present at the last visit must be followed up until resolution of the event.

9.1. DEFINITIONS

Adverse Event (AE)

Any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with the study intervention.

Adverse Reaction (AR)

Any untoward and unintended response that has occurred due to the intervention.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

Any AE or AR that:

- results in death of the study participant
- is life-threatening*
- requires inpatient hospitalisation[^] or prolongation of existing inpatient 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

* 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.

[^] Any hospitalisation that was planned prior to randomisation will not meet SAE criteria. Any hospitalisation that is planned post randomisation, will meet the SAE criteria.

9.2. IDENTIFYING AEs AND SAEs

All AEs and SAEs that meet the reporting criteria in sections 9.2.1 and 9.2.2 will be recorded from the time a participant signs the consent form to take part in the study until 10 days afterwards. . Patients who have consented to the trial will be asked to contact the research team if they experience any untoward effects within these 10 days.

AEs and SAEs may also be identified via information from support departments e.g. laboratories or the patient record. These will be reported to the investigator within 7 days of identification.

Any AEs or SAEs out-with the given definitions will not be recorded during the study.

9.2.1 Adverse Events relating to CT Scanning

The following Adverse Events can be attributed to the application of CTCA and should be recorded as an AE (and reported as an SAE if appropriate):

- Contrast related anaphylaxis/allergy requiring treatment, requiring critical care admission or resulting in cardiac arrest or death.

- Contrast related AKI or Acute on CKD
- Side effects or complications related to beta blocker (or alternative HR-limiting medication) or Glyceryl Trinitrate premedication.

No other AEs out-with this definition will be recorded on the CRF.

9.2.2 SAE reporting and exemptions

All SAEs that meet the definition given in section 9.1 should be reported to the Sponsor unless they meet the exemption criteria below. SAEs should be reported from consent until 10 days afterwards.

These events are anticipated to occur in this patient group and will not be reported to the Sponsor but will be collected in the CRF for all participants:

- Malignant arrhythmia – CHB requiring pace maker; VT/VF/SVT requiring cardioversion or defibrillation
- Cardiac Arrest
- Death
- ICU admission
- Procedure related MI, coronary artery dissection, pseudo aneurysm

9.3. RECORDING AEs AND SAEs.

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the CRF and on the SAE form (if the AE meets the criteria of serious).

9.4 ASSESSMENT OF AEs AND SAEs

Each AE must be assessed for seriousness, causality, severity and expectedness by the PI or another suitably qualified physician in the research team who is trained in recording and reporting AEs and who has been delegated this role.

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SAR but can upgrade an AE to an SAE or SAR if appropriate.

The Investigator will make an assessment of seriousness (as defined in section 9.1).

9.4.1. Assessment of Causality

The Investigator will make an assessment of whether the AE is likely to be related to the study intervention according to the following definitions:

Unrelated: where an event is not considered to have occurred as a result of the study intervention.

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 study intervention.

Where there are two assessments of causality (e.g. between PI and CI), the causality assessment by the Investigator cannot be downgraded. In the case of a difference of opinion, both assessments are recorded and the 'worst case' assessment is used for reporting purposes.

9.4.2. Assessment of Expectedness

If the AE is judged to be related to the study intervention, the Investigator will make an assessment of expectedness.

Expected: The type of event is expected in line with the study intervention.

Unexpected: The type of event was not listed in the protocol or related documents/literature as an expected occurrence.

9.4.3. Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE and record this on the CRF or 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.

9.5 REPORTING OF SAEs/SARs

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance & QA Office **immediately or within 24 hours**. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 9.4.2, Assessment of Causality and 9.4.3, Assessment of Expectedness.

The SAE form will be transmitted by fax to ACCORD on **+44 (0)131 242 9447** or may be transmitted by hand to the office or submitted via email to Safety.Accord@ed.ac.uk. 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 faxed to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

9.6 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator will follow each participant until resolution or death of the participant. Follow up information on an SAE will be reported to the ACCORD office.

AEs still present in participants at the last study visit will be monitored until resolution of the event or until no longer medically indicated.

10 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

The Edinburgh CTU will be responsible for trial management including: organisation of management group meetings, organisation of the steering committee and data monitoring committee, contracting with other organisations, preparation of REC and R&D applications, standard operating procedures, provision of the randomisation system, database development, data management, data analysis, writing the report and dissemination of findings.

10.1 TRIAL MANAGEMENT GROUP

The trial will be led by Alasdair Gray and coordinated by an experienced ECTU trial manager and emergency medicine research nurse coordinator with support from ECTU. A project management group (PMG) comprising the applicants and relevant members of the ECTU team will be formed. The Academic and Clinical Central Office for Research & Development (ACCORD) in Edinburgh will provide Sponsorship and monitoring oversight for the project and the trial will be conducted in line with the relevant Sponsor SOPs which are <http://www.accord.ed.ac.uk/standardopprocs/CRSOPs.html>.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

10.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the study. The terms of reference of the Trial Steering Committee, the draft template for reporting and the names and contact details are detailed in the TSC charter.

10.3 DATA MONITORING COMMITTEE

A Data Monitoring Committee will be composed of independent members and at a minimum will include a statistician, a cardiologist, a radiologist and an emergency or acute medicine physician. The Peto-Haybittle rule will be used by the Data Monitoring Committee as a guideline on the primary endpoint to trigger discussions on stopping the trial. Importantly the decision to stop the trial will not rely on p-values alone and will consider whether the results are convincing to the clinical community and patients.

10.4 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor and REC review. In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation.

11 GOOD CLINICAL PRACTICE

11.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP).

A favorable ethical opinion will be obtained from the appropriate REC and local R&D approval will be obtained prior to commencement of the study.

11.2 INVESTIGATOR RESPONSIBILITIES

The PI 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 GCP, the following areas listed in this section are also the responsibility of the PI. Responsibilities may be delegated to an appropriate member of study site staff.

11.2.1 Informed Consent

The Principal Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out and this process should be carried out as detailed in section 5.2 of the protocol.

11.2.2 Study Site Staff

The Investigator must be familiar with the intervention, 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 intervention, protocol and their trial related duties.

11.2.3 Data Recording

The PI is responsible for the quality of the data recorded in the CRF at each Investigator Site. The source data plan identifies which source data correspond to CRF data and states which data are recorded directly into the CRF.

11.2.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);

- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.

The ACCORD Research Governance & QA Office will ensure all other documents required by GCP are retained in a Trial Master File (TMF), where required, and that appropriate documentation is available in local ISFs.

11.2.5 GCP Training

Principal Investigators at each site should hold evidence of GCP training and ensure their staff are aware of the guidelines. All staff on the delegation log should have appropriate and relevant training in the research tasks that they undertake.

11.2.6 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, confidential information 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.

11.2.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to those clinicians treating the participants, representatives of the sponsor(s).

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.

12 STUDY CONDUCT RESPONSIBILITIES

12.1 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.

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

12.2 PROTOCOL VIOLATIONS AND DEVIATIONS

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.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 6 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation.

12.3 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

12.4 END OF STUDY

The end of study is defined as 15 months after the recruitment of the last participant.

The Investigators and/or the trial steering committee and/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 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.

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

12.5 INSURANCE AND INDEMNITY

The co-sponsors 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 co-sponsors' 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 co-sponsors 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 Nation Health Service will have the benefit of NHS Indemnity.

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

The protocol for this trial will be submitted for publication and the trial results will be submitted for publication even if this trial stops early. If successfully completed the main paper from this project will be submitted for publication in a leading international general medical journal.

The main outputs will be provided to guideline developing bodies (including NICE, SIGN and the European Society of Cardiology), key professional organisations (such as the College of Emergency Medicine) and patient representative organisations (such as the British Heart Foundation).

13.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a study report will be prepared in accordance with the funders requirements. The authors for this project are listed in the trial's writing committee and publication policy document.

13.2 PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their centres (where appropriate and according to their discretion).

13.3 PEER REVIEW

The trial has been reviewed by the Edinburgh Clinical Trials Unit executive group, the NIHR national cardiovascular group and HTA reviewers.

14 REFERENCES

Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health*. (2010); 13:509-518.

Bateman DN, Dear J, Thanacoody R, Thomas S, Eddleston M, Sandilands E, Coyle J, Cooper J, Rodriguez A, Butcher I, Lewis S, Vliegenthart B, Veiraiha A, Webb D and Gray A. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomised controlled trial. *The Lancet*. Early Online Publication, 28 November 2013. doi: 10.1016/S0140-6736(13)62062-0

Body R, Carley S, McDowell G, Jaffe AS, France M, Cruickshank K, Wibberley C, Nuttall M, Mackway-Jones K. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. *J Am Coll Cardiol*. (2011); 58(13):1332-9.

British Cardiology Interventional Society. Audit Returns: Adult Interventional Procedures. 2012. http://www.bcis.org.uk/resources/BCIS_Audit_2012_for_web_V2_14-10-20131.pdf

Chang A, Litt H, Shofer FS, McCusker C, Baxt WG, Hollander JE. CT coronary angiography during initial visit decreases rate of return visits relative to standard care. *Annals of Emergency Medicine*. (2007); 50:Suppl: S7.

Das R, Kilcullen N, Morrell C, Robinson MB, Barth JH, Hall AS. The British Cardiac Society Working Group definition of myocardial infarction: implications for practice. *Heart*. (2006); 92:21-6.

Department of Health. Tariff information: confirmation of payment by results (PbR) arrangements for 2009-10. 2011.

D'Ascenzo F, Cerrato E, Biondi-Zoccai G, Omedè P, Sciuto F, Presutti DG, Quadri G, Raff GL, Goldstein JA, Litt H, Frati G, Reed MJ, Moretti C, Gaita F. Coronary computed tomographic angiography for detection of coronary artery disease in patients presenting to the emergency department with chest pain: a meta-analysis of randomized clinical trials. *Eur Heart J Cardiovasc Imaging*. (2012); 14:782-9.

Dunham M, Challen K, Walter D. Risk stratification of patients with acute chest pain without a rise in troponin: current practice in England. *Emergency Medicine Journal*. (2010); 27:461-4.

Fox KA, Poole-Wilson PA, Henderson RA, et al, for the Randomized Intervention Trial of unstable Angina (RITA) investigators. Interventional Versus Conservative Treatment for Patients With Unstable Angina or Non-ST-Elevation Myocardial Infarction: the British Heart Foundation RITA 3 Randomised Trial. *Randomized Intervention Trial of unstable Angina*. *Lancet*. (2002); 360:743-751.

Fox KA, Steg PG, Eagle KA, Goodman SG, Anderson FA Jr, Granger CB, Flather MD, Budaj A, Quill A, Gore JM; GRACE Investigators. Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. *JAMA*. (2007); 297:1892-900.

Goldberg RJ, Currie K, White K, Brieger D, Steg PG, Goodman SG, Dabbous O, Fox KA, Gore JM. Six-month outcomes in a multinational registry of patients hospitalized with an acute coronary syndrome (the Global Registry of Acute Coronary Events [GRACE]). *American Journal of Cardiology*. (2004); 93:288-93.1

Goldstein JA, Chinnaiyan KM, Abidov A, Achenbach S, Berman DS, Hayes SW, Hoffmann U, Lesser JR, Mikati IA, O'Neil BJ, Shaw LJ, Shen MY, Valeti US, Raff GL; CT-STAT Investigators. The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trial. *J Am Coll Cardiol*. 2011 Sep 27; 58(14):1414-22.

Goodacre S, Cross E, Arnold J, Angelini K, Capewell S, Nicholl J. The health care burden of acute chest pain. *Heart*. (2005); 91:229-30.

Goodacre S, Cross E, Lewis C, Nicholl J & Capewell S, on behalf of the ESCAPE Research Team. The ESCAPE cluster randomised trial: Effectiveness and Safety of Chest pain Assessment to Prevent Emergency admissions. *BMJ*. (2007); 335:659-662.

Goodacre S, Bradburn M, Fitzgerald P, Cross E, Collinson P, Gray A, Hall A. The RATPAC (Randomised Assessment of Treatment using Panel Assay of Cardiac markers) trial: a randomised controlled trial of point-of-care cardiac markers in the emergency department. *Health Technol Assess*. (2011)15(23):1-108.

Goodacre S, Thokala P, Carroll C, Stevens JW, Leaviss J, Al Khalaf M, et al. Systematic review, meta-analysis and economic modelling of diagnostic strategies for suspected acute coronary syndrome. *Health Technol Assess*. (2013)17(1).

Goodacre S, Cohen J, Bradburn M, Gray A, Bengner J, Coats T on behalf of the 3Mg Research Team. Intravenous or nebulised magnesium sulphate versus standard therapy for severe acute asthma (3Mg trial): a double-blind, randomised controlled trial. *The Lancet Respiratory Medicine*. *The Lancet Respiratory Medicine*. 2013;293 – 300. Gray A, Goodacre S, Newby D, Masson M, Sampson F and Nicholl J on behalf of the 3CPO trialists. Noninvasive Ventilation in Acute Cardiogenic Pulmonary Edema. *New Eng J Med*. (2008); 359:24-33

Hamm CW, Bassand J-P, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D, Neyses L, Perk J, Roffi M, Romeo F, Ruda M, Swahn E, Valgimigli M, Vrints CJ, Widimsky P. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. (2011); 32:2999-3054.

Health and Social Care Information Centre (HSCIC). Hospital episode statistics, admitted patient care - England 2011-12: primary diagnosis, 4 characters table [Internet]. Health & Social Care Information Centre (HSCIC), 2012 [accessed 5.1.14]. Available from: <http://www.hscic.gov.uk/catalogue/PUB08288>.

Hoffmann U, Truong QA, Schoenfeld DA, Chou ET, Woodard PK, Nagurney JT, Pope JH, Hauser TH, White CS, Weiner SG, Kalanjian S, Mullins ME, Mikati I, Peacock WF, Zakrofsky P, Hayden D, Goehler A, Lee H, Gazelle GS, Wiviott SD, Fleg JL, Udelson JE; ROMICAT-II Investigators. Coronary CT angiography versus standard evaluation in acute chest pain. *N Engl J Med*. (2012); 367:299-308.

Hulten E, Pickett C, Bittencourt MS, Villines TC, Petrillo S, Di Carli MF, Blankstein R. Outcomes After Coronary Computed Tomography Angiography in the Emergency Department <http://www.sciencedirect.com/science/article/pii/S073510971300123X> - item1#item1: A Systematic Review and Meta-Analysis of Randomized, Controlled Trials. *J Am Coll Cardiol*. (2013); 61:880-92

Litt H, Gatsonis C, Snyder B, Singh H, Miller C, Entikin D, Leaming J, Gavin L, Pacella C, and Hollander J. Angiography for Safe Discharge of Patients with Possible Acute Coronary Syndromes. *New England Journal of Medicine*. (2012); 366:1393-403.

Mills NL, Churchhouse AM, Lee KK, Anand A, Gamble D, Shah AS, Paterson E, MacLeod M, Graham C, Walker S, Denvir MA, Fox KA, Newby DE. Implementation of a sensitive troponin I assay and risk of recurrent myocardial infarction and death in patients with suspected acute coronary syndrome. *JAMA*. (2011); 305:1210-6.

Mills NL, Lee KK, McAllister DA, Churchhouse AM, MacLeod M, Stoddart M, Walker S, Denvir MA, Fox KA, Newby DE. Implications of lowering threshold of plasma troponin concentration in diagnosis of myocardial infarction: cohort study. *BMJ*. (2012)15; 344:e1533.doi: 10.1136/bmj.e1533.

Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, et al. Diagnostic Performance of Coronary Angiography by 64-Row CT. *New Engl J Med* (2008); 359:2324-2336.

Mowatt G, Cummins E, Waugh N, Walker S, Cook J, et al. Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease. *Health Technology Assessment* 2008;12:1-164.

National Institute for Health and Care Excellence. Unstable angina and NSTEMI: The early management of unstable angina and non-ST-segment-elevation myocardial infarction. NICE clinical guideline 94 [Internet]. Manchester: NICE, 2010

National Institute for Health and Care Excellence. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. NICE clinical guideline 95 [Internet]. London: NICE, 2012.

National Institute for Health and Care Excellence <http://publications.nice.org.uk/newgeneration-cardiac-ct-scanners-aquilion-one-brilliance-ict-discovery-ct750-hd-and-somatomdg3/outcomes>. London: NICE, 2013.

Office for National Statistics (ONS). Interim Life Tables 2006-08. 2008.

Office for National Statistics (ONS). Death registration summary tables - England and Wales, 2011 (Final) [Internet]. 2012 [accessed 5.1.14]. Available from: <http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-276695>

Polanczyk CA, Kuntz KM, Sacks DB, Johnson PA, Lee TH. Emergency department triage strategies for acute chest pain using creatine kinase-MB and troponin I assays: a cost effectiveness analysis. *Ann Intern Med* 1999 Dec 21; 131(12):909-18.

Redberg RF. Coronary CT angiography for acute chest pain. *N Engl J Med*. (2012); 367:375-

Schroeder S, Achenbach S, Bengel F, Burgstahler C, Cademartiri F, de Feyter P, George R, Kaufmann P, Kopp AF, Knuuti J, Ropers D, Schuijf J, Tops LF, Bax JJ. Cardiac computed tomography: indications, applications, limitations, and training requirements: Report of a Writing Group deployed by the Working Group Nuclear Cardiology and Cardiac CT of the European Society of Cardiology and the European Council of Nuclear Cardiology. *Eur Heart J*. (2008); 29:531-56.

Scottish Intercollegiate Guidelines Network. SIGN 93. Acute coronary syndromes. A national clinical guideline. Edinburgh: SIGN, 2013.

Shaw LJ, Peterson ED, Kesler K, Hasselblad V, Califf RM. A metaanalysis of predischARGE risk stratification after acute myocardial infarction with stress electrocardiographic, myocardial perfusion, and ventricular function imaging. *Am J Cardiol*. (1996); 78:1327-37.

Thokala P, Goodacre SW, Collinson P, Stevens JW, Mills NL, Newby DE, Morris F, Kendall J, Stevenson MD. Cost-effectiveness of presentation and delayed troponin testing for acute myocardial infarction. *Heart*. (2012); 98:1498-1503.

Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. *Eur Heart J*. (2012); 33:2551-67.

Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, for the PLATO Investigators. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. *N Engl J Med*. (2009); **361**:1045-1057

Ward S, Lloyd JM, Pandor A, Holmes M, Ara R, Ryan A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess*. (2007); 11(14):1-4.

Wiener RS, Schwartz LM, Woloshin S. When a test is too good: how CT pulmonary angiograms find pulmonary emboli that do not need to be found. *BMJ* (2013); 347:f3368

Appendix 1 - Management guideline for trial intervention arm

CTCA result	Troponin result	Trial treatment recommendation
Obstructive Disease: Stenosis $\geq 70\%$	Positive or Negative	1. ACS and secondary preventative therapies; 2. Invasive Coronary Angiography \pm revascularisation.
Moderate Non-obstructive Disease: Stenosis 50-69%	Positive	1. ACS and secondary preventative therapies; 2. Consider Invasive Coronary Angiography if uncertainty about the presence of obstructive coronary artery disease or functional testing.
Moderate Non-obstructive Disease: Stenosis 50-69%	Negative	1. Secondary preventative therapies; 2. Consider Invasive Coronary Angiography if uncertainty about the presence of obstructive coronary artery disease or functional testing.
Mild Non-obstructive Disease: Stenosis $< 50\%$	Positive	1. Consider ACS and secondary preventative therapies. 2. Consider alternative cause of chest pain and troponin rise
Mild Non-obstructive Disease: Stenosis $< 50\%$	Negative	1. Discharge with no further follow up; 2. Consider secondary preventative therapies.
Normal (no evidence of CAD)		Discharge with no further follow up.