COMPUTED TOMOGRAPHY CORONARY ANGIOGRAPHY FOR THE PREVENTION OF MYOCARDIAL INFARCTION

THE SCOT-HEART 2 TRIAL

Sponsor	The University of Edinburgh and Lothian Health Board ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
Protocol authors	Professor David Newby
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Amendment classification and number	Summary of change(s)
Substantial Amendment 01	Addition of >60 years age as risk factor in inclusion criteria Addition of detail on process for sending invitation letters. Other minor administrative changes
Substantial Amendment 03	Section 5.1 Addition of description of Study Within a Trial (SWAT) Section 5.5 Blood sample management from withdrawn participants Section 6 Volume of blood taken during baseline visit Section 6.3 Provision of email account for clinical queries Section 8.1 Event rate analysis moved to remit of the Trial Steering Committee Section 14 Appendix 1: SWAT protocol

SUMMARY

Prevention of cardiovascular disease is currently guided by probabilistic risk scores that both over and under treat individuals, commit most middle-aged people to pharmacotherapy, and have little evidence base. We have demonstrated that use of computed tomography coronary angiography (CTCA) is associated with changes in the diagnosis and treatment of patients presenting with stable chest pain, and that this leads to a marked reduction in the future risk of myocardial infarction. Importantly, the proportionate reduction in coronary events was most marked in those with non-anginal chest pain irrespective of their cardiovascular risk score which again demonstrated poor discrimination. We here propose a randomised controlled trial of at least 6,000 middle-aged individuals at risk of cardiovascular disease that will compare these two strategies of targeting preventative therapies: a probabilistic cardiovascular risk score, and screening with CTCA. This trial will determine if CTCA guided management will be associated with better targeted intervention, prevent over medicating the general population, and result in fewer future coronary heart disease events than the current standard of care using a cardiovascular risk score.

LAY SUMMARY

‘Risk scores’ are a tool commonly used by Doctors to help them decide which patients need medication to prevent heart disease. Risk scores look at your chance of getting heart disease by looking at factors such as age, smoking habit and whether heart disease runs in the family. However, these scores are not always accurate and can mean that some patients are given unnecessary medication and others are not given the medication they need.

In a previous study (the first SCOT-HEART trial), we showed that the use of Computed Tomography Coronary Angiography or CTCA (a scan that gives very clear images of diseased blood vessels of the heart) changed the way

patients with chest pain were diagnosed and treated, and fewer people went on to have heart problems than those only given a risk score.

In the SCOT-HEART 2 trial, we will recruit at least 6,000 people from Scotland who are at risk of heart disease and will compare two ways of deciding how to prevent future heart problems. We will compare the current standard of care, using a Scottish 'risk score', with a CTCA scan to look at the heart. This will help us find out if making decisions based on the results of a CTCA will stop too many people being given medicines they don't really need, and see whether it lowers the number of people developing heart disease.

CONTENTS

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
AE	Adverse Event
CHI	Community Health Index
CI	Chief Investigator
CRF	Case Report Form
eCRF	electronic Case Report Form
CTCA	Computed Tomography Coronary Angiography
DMC	Data Monitoring Committee
ECTU	Edinburgh Clinical Trials Unit
eDRIS	electronic Data Research and Innovation Service
GCP	Good Clinical Practice
GP	General Practitioner
ICH	International Conference on Harmonisation
SLE	Systemic Lupus Erythematosus
NHS	National Health Service
NICE	National Institute of health and Care Excellence
NRS	NHS Research Scotland
PI	Principal Investigator
QA	Quality Assurance
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TSC	Trial Steering Committee

1 INTRODUCTION

1.1 BACKGROUND

Coronary heart disease is the commonest cause of death across the world. The World Health Organisation estimates that 3.8 million men and 3.4 million women die from coronary heart disease each year. Since 1990, more people have died from coronary heart disease than any other cause. In the United Kingdom, coronary heart disease is the single biggest killer. It is responsible for nearly one in six deaths for men and one in ten for women: three times more women die from coronary heart disease than they do from breast cancer. Indeed, 73,000 people die of coronary heart disease in the United Kingdom every year: one person every seven minutes. The death rates are particularly high in Scotland and the North of England, especially in areas of social deprivation. Because deaths are often sudden and unheralded, this is very distressing for those left behind. Coronary heart disease also causes a devastating effect on peoples' lives not just from the large numbers of those who die from it. Disability-adjusted life years, a measure of "healthy years of life lost", can be used to indicate the burden of disease rather than the resulting deaths. The World Health Organisation estimates that coronary heart disease is responsible for 10% of disability-adjusted life years (DALYs) in low-income and 18% in high-income countries. In the United Kingdom, the British Heart Foundation estimates that 2.3 million people are living with coronary heart disease [BHF, 2012].

1.1.1 Prevention of Coronary Heart Disease

1.1.1.1 Cardiovascular Risk Scores

Prevention of coronary heart disease is a major goal of the medical community across the world. In the United Kingdom, the National Institute of health and Care Excellence (NICE) and the Scottish Intercollegiate Guideline Network (SIGN) recommends that a systematic strategy should be undertaken to identify people who are at risk of cardiovascular disease [NICE, 2008 and 2014; SIGN 2017]. The guidance goes on to recommend full assessment and offer statin therapy if the 10-year risk of cardiovascular disease is intermediate-high (≥10%). Cardiovascular risk can be calculated using many of the widely available cardiovascular risks scores: indeed, over 100 such scoring systems have been in existence for more than 10 years [Beswick et al, 2008] including the ASSIGN score (www.assign-score.com) which has been calibrated for the Scottish population [Woodward et al, 2007]. The use of such cardiovascular risk scores is now the current standard of care across the United Kingdom, and similar strategies and recommendations have been made by other bodies in the United Kingdom, such as the Joint British Societies (JBS3) [JBS 3 Board, 2014] and the Scottish Intercollegiate Guideline Network [SIGN, 2017], and across the world including the European Society of Cardiology [Piepoli et al, 2016], and the American College of Cardiology and the American Heart Association [Stone et al, 2014]. The rationale for this practice is to select those individuals at greatest risk to maximise the cost-effectiveness of treatment without recommending therapy in the entire population. However, many risk scores inevitably end up recommending treatment for nearly all patients who are middle aged given that age is such a dominant predictor of cardiovascular risk. Indeed, some have suggested all individuals over 50 years of age should receive a statin [CTTC 2012; Ebrahim & Casas, 2012]. Despite its widespread and near universal adoption as well as the substantial associated healthcare resource

utilisation and cost, the use of cardiovascular risk scores is empirical, often results in resistance to taking statin therapy [Gale et al, 2011; Fong et al, 2018], and has never been validated by clinical trial evidence [Lloyd-Jones et al, 2001; Karmali et al, 2017].

A Cochrane Systematic Review [Karmali et al, 2017] assessed the practice of using risk scores to select individuals for the primary prevention of cardiovascular disease. Although the systematic review identified 41 trials incorporating nearly 200,000 participants, these studies had a high risk of bias and were of low quality. The principal finding of the systematic review was that there was little or no effect on cardiovascular disease events by providing clinicians with cardiovascular risk scores when compared to standard of care (5.4% versus 5.3%; relative risk 1.01, 95% confidence intervals 0.95 to 1.08). The authors concluded that there is major uncertainty whether current strategies for providing risk scores affect subsequent cardiovascular events and called for further research to address this concern.

1.1.1.2 Detection of Coronary Heart Disease in Asymptomatic Individuals

An alternative strategy to applying scores that calculate the probabilistic risk for a disease is to use a diagnostic test that directly identifies the presence of that condition. To date, there have been five trials (n=450 to 2,137) that have assessed imaging to screen for coronary heart disease with a view to primary prevention. One trial used radionuclide myocardial perfusion imaging (the DIAD trial [Young et al, 2009]), three used coronary artery calcium scoring (the St Francis Heart [Arad et al, 2005], PACC [Taylor et al, 2008] and EISNER [Rozanski et al, 2011] trials), and one used computed tomography coronary angiography (the FACTOR-64 trial [Muhlestein et al, 2014]). Although coronary artery calcification is a very good surrogate of coronary heart disease, it does not provide direct information about the total plaque burden or stenosis severity, and can be absent in middle-aged patients with soft non-calcified plaque. Coronary artery calcium scoring and myocardial perfusion imaging are therefore surrogates of disease rather than truly identifying the presence or absence of coronary heart disease. In this regard, CTCA is the gold standard non-invasive imaging technique that can detect the presence of both calcified and non-calcified coronary heart disease with a high degree of accuracy. The advent of modern computed tomography scanners facilitates the use of low radiation dose protocols that can be rapidly applied in a timely and safe manner. NICE recommends CTCA as the first line test in symptomatic patients with possible angina given its high diagnostic performance and cost-effectiveness. This therefore begs the question of whether CTCA can be used to better identify asymptomatic individuals with subclinical coronary heart disease.

The FACTOR-64 trial [Muhlestein et al, 2014] has been the only CTCA trial in primary prevention, and it specifically recruited 900 patients with type 1 or 2 diabetes mellitus only. Participants found to have coronary heart disease on CTCA were targeted for more intensive risk factor modification although 75% of trial participants were already on a statin at baseline. Compared to standard of care, those assigned to CTCA had an LDL-cholesterol concentration that was 0.06 mmol/L lower (p=0.02) but there was no difference in blood pressure or haemoglobin A1c concentrations. In the intention-to-treat analysis, the primary end-point occurred in 6.2% of the CTCA group compared to 7.6% in the control group (hazard ratio, 0.80 [95% confidence interval, 0.49-1.32]; p=0.38). In the as-treated analysis, the respective event rates were 5.6% vs 7.9% (hazard ratio, 0.69 [95% confidence interval, 0.41-1.16]; p=0.16). The failure to demonstrate a benefit is therefore

likely to represent the inability to deliver a major difference in treatment and management consequent on the application of the imaging test, and a lack of power due to the small sample size and lower than anticipated event rate.

1.1.1.3 Detection of Coronary Heart Disease in Individuals with Chest Pain

We previously conducted the Scottish COmputed Tomography of the HEART (SCOT-HEART) trial. This was a large multicentre randomised controlled trial of 4,146 patients presenting to rapid access chest pain clinics across Scotland with suspected angina pectoris due to coronary heart disease [SCOT-HEART, 2015]. Patients were randomised (1:1) to CTCA plus standard of care, or standard of care alone. In those undergoing CTCA, 38% had normal coronary arteries, 37% had non-obstructive coronary artery disease, and 25% had obstructive coronary artery disease. In the standard care group (as well as the CTCA group), the mean age was 57±10 years and the median ASSIGN cardiovascular risk score was 15% over 10 years. Clinicians attending the patients in the CTCA group were prompted to prescribe preventative therapies in the presence of obstructive or non-obstructive coronary heart disease. Clinicians attending the patients in the standard care group were prompted to prescribe preventative therapies when the ASSIGN score exceeded a 10-year risk of 20% (the standard of care at the time of study inception) [Newby et al, 2012; SIGN, 2017]. Ultimately, less than a third of patients were diagnosed with angina due to coronary heart disease. Overall, the trial showed that CTCA changed the diagnosis in 1 in 4, investigations in 1 in 6, and treatment in 1 in 4 [SCOT-HEART, 2015; Williams et al, 2016]. Although symptoms of angina were similar at 6 months [Williams et al, 2017], CTCA was associated with a markedly reduced rate of coronary heart disease death or non-fatal myocardial infarction at 5 years (hazard ratio 0.59, 95% confidence intervals 0.41 to 0.84; p=0.004) [SCOT-HEART, 2018]. Interestingly, many of these events occurred in patients with non-anginal chest pain or non-obstructive coronary artery disease. This trial therefore provides strong evidence that CTCA guided management can have major benefits, albeit in those with symptoms suggestive of coronary heart disease.

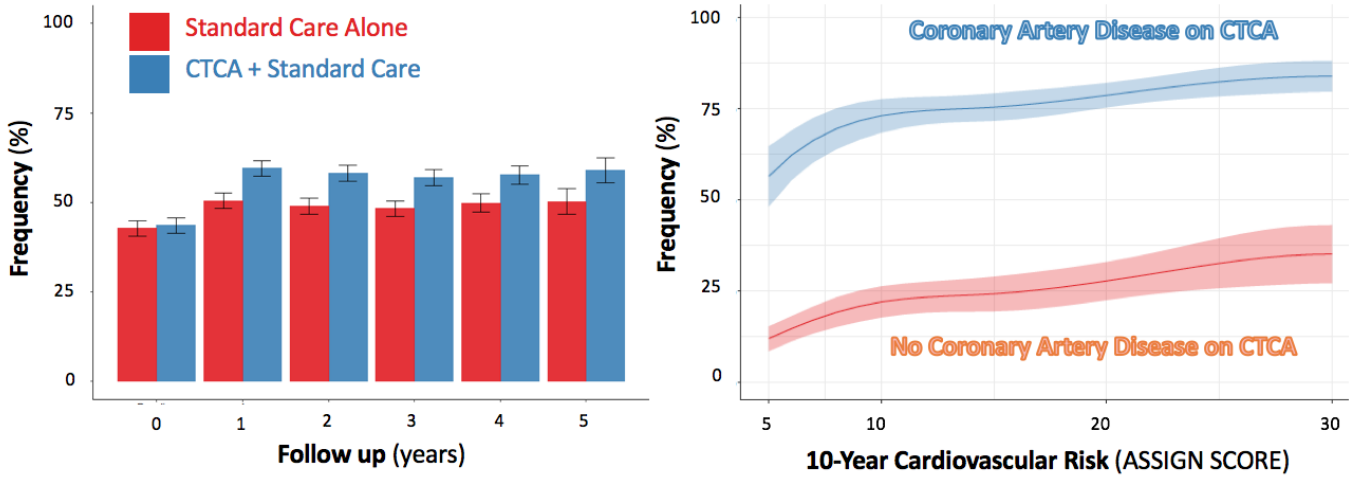
1.1.2 Sub-analyses of the SCOT-HEART Trial

There are several interesting observations from the SCOT-HEART trial [SCOT-HEART 2015 and 2018]. First, the reduction in fatal and non-fatal coronary events was independent of symptoms. Indeed, the point estimates suggested that patients with non-anginal chest pain showed at least as much benefit from CTCA (hazard ratio 0.45, 95% confidence intervals 0.19 to 1.03) as those with possible angina (hazard ratio 0.60, 95% confidence intervals 0.37 to 0.96) and those with known coronary heart disease (hazard ratio 0.65, 95% confidence intervals 0.32 to 1.32).

Second, a large proportion (40-50%) of patients were on antiplatelet or statin therapy at baseline [SCOT-HEART, 2015] and, after 5 years of follow up, the overall rates of prescription of these drugs varied by ~10% [SCOT-HEART, 2018]. Indeed, the relative reduction in coronary events was similar whether participants were taking statin therapy at baseline (hazard ratio 0.57, 95% confidence intervals 0.34 to 0.95) or not (hazard ratio 0.57, 95% confidence intervals 0.28 to 1.15). However, CTCA guided management markedly increased statin use in those with non-anginal chest pain who had coronary artery disease on the computed tomography scan irrespective of the ASSIGN score (see Figure). The overall rates of change in statin therapy therefore encompasses both

cessation and initiation of therapy, suggesting that CTCA is a better guide for patient management.

Figure



Frequency of statin therapy use in the SCOT-HEART Trial (a) according to study allocation in all patients (left panel), and (b) in the presence or absence of coronary heart disease on CTCA across the range of cardiovascular risk in patients with non-anginal chest pain (right panel).

Third, the ASSIGN risk score was a poor predictor of coronary artery disease. The average ASSIGN score (10-year cardiovascular risk) was 13 (range 1-59) in patients with normal coronary arteries, and 23 (range 2-62) in those with obstructive coronary artery disease. Indeed, in those undergoing CTCA, 39% of patients were misclassified using an ASSIGN score of 20, and 33% were misclassified using an ASSIGN score of 10.

Finally, the prevention of myocardial infarction requires the targeting of non-obstructive coronary artery disease as 50-65% of patients who suffered a subsequent myocardial infarction had non-obstructive disease on CTCA at baseline [SCOT-HEART, 2018; Ferenick et al, 2018]. Thus, **the relative reductions in coronary events were similar irrespective of symptoms** (indeed absolute reductions were also similar: 1.5% for possible angina and 1.3% for non-anginal chest pain)**, independent of baseline statin use or cardiovascular risk score, and driven by both non-obstructive and obstructive coronary artery disease**.

Our findings suggest that using a cardiovascular risk score both over and under treats individuals, and that CTCA appears to be associated with better reductions in coronary events irrespective of the risk score. The reasons for the benefits of CTCA are many fold and we hypothesise that this relates to better targeted secondary prevention (see Figure), closer adherence to lifestyle modifications and preventative therapies, and coronary revascularisation in those with prognostically significant disease. **The right patient gets the right treatment**.

Some would argue that over treatment with statins is perhaps less important [CTTC 2012; Ebrahim & Casas, 2012]. This is because the costs of statins are relatively cheap: for

example, one year of simvastatin 40 mg daily is only around £15 in the United Kingdom. However, this ignores the substantial medical costs of risk scoring, monitoring response to therapy, and prescribing and pharmacy costs. Perhaps more importantly, there is the impact on patients. In the SCOT-HEART trial, the biggest improvements in quality of life were seen in patients who stopped taking statin therapy because of a normal computed tomography coronary angiogram [Williams et al, 2017]. If a patient does not need treatment, they cannot obtain clinical benefit and can only run the risk of potential side effects, no matter how low such a risk is. Although the benefits of cessation of statin therapy will not be seen through an impact on clinical events, they are important for our patients [Kutner et al, 2015; Linsky et al, 2015] and something that has come through very strongly from our patient focus groups. Current risk scores over medicate a large proportion of the general population and this is a real concern for many individuals. Such overtreatment will inevitably affect compliance [Clifford et al, 2008] and quality of life.

1.2 RATIONALE FOR STUDY

The scientific principles and rationale underlying our trial are:

- cardiovascular risk scores are a blunt tool to determine who should receive preventative therapy leading to both under and over treatment
- current approaches lead to over medicalising and medicating nearly all middle-aged individuals
- futile treatment is pointless and asymptomatic middle-aged individuals prefer not to take medication unless it is necessary for their future health
- CTCA is a safe, acceptable and cost-effective method of screening for the presence of obstructive or non-obstructive coronary heart disease
- CTCA guided management causes substantial reductions in future coronary events irrespective of symptoms or risk score estimates
- individuals may engage better with lifestyle and preventative interventions if they definitively know that they have coronary heart disease

2 STUDY OBJECTIVES

2.1 OBJECTIVES

We hypothesise that, in individuals being considered for cardiovascular preventative therapy, CTCA guided management will reduce the future risk of coronary heart disease death or non-fatal myocardial infarction compared to management guided by a cardiovascular risk score.

2.1.1 Primary Objective

The primary research objective of the trial is to determine whether, in individuals with risk for cardiovascular disease, coronary heart disease screening with CTCA is associated with a reduction in the rate of coronary heart disease death or non-fatal myocardial infarction when compared to a probabilistic cardiovascular risk score approach.

2.1.2 Secondary Objectives

The secondary objectives are to assess the impact of the two approaches (risk score versus CTCA) on the following:

- **Lifestyle Changes.** To include self-reported smoking habit, body weight, physical activity and diet.
- **Pharmaceutical Preventative Therapy.** To include antiplatelet and statin therapy. Initial and ongoing prescribing practice as well as overall compliance will be examined.
- **Quality of Life.** To assess of the impact of the two management strategies on patient well-being and quality of life.
- **Incidental Findings and Radiation Exposure.** This will be specifically to look at the incidence and impact of incidental findings as well as the radiation dose of CTCA in those randomised to receive this scan.
- **Referral to Secondary Care.** To include onward referral to outpatient cardiology and respiratory services.
- **Procedural Outcomes.** To include rates of invasive coronary angiography and coronary revascularisation.
- **Cardiovascular Events.** Fatal and non-fatal myocardial infarction or stroke.
- **Mortality.** All-cause death, cardiovascular (coronary and non-coronary) death or non-cardiovascular death.
- **Cost-effectiveness.** Health economic analysis will used to assess cost-effectiveness as we have described previously for the SCOT-HEART trial [Williams et al, 2016].

2.2 ENDPOINTS

2.2.1 Primary Endpoint

The primary outcome will be coronary heart disease death or non-fatal myocardial infarction.

2.2.2 Secondary Endpoints

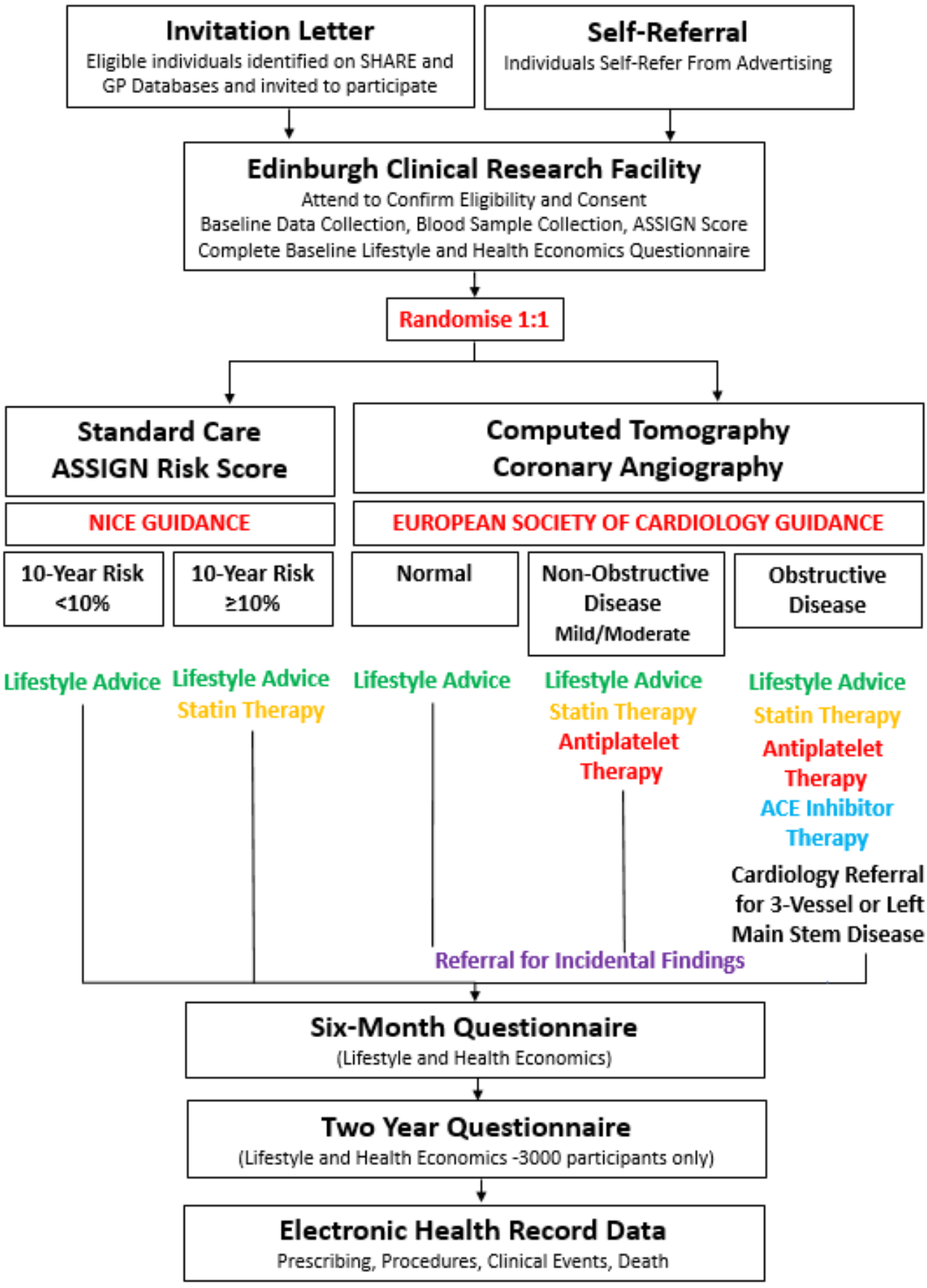
The secondary outcomes will include:

(i) death: all-cause, cardiovascular, coronary heart disease and non-cardiovascular death,
(ii) cardiovascular events: fatal and non-fatal myocardial infarction or stroke,
(iii) cardiovascular procedures: invasive coronary angiography and coronary revascularisation,
(iv) quality of life
(v) rates of prescription of preventative therapies (anti-platelet, statin and angiotensin-converting enzyme inhibitor therapies),
(vi) uptake of lifestyle modifications (smoking, exercise and diet),
(vii) radiation dose and incidental findings from CTCA,
(viii) health economic assessment of cost-effectiveness.

There will also be numerous exploratory and mechanistic outcomes that will be exploited from the trial dataset (to be fully pre-specified in the comprehensive Statistical Analysis Plan).

3 STUDY DESIGN

This will be a prospective open-label parallel-group randomised controlled trial. It will assess the two current approaches of either risk stratification or screening of individuals at risk of coronary heart disease. Both trial groups will be managed by current standard of care guidelines. For the cardiovascular risk score group, treatment will follow current NICE guidance [NICE, 2014]. For the CTCA group, treatment will follow current European Society of Cardiology guidance for stable coronary heart disease [Montalescot et al, 2013].


Invitation Letter
Eligible individuals identified on SHARE and GP Databases and invited to participate
Self-Referral
Individuals Self-Refer From Advertising
Edinburgh Clinical Research Facility
Attend to Confirm Eligibility and Consent
Baseline Data Collection, Blood Sample Collection, ASSIGN Score
Complete Baseline Lifestyle and Health Economics Questionnaire
Randomise 1:1
Standard Care
ASSIGN Risk Score
Computed Tomography
Coronary Angiography
NICE GUIDANCE
EUROPEAN SOCIETY OF CARDIOLOGY GUIDANCE
10-Year Risk <10%
10-Year Risk ≥10%
Normal
Non-Obstructive Disease Mild/Moderate
Obstructive Disease
Lifestyle Advice
Lifestyle Advice
Statin Therapy
Lifestyle Advice
Lifestyle Advice
Statin Therapy
Antiplatelet Therapy
Lifestyle Advice
Statin Therapy
Antiplatelet Therapy
ACE Inhibitor Therapy
Cardiology Referral for 3-Vessel or Left Main Stem Disease
Referral for Incidental Findings
Six-Month Questionnaire
(Lifestyle and Health Economics)
Two Year Questionnaire
(Lifestyle and Health Economics -3000 participants only)
Electronic Health Record Data
Prescribing, Procedures, Clinical Events, Death

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

We will recruit at least 6,000 middle-aged subjects from Scotland with at least one cardiovascular risk factor. Potential participants will be approached through their General Practitioner, the SHARE database or self-refer through a website portal. They will be asked to attend the Edinburgh Clinical Research Facility for consent, estimation of serum creatinine and total cholesterol, randomisation, and where appropriate, a CTCA scan.

A maximum of 50% of all participants will have taken a statin prior to enrolment. Once this threshold has been crossed, no further prior statin users will be recruited.

4.2 INCLUSION CRITERIA

- ≥40 and ≤70 years of age
- Resident in Scotland and have a Community Health Index (CHI) number
- One or more of the following risk factors:
  - Current or recent (within 12 months) smoker
  - Clinical diagnosis of hypertension
  - Known hypercholesterolaemia (total cholesterol >6.0 mmol/L or receiving statin therapy)
  - Diabetes mellitus
  - Rheumatoid arthritis
  - Systemic lupus erythematosus (SLE)
  - Over 60 years of age
  - Family history of premature cardiovascular disease (first degree relative with atherosclerotic cardiovascular disease below 60 years)
  - Chronic kidney disease stage 3 (estimate glomerular filtration rate 30-59 mL/min/1.73 m^2).

4.3 EXCLUSION CRITERIA

- Inability to give informed consent
- Inability to undergo CTCA
- Pregnant or breastfeeding
- Known coronary heart disease or other major atherosclerotic cardiovascular disease
- Prior invasive or non-invasive coronary angiography within the last 5 years
- Chronic kidney disease stage ≥4 (estimate glomerular filtration rate <30 mL/min/1.73 m^2)
- Known homozygous familial hypercholesterolaemia or other serious inherited disorders of lipid metabolism requiring statin therapy
- Intolerance of all statins
- Statin therapy for >2 years.

4.4 CO-ENROLMENT

Given the simplicity of the intervention, the minimal burden on the trial participant and the current diversity of clinical practice, it is anticipated that co-enrolment in other studies will be permitted for most patients except where this would undermine the primary end-points of the trials. Co-enrolment in observational studies will be permitted. Co-enrolment in cardiovascular interventional trials or studies requiring additional radiation exposure will require agreement between the Chief Investigators and Trial Steering Committees of the respective trials as well as the trials' Sponsors and will be performed in accordance with the ACCORD guidelines for co-enrolment GL001.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Potential study participants will be approached in through the NHS Research Scotland (NRS) Primary Care Network which is directed by co-investigator, Professor Bruce Guthrie. NRS Primary Care Network will arrange for letters to be sent to each potential participant from their registered General Practitioner as we have previously undertaken for other research projects. For example, an early lung cancer detection study recruited 12,000 patients (from 150-200 General Practices) having sent out 77,066 invitation letters. The letters will be printed and posted by Docmail, a ISO/IEC 27001 accredited company. We will also have the option of approaching the Scottish Health Research Register or SHARE (https://www.registerforshare.org). This is a national register of Scottish residents who are willing and keen to take part in research with over 200,000 people currently registered. This has been an extremely useful resource for other trials and enables pre-identification of eligible patients. Finally, we will set up a website where individuals can volunteer to participate in the trial (self-referral).

A Study Within a Trial (SWAT) will be embedded into the main study. This SWAT will assess the impact of two interventions on response rates to the invitation letters sent out by the Primary Care Network. One of the interventions is the inclusion of a one-page Participant Information Sheet with the invitation letter. If a participant proceeds to attend for a screening visit, they will be provided with the standard length version before their appointment. The protocol for this study is detailed in Appendix 1.

5.2 CONSENTING PARTICIPANTS

Potential participants will be provided with an information sheet prior to attendance at the study clinic. They will attend the Edinburgh Clinical Research Facility where eligibility will be confirmed, and consent obtained by appropriately trained and delegated research staff and recorded in the participant's medical records.

5.3 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

All ineligible and non-recruited participants attending the CRF will be recorded on the screening log with a reason given (if known).

5.4 RANDOMISATION

5.4.1 Randomisation Procedures

Participants will be randomised using a web-based randomisation service (managed by the Edinburgh Clinical Trials Unit). Participants will be allocated to receive either CTCA plus standard care or standard care only in a 1:1 ratio and will be minimised by ASSIGN score (<10, 10-20 and >20) and will include a random element.

5.4.2 Intervention Allocation

Participants allocated to CTCA will have an appointment arranged to complete the scan.

5.5 WITHDRAWAL OF STUDY PARTICIPANTS

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator. After withdrawal, no further data will be collected about the participant (including long term data linkage). If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form, if possible. Data collected up until that point will be retained. To safeguard rights, the minimum personally identifiable information possible will be collected. If a participant chooses to withdraw from the study, they are informed to contact the trial team if they want any blood samples stored for future research to be destroyed. Not wishing to attend the CTCA scan or complete trial questionnaires does not constitute withdrawal from the study. These requests will be documented in the eCRF and the participant will continue to have an 'Active' status and be followed up.

6 STUDY ASSESSMENTS

6.1 STUDY ASSESSMENTS

At the study visit, participants will:

- Complete a clinical proforma with the study team member
- Have up to 45 mL of blood taken. A 5 mL serum gel tube will be used to assess lipid profile and renal function with excess blood being retained for future study biomarker analysis.
- Have blood pressure and heart rate taken
- Complete questionnaires on lifestyle and quality of life
- Have an ASSIGN score calculated

6.2 COMPUTED TOMOGRAPHY

Computed tomography will be performed with a 64-detector row (or more) scanner. Rate limiting medication (e.g beta blocker) will be prescribed as required to obtain a heart rate of <60 bpm at time of imaging. Glyceryl trinitrate (GTN) will be administered unless contraindicated. Non-contrast electrocardiogram-gated computed tomography will be performed for calcium scoring. Contrast enhanced electrocardiogram gated CTCA will be performed using iodinated contrast.

6.3 FEEDBACK OF RESULTS

The research team will provide all participants and their GPs written recommendations based on the current standard of care guidelines dependant on the results of their ASSIGN score or CTCA scan. Recommendations will include lifestyle advice, use of statins/antiplatelet therapy/ ACE inhibitors or referral to Cardiology. Feedback will also be given to participants and their GP about incidental findings from CTCA and referral for further treatment will be arranged by the research team. An NHS email account will be created to provide a point of contact for clinical queries following communication of the risk score and CTCA results.

6.4 LONG TERM FOLLOW UP ASSESSMENTS

Outcome measures will be obtained through the electronic Data Research and Innovation Service (eDRIS) and the General Register Office as we have successfully achieved with the SCOT-HEART [SCOT-HEART, 2015; Williams et al, 2016; SCOT-HEART, 2018] and HighSTEACS [Shah et al, 2015a; Shah et al, 2015b] trials. We will capture all hospital admission events and will have access to clinical records and imaging as required through NHS Safe Havens. We will collect clinical outcomes, coronary procedures and prescribing data through NHS data systems and eDRIS as we have for the [SCOT-HEART, 2015; Williams et al, 2016; SCOT-HEART, 2018] trial. These datasets alongside unscheduled care (ambulance service, NHS 24 etc) and social care will be used to evaluate healthcare resource use for the health economic analysis.

Health economic (healthcare-related quality of life (EQ-5D-5L) and NHS resource use) and lifestyle questionnaires on will be sent to all study participants at 6 months. The first 3,000 participants who respond to these questionnaires will be followed up again at 2 years.

6.5 STORAGE AND ANALYSIS OF SAMPLES

Blood samples will be obtained by standard venesection and sent to Clinical Biochemistry Laboratories of the Royal Infirmary of Edinburgh for lipid analysis and renal function (5 mL serum gel tube). Up to an additional 40 mL of blood will be obtained and processed for future genetic and plasma biomarker discovery studies.

7 DATA COLLECTION

Study data will be entered into an electronic case report form (eCRF) developed by Edinburgh Clinical Trials Unit (ECTU). A source data plan will be created to indicate where

the study data are originally documented. The study data obtained from electronic health records will be entered directly into the eCRF.

7.1 DATA MANAGEMENT

7.1.1 Personal Data

Personal data will be stored securely within ECTU according to their standard operating procedures. This will include the patient's name, address and CHI number.

7.1.2 Transfer of Data

Identifiable 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). We do intend to share anonymised data with external collaborators and scientists.

7.1.3 Data Controller

The University of Edinburgh and NHS Lothian are joint data controllers. ECTU and eDRIS will act as data processors.

7.1.4 Data Breaches

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

8 STATISTICS, HEALTH ECONOMICS AND DATA ANALYSIS

8.1 SAMPLE SIZE CALCULATION

There is uncertainty in this asymptomatic primary care population as to the underlying 5-year event rate for the primary outcome of coronary heart disease death or non-fatal MI. We believe the closest match to our proposed study population will be that observed in the non-anginal chest pain group in the SCOTHEART trial (18/735, or around 2.5% at 5 years) [SCOT-HEART 2018]. Again, from the SCOTHEART trial, there were treatment effects equating to a hazard ratio of between 0.45 and 0.65 across many subgroups with differing levels of risk. Outcome data (e.g. at 5 years) will not mature until after recruitment is finished. If we randomise 6,000 participants 1:1 to CTCA or ASSIGN risk score then if the control (treatment based on ASSIGN score) 5-year primary outcome rate is 2.0, 2.5, 3.0, 3.5 or 4.0 we will have 90% power at a 5% level of significance to detect treatment effects corresponding to hazard ratios of 0.49, 0.54, 0.57, 0.60 and 0.62 (corresponding to observing an aggregate of around 90, 116, 142, 169 and 196 events). Where insufficient events have accrued, we do have the option of further extending follow up at minimal cost. The Trial Steering Committee (TSC) will review the event rate at 4 years after study start and recommend whether to extend recruitment including a sample size re-estimation. The

TSC will also consider factors such as event rates in sub-groups of age (40-50 vs 50-70 year olds) and pre-existing statin use.

The Data Monitoring Committee will review the results of formal interim analyses under a a Lan DeMets alpha spending approach (using O'Brien Fleming boundaries) at 4, 5, 6 and 7 years after study start. This will allow the findings of the study to be declared when they have become definitive – either for overwhelmingly evidence of benefit or for futility. Full details of the group sequential design and the operationalisation of interim analyses will be given in the comprehensive Statistical Analysis Plan.

We therefore propose to recruit at least 6,000 subjects over the initial 4-year recruitment period.

8.2 PROPOSED STATISTICAL ANALYSES

All statistical analyses will be governed by a comprehensive Statistical Analysis Plan, authored by the study statistician and approved by both the Trial Steering Committee and independent Data Monitoring Committee. The primary outcome of time-to-first coronary heart disease death or non-fatal MI will be compared (using an intention-to-treat approach) between the randomised groups (risk score or CTCA guided management) using a Cox proportional hazards regression model. This will adjust for pre-specified prognostic covariates, such as age, sex, baseline 10-year cardiovascular risk score, risk factors such as diabetes, and prior statin therapy. In the case of non-proportional hazards, we will use a restricted mean survival time (RMST) approach. Secondary outcomes (e.g. lifestyle changes such as smoking, body weight, physical activity, diet; cardiovascular medications (use and compliance with); quality of life; procedural outcomes (e.g. invasive coronary angiography and coronary revascularisation); major adverse cardiovascular events; mortality) will be analysed using a model suitable to the nature of the outcome – e.g. time to event as per the primary outcome; or binary or ordinal logistic regression; or linear regression; or negative binomial regression. The study is not powered for subgroup analyses so these will be undertaken as exploratory analyses to assess moderation of treatment effects. For the mechanistic outcomes, we may use mediation type analyses (e.g. causal models using instrumental variables). We would also intend to build both prediction models (to predict response to intervention) and prognostic models (to predict disease course, adjusting for any intervention effect). For the primary outcome (obtained through record linkage into routine data), the level of missingness is expected to be negligible. For some secondary outcomes (e.g. the patient reported outcomes), the level of missingness may be around 20%, and so sensitivity type analyses (e.g. assuming data are missing at random; or possibly not missing at random i.e. informatively missing) will be considered to explore whether the findings are robust to the patterns of missingness.

We will undertake a range of sub-group analyses as we have performed in the SCOT-HEART trial including age, sex, baseline 10-year cardiovascular risk, and risk factors (such as diabetes mellitus and smoking habit). We will also explore more detailed mechanistic analyses relating to computed tomography features, such as coronary artery calcification, plaque volume, plaque vulnerability and perivascular adipose tissue, as we have for the SCOT-HEART trial.

8.3 PROPOSED HEALTH ECONOMIC ANALYSES

The health economics analysis for SCOT-HEART 2 will consist of an assessment of the short and long-term effectiveness, costs, and cost-effectiveness of CTCA plus standard care compared to standard care alone from an NHS and personal social services (PSS) perspective. Health-related quality of life (HRQoL) data will be collected using the EuroQol-5 dimension-5 levels (EQ-5D-5L) instrument [EuroQol Group 1990] (at baseline, 6 months and 2 years) and converted to quality-of-life weights using published UK tariffs. These data will then be used to calculate QALYs. Information about health care resource use (e.g. GP visits, hospitalisations: out-patient, day case, inpatient stay, prescribed medicines, imaging) and intervention-related costs will be included in the economic evaluation. These will be collected using a number of approaches including patient questionnaire, routine data linkage, trial records. National sources of unit cost data will be applied to value resource use (NHS Healthcare Resource Group (HRG) Reference Costs, Unit Costs of Health and Social Care).

The main within-trial analysis will be reported using a cost-utility analysis framework, to calculate the incremental cost per QALY gained (for 6 months and 2 years' time horizons). Further reporting will include the incremental cost per coronary event prevented. We will also develop a simple long-term decision model to synthesise the SCOT-HEART 2 trial data, routine linked data (e.g. to inform health care resource use such as on hospital admissions), and key parameters informed by the literature (e.g. long term HRQoL) to evaluate the long-term cost-effectiveness (e.g. using a 10 year time horizon). The results of the analysis will be presented as incremental costs, effects and incremental cost-effectiveness ratios (in terms of cost per QALY gained or cost per coronary event avoided). A range of one- and multi-way deterministic sensitivity analyses (or probabilistic sensitivity analysis if more appropriate) will be conducted to address uncertainty in these estimates and robustness of the results. Cost per QALY data will also be presented in the form of cost-effectiveness acceptability curves (CEAC) to show the probability that different the intervention is cost effective for different values of willingness to pay per additional QALY. A Health Economics Analysis Plan (HEAP) will be developed describing all the health economics analyses to be carried out.

9 ADVERSE EVENTS

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

All adverse events (AEs) requiring recording will be documented in detail by the Investigator or designee and appropriate treatment initiated according to their medical judgment. This is limited to the events attributed to the application of CTCA as defined in section 9.1.

9.1 Adverse Events of Scanning

Adverse events that can be attributed to the application of computed tomography calcium score and coronary angiography are:

(i) Reactions to drugs administered immediately prior to scanning (such as beta blockade and glyceryl trinitrate);
(ii) Reactions to contrast agent administration including extravasation;
(iii) Vasovagal reactions to procedure

9.2 Definitions

An AE is any untoward medical occurrence in a clinical trial participant who is administered an intervention, which does not necessarily have a causal relationship with the intervention.

An adverse reaction (AR) is any untoward and unintended response to an intervention which is related administration of that intervention to that participant.

A serious adverse event (SAE) serious adverse reaction (SAR) is any AE or AR that:

- results in death;
- is life threatening (i.e. the subject 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);
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect.

*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 enrolment will not meet SAE criteria. Any hospitalisation that is planned post enrolment will meet the SAE criteria.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be related to the intervention.

9.3 Detecting Adverse Events and Serious Adverse Events

Adverse events and serious adverse events related to CTCA will be recorded during the scan appointment and up to 48 hours after undertaking CTCA.

9.4 Recording of Adverse Events and Serious Adverse Events

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).

9.5 Evaluation of Adverse Events and Serious Adverse Events

Seriousness, causality, severity and expectedness should be evaluated. The Investigator should make an assessment of seriousness as defined below.

9.5.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 9.2.

9.5.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the CTCA scan according to the definitions below.

- Unrelated: where an event is not considered to have occurred as a result of the CTCA scan.
- 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 CTCA scan.

9.5.3 Assessment of Expectedness

If an event is judged to be related to the CTCA scan, the Investigator will make an assessment of expectedness. The event may be classed as either:

- Expected: the event is expected in line with the CTCA scan.
- Unexpected: the event was not expected, given the knowledge of participant, and the CTCA scan.

9.5.4 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.

9.6 Reporting of SAEs/SAR/SUSARs

Once the Investigator becomes aware that an SAE/SAR/ SUSAR has occurred in a study participant, the information will be reported to the ACCORD Research Governance & Quality Assurance (QA) Office **immediately or 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 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 9.5.2, Assessment of Causality and 9.5.3 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). ACCORD is responsible for reporting fatal or life threatening SUSARs to the Research Ethics Committee (REC) within 7 calendar days after ACCORD is first aware of the reaction. All other SUSARs will be reported within 15 calendar days after ACCORD is first aware of the reaction.

9.7 Follow-up Procedures

After initially recording an AE or recording and reporting an SAE/SAR/SUSAR, the Investigator is required to follow each participant until resolution. Follow up information on an SAE/SAR/SUSAR should be reported to the ACCORD Governance & QA Office. AEs still present in participants at the last study visit should be monitored until resolution of the event or until no longer medically indicated.

10 OVERSIGHT ARRANGEMENTS

10.1 TRIAL MANAGEMENT GROUP

The trial will be led by Professor David Newby and managed and run by the ECTU which has full registration with the United Kingdom Clinical Research Collaboration. The study will be managed by an experienced trial manager with support from a data programmer, data manager and administrative staff. The Clinical Trials Unit will also oversee the statistical, health economic and analytic aspects of the trial conduct. The project will also require close collaboration and cooperation of eDRIS. A Trial Management Group (TMG) comprising the applicants and relevant members of these teams will be formed to ensure successful on-going management of the study.

10.2 TRIAL STEERING COMMITTEE.

The Trial Steering Committee (TSC) will be composed of external independent clinical trialists. They will oversee and support the strategic delivery of the trial by working the Trial Management Group to deliver the goals of this innovative and challenging study. The terms of reference of the Trial Steering Committee, and the names and contact details are detailed in the TSC charter.

10.3 DATA MONITORING COMMITTEE.

The Data Monitoring Committee (DMC) will be composed of external independent experts. They will review emerging trial data to ensure the safety of patients and the integrity of the trial data as it emerges during study conduct. Interim analyses will ensure there is no overwhelming evidence of safety or efficacy that would require early termination of the trial. The terms of reference of the Data Monitoring Committee and the names and contact details are detailed in the DMC charter

10.4 PATIENT PUBLIC INVOLVEMENT.

Patient and Public Involvement (PPI) Representatives and the Cardiology Research Group Patient Advisory Group will be consulted during the study at key points so they can influence study documentation development, study management and the discussion of findings at the end of study so they can be involved in determining dissemination and public engagement strategies. At least one PPI representative will be appointed to the TSC so they will be involved in all aspects of study oversight and management.

10.5 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial 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.

10.6 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.

Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and third parties may be performed.

11 GOOD CLINICAL PRACTICE

11.1 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 required approvals will be obtained and any conditions of approvals will be met.

11.2 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.

11.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol 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 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 participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes (if applicable).

11.2.2 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 trial related duties.

11.2.3 Data Recording

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

11.2.4 Investigator Documentation

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

11.2.5 GCP Training

All researchers are encouraged to undertake GCP training in order to understand the principles of GCP.

11.2.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant except to communicate clinical findings to the patient's General Practitioner. 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.

11.2.7 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 and be of a form where individuals are not identified and re-identification is not likely to take place

STUDY CONDUCT RESPONSIBILITIES

11.3 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 will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

11.4 MANAGEMENT OF PROTOCOL NON-COMPLIANCE

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. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred.

11.5 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 trial; or

(b) the scientific value of the trial.

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

11.6 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 not be destroyed without permission from the sponsor.

11.7 END OF STUDY

The end of study is defined as the last participant's last 6-month follow up. However, electronic health record follow up is planned thereafter.

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.

11.8 CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

CTCA is a diagnostic tool and not a treatment. Any treatment initiated during the study would be continued as recommended by the NICE or European Society of Cardiology Guidelines after the study conclusion.

11.9 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 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.

12 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

12.1 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 clinical study report will be prepared. Any publications will be written in accordance with the ECTU Publication Policy.

12.2 PUBLICATION

The Clinical Study Report (CSR) will be submitted to the Sponsor and REC within 1 year of the end of the study. Where acceptable, a published journal article may be submitted as the CSR. The Chief Investigator will provide the CSR to ACCORD, for review, prior to finalisation. The clinical study report may be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

12.3 DATA SHARING

Following publication of the primary paper, a de-identified individual participant data set will be submitted to a data archive for sharing purposes. Access to the de-identified dataset will be under a controlled access model in line with ECTU policies at that time.

12.4 PEER REVIEW

The study protocol has undergone independent review by an ECTU statistician and by the British Heart Foundation. The protocol has been developed in accordance with their recommendations.

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14 APPENDIX 1: SCOT-HEART 2 embedded recruitment study

14.1.1 Background

Many trials either fail to achieve their target numbers or require extensions and changes to recruitment strategies during trials to improve recruitment.[1] In the UK, a review of Medical Research Council and NIHR Health Technology Assessment Programme trials found that two thirds failed to reach their target recruitment despite more than half having extensions,[2] with follow-up studies finding no evidence of improvement over time.[1,3] Failure to recruit is an international problem[4,5] which has important negative consequences, including trials being underpowered, meaning that negative results are difficult to interpret, and abandonment of trials of potentially effective interventions.[6] It also leads to considerable waste of resources. In one US academic centre over a four year period, 260 trials were abandoned after recruiting <2 patients costing the centre ~$1 million in ethical review, set-up and contract negotiation.[5]

In response, all four UK countries have created infrastructure, like research networks, to improve trial recruitment, but there is also a need for research evaluate methods for optimising recruitment. The MRC START collaboration has published guidance on the design and reporting of such studies,[7] which emphasises the importance of carrying out embedded randomised recruitment trials across a range of host trials to allow meta-analysis to maximise generalisability, explore heterogeneity, and to ensure adequate power.[1,6] A recent Cochrane review of interventions to improve recruitment to trials identified relatively few such studies. Three strategies with some evidence of effectiveness were telephone reminders to initial non-responders, use of opt-out rather than opt-in procedures for contacting potential participants, and open designs where participants are not blinded to treatment allocation.[8] The first two of these involve researchers directly contacting potential participants without their prior consent which is not standard practice in the UK, and the third is problematic from a risk of bias perspective.

This recruitment study is embedded in the SCOT-HEART 2 study. SCOT-HEART 2 is a two-parallel arm randomised trial examining two strategies for cardiovascular risk stratification to determine recommended cardiovascular primary prevention treatment: Computerised Tomography Coronary Angiography (CTCA) scanning to evaluate the presence of coronary artery disease vs usual care cardiovascular risk prediction tools based on measured characteristics like age, sex, blood pressure, smoking or cholesterol.

Recruitment from General Practitioner (GP) practices will be supported by the NHS Research Scotland (NRS) Primary Care research network (previously known as the Scottish Primary Care Research Network) using standard processes. The vast majority of patients invited will be identified in searches of GP records for potentially eligible patients, with the initial contact letter from the GP enclosing information about the study and inviting the patient to contact the research team if they

are interested (Appendix 1). The embedded Study Within a Trial (SWAT) will use a randomised controlled design to evaluate two interventions that may improve recruitment in this context of identification and initial contact in writing from the GP. Given that the chosen two interventions are of minimal cost, then even small increases in recruitment rates would be of value, and both interventions are straightforwardly applicable in other studies.

Intervention 1: short (intervention) vs full participant information sheet (PIS; standard practice control) enclosed with the initial GP contact letter

The study information included with the GP contact letter varies widely between studies in length and complexity. The full PIS is often excessive for the decision the patient is making (whether or not to contact the research team for more information) because it is designed to inform the decision to take part in the research (which comes after contacting the research team). There has been interest in whether providing more focused information at initial contact by the GP might lead to a higher recruitment rate, but there have been few trials investigating this.

The most recent Cochrane review identified two trials in this area,[9,10] although one is only reported in abstract so information is limited.[9] The fully reported study was embedded in the REEACT trial evaluating computerised CBT in people with depression. 2479 patients were intended to be randomly sent either the full PIS (eight pages, conventional text-dominated comprehensive document aiming to inform the decision to participate) or a short PIS (two pages, leaflet format, including images aiming to inform the decision to initially contact the research team to discuss the study). 2230 were actually sent an embedded trial recruitment pack. In the short PIS arm, 134 (11.5%) responded and 63 (5.4%) were recruited. In the full PIS arm, 108 (9.3%) responded and 59 (5.1%) were recruited. In the context of a low overall recruitment rate, recruitment rates were higher in the short PIS arm (a 5.9% relative difference; absolute different 0.3%, 95%CI -1.5 to 2.2) but not statistically significantly different. There was a statistically significant difference in the proportion of those initially contacted who were ineligible at screening (3.6% vs 2.2% of all patients responded and were ineligible, difference 1.4%, 95%CI 0.03 to 2.8). The authors concluded that a short PIS was ineffective, although their power calculation was based on an assumed response rate of 15% in the long PIS arm, and the observed relative difference of 5.9% exceeded their pre-specified effect size of 4.5%. The study was therefore underpowered, but did find evidence that a short PIS may decrease trial efficiency.[10] The study reported only in abstract found differences in recruitment rate which were of similar magnitude but were not statistically significant.[9] The Cochrane review concluded there was no evidence of benefit to recruitment, but that evidence quality was only moderate (that is “further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate”). The objective of this study is therefore to definitively evaluate the impact on recruitment of a short vs long (standard practice) PIS.

Intervention 2: contact letter envelope with an NHS logo printed on it (intervention) vs plain envelope (standard practice control)

There is no evaluation of this intervention in the trial literature that we are aware of, although there is literature in the related field of interventions to increase response to surveys, and some of these are potentially relevant to trial recruitment.[11] In the most recent Cochrane review, there was a single relatively small trial comparing envelopes with a study logo printed on them vs plain envelope which did not find a statistically significant difference.[11] However, there is a general belief that recruitment via the NHS (in this context, by the initial contact by the patient's GP) improves recruitment. It is therefore plausible that placing an NHS logo on the envelope increases the likelihood of the letter being opened and read. Although any intervention effect may be relatively small, the intervention is essentially zero-cost so even small effects would be worthwhile.

14.1.2 Aim and objectives

The aim of this embedded recruitment study is to examine the effect on recruitment of two interventions:

1. Short (intervention) vs full PIS (standard practice control) enclosed with the initial GP contact letter
2. Contact letter envelope with an NHS logo printed on it (intervention) vs plain envelope (standard practice control)

Objective 1: To examine the effect of each intervention compared to standard practice on rates of final trial recruitment

14.1.3 Methods

14.1.3.1 Public and patient participation

We have previously discussed recruitment studies of this type with the NRS Primary Care network West Node Public and Patient Participation group, and at a national meeting which included public and patient participants, members of NHS Research Ethics Committees and a representative from the Health Research Authority. There was agreement that improving recruitment is a legitimate concern, and that the decision to contact the research team was different to the decision to take part in the study (justifying the use of different participant information at each stage).

14.1.3.2 Trial design

This is a 2x2 factorial, parallel-group, 1:1:1:1 randomised trial.

14.1.3.3 Participants

All people sent an initial contact letter as part of SCOT-HEART 2 recruitment (broadly all adults aged 40-70 years with at least one risk factor for cardiovascular disease (Appendix 1; SCOT-

HEART 2 protocol for full details), who are not considered by the practice to be unsuitable to receive a letter.

14.1.3.4 Interventions

Intervention 1: Short (intervention) vs full PIS (standard practice control) enclosed with the initial GP contact letter

Intervention 2: Contact letter envelope with an NHS logo printed on it (intervention) vs plain envelope (standard practice control)

14.1.3.5 Outcomes

The primary outcome is:

(1) The proportion of people sent a GP contact letter who are randomised into the SCOT-HEART 2 trial (overall recruitment rate).

14.1.3.6 Sample size

The Studies Within a Trial (SWAT) initiative[12] was established to develop protocols for embedded methodology studies that support pooling of data because sample sizes are defined by the host trial, not the embedded trial.[6,7] Power calculations therefore do not determine study size, but inform estimates of how likely any single SWAT is to definitively evaluate the trialled recruitment intervention.

In this study, if 5% of those approached are randomised, and 5,000 remain to be randomised in SCOT-HEART 2 at the point where this study commences, then 100,000 could be approached and take part in this recruitment study. This would give us 90% power, with p=0.025, to detect a change from 5.0% to 5.5%.

If 10% of those approached are randomised, and 5,000 remain to be randomised in SCOT-HEART 2 at the point where this study commences, then 50,000 could be approached and take part in this recruitment study. This would give us 90% power, with p=0.025, to detect a change from 10.0% to 11.0%.

14.1.3.7 Randomisation

14.1.3.8 Randomisation will be stratified by GP practice and use permuted blocks.

14.1.3.9 Analysis

Statistical analysis will assume a null hypothesis of no difference in outcomes in the intervention and control arms. The primary analysis will compare the proportion of patients randomised, of those approached, by allocated intervention, separately for each intervention comparison. Results will be presented as risk ratios plus 95% confidence intervals, and corresponding p-value, from Poisson regression. The results will also be reported as an absolute difference. The primary analysis will assume that there is no interaction between the interventions, but a sensitivity analysis

will be performed to test this assumption (such as is possible, given the underpowered nature of interaction tests in this context). The primary analysis will be adjusted for GP practice and the effect of the other intervention comparison, but unadjusted analyses will also be presented. For each allocated intervention, separately for each comparison, the statistical report will provide the numbers of patients who are approached and the numbers randomised.

14.1.3.10 Dissemination

As well as peer-reviewed publication of the findings, the study will contribute to future updates of the Cochrane systematic review of interventions to improve recruitment,[1] and other trial teams will be encouraged to follow this protocol through the Trial Forge initiative (see http://www.trialforge.org and this paper[13]) to ensure the availability of data for meta-analysis.

14.1.4 References

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