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Academic and Clinical Central Office for Research and Development

Study Protocol

Dual ACS

Duration of Dual Anti-Platelet Therapy in Acute Coronary Syndrome
The DUAL-ACS Trial

UK Protocol

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LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development *Joint Office for University of Edinburgh and NHS Lothian*
AE	Adverse Event
AR	Adverse Reaction
BCIS	British Cardiovascular Society Intervention
CRF	Case Report Form
CTIMP	Clinical Trial of Investigational Medicinal Product
ECG	Electrocardiogram
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
UAR	Unexpected Adverse Reaction

SUMMARY

Despite substantial evidence supporting the use of dual anti-platelet therapy in patients with acute coronary syndrome, there remains major uncertainty regarding the optimal duration of therapy. Recent evidence suggests that shorter durations of dual anti-platelet therapy are superior because the avoidance of atherothrombotic events is counterbalanced by the greater risks of excess major bleeding with apparent increases in all-cause mortality with longer durations. We here propose an international randomised controlled trial of 18,318 patients with type 1 myocardial infarction allocated to differing durations of dual anti-platelet therapy. We will use electronic health record linkage to track duration of therapy and clinical outcomes in a real-world, real-time, efficient and highly cost-effective trial. This has the potential to define treatment duration, settle a major outstanding international controversy, and influence modern cardiology practice across the world.

It was planned that 18,318 participants would be recruited to the trial but recruitment in the UK was halted after 4,576 patients because the funder felt the trial was undeliverable due to the current challenging environment.

1. INTRODUCTION

Coronary heart disease is the commonest cause of death worldwide. 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 also 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 breast cancer. Indeed, 73,000 people die in the United Kingdom every year: one person every 7 minutes. Death rates are particularly high in Scotland, especially in areas of social deprivation. Deaths are sudden and unheralded, increasing the distress of those left behind. Coronary heart disease also has 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 in low-income and 18% in high-income countries. In the United Kingdom, 2.3 million people are living with coronary heart disease [BHF, 2012].

A ruptured or eroded coronary atherosclerotic plaque is the underlying cause of an acute coronary syndrome. This plaque heals in combination with therapeutic interventions, such as dual anti-platelet therapy, statins and coronary revascularisation. The greatest "at risk" period is during this early phase of plaque instability and healing, with recurrent event rates peaking in the first month. By three months, the plaque has usually stabilised and subsequent event rates return to the background rates seen in patients with stable coronary heart disease [CURE, 2001; Bhatt et al, 2006]. Indeed, beyond three months, recurrent events commonly occur on 'non-culprit' plaques at other sites within the coronary circulation [Stone et al, 2011]. Therefore, from first principles, the first three months are the most time critical for interventions to reduce recurrent cardiovascular events after an acute coronary syndrome. This is consistent with event rates seen in all clinical trials of patients with acute coronary syndrome: an initial (0-3 months) time-varying high event rate that reverts to a consistent linear lower event rate from 3 months onwards (Table 1) [CURE, 2001; Chen et al, 2005; Bhatt et al, 2006; Wiviott et al, 2007; Fox et al, 2008; Wallentin et al 2009].

When used in addition to aspirin, the CURE [CURE, 2001] and COMMIT-CCS [Chen et al, 2005] trials demonstrated reductions in cardiovascular events with clopidogrel, and the TRITON [Wiviott et al, 2007] and PLATO [Wallentin et al, 2009] trials demonstrated superior efficacy of prasugrel and ticagrelor above clopidogrel. However, these trials have included considerable variations in the duration of dual anti-platelet therapy: from 1 to 15 months. This in itself has generated confusion regarding the duration of dual anti-platelet therapy. Given the early cardiovascular hazards, the biggest absolute reductions in events with dual antiplatelet therapy are seen in the first 3 months after an acute coronary syndrome [CURE, 2001; Wiviott et al, 2007; Wallentin et al, 2009] (Table 1). The CHARISMA [Bhatt et al, 2006] (Table 1) and PEGASUS [Bonaca et al, 2015] trials assessed the potential benefits of long-term maintenance dual anti-platelet therapies in patients without a

recent (>12 months) acute coronary syndrome and demonstrated reductions in cardiovascular events. However this came at a cost. Both trials reported increases in major bleeding events and a neutral effect on overall mortality. For major and serious bleeding (including fatal bleeds), the average number needed to harm per month is 900 for the CURE trial [CURE, 2001] and 2333 for the CHARISMA trial [Bhatt et al, 2006]. More contemporary trials show similar balances for benefit and harm. In the DAPT trial [Mauri et al, 2014], the number needed to treat to avoid a major adverse cardiovascular events was 1124 per month and the number needed to harm from major bleeding was 666 per month. For the PEGASUS trial [Bonaca et al, 2015], this was 2927 and 2590 respectively. For all of these trials, the risk of major bleeding exceeded the prevention of myocardial infarction without affecting all-cause mortality.

Table 1.
Temporal Relationship with the Clinical Benefits of Clopidogrel Therapy

Time Interval (months)	Primary end point						
	Clopidogrel (%)	Placebo (%)	ARR (%)	RRR (%)	95% CIs	NNT (per interval)	NNT (per month)
CURE trial							
0-1	4.3	5.5	1.2	22	9 to 32%	84	84
1-3	1.8	2.5	0.8	32	13 to 46%	120	240
3-6	1.8	1.8	0.0	4	-27 to 27%	1725	5174
6-9	1.3	1.4	0.1	6	-34 to 34%	1057	3171
9-12	1.1	1.3	0.2	14	-32 to 44%	533	1600
0-12	10.3	12.6	2.4	19		42	507
CHARISMA trial							
0-28	6.8	7.3	0.5	7*	-5 to 17%	200	5591
0-28*	6.9	7.9	1.0	12	0 to 23%	100	2800

*Subgroup of patients with clinically evident atherosclerotic disease
ARR – absolute risk reduction; RRR – relative risk reduction; CI – confidence intervals; NNT– number needed to treat

It is important to highlight that populations included in randomised controlled trials have lower rates of bleeding and non-cardiovascular death than the general population (Table 2) because patients with any history of bleeding or major comorbidity were specifically excluded from such trials. The introduction of dual antiplatelet therapy into routine clinical practice and the inclusion of a broader population of patients with acute coronary syndrome runs the risk of exaggerated harm without necessarily conferring greater benefit. The critical clinical question is: what is the optimal duration of dual anti-platelet therapy in a broad unselected population of patients with acute coronary syndrome? Does the excess bleeding risk negate the avoidance of atherothrombotic events?

1.1 META-ANALYSES

Recent meta-analyses of trials using dual anti-platelet therapy in patients receiving intracoronary stents (including patients with acute coronary syndrome) have compared short (3-6 months), 12-month and extended (>12 months) durations of

therapy [Navarese et al, 2015; Palmerini et al, 2015]. These analyses have shown that more prolonged durations of therapy reduce the risk of stent thrombosis and myocardial infarction but have no effect on cardiovascular death and increase the risk of major bleeding. Indeed, prolonged durations of therapy had either no or adverse effects on overall total mortality because of an increase in non-cardiovascular death. However, switching from dual anti-platelet therapy to monotherapy (usually aspirin alone) is associated with a rebound prothrombotic effect especially with regard to an excess of stent thrombosis [Mauri et al, 2014; Bonaca et al, 2016; Bueno et al, 2016]. In the DAPT trial [Mauri et al, 2014], this phenomenon occurred irrespective of the timing of switching to monotherapy with rebound stent thrombosis and myocardial infarction seen whether dual anti-platelet therapy was stopped after 12 or 30 months. So, unless dual anti-platelet therapy is life-long, there will remain a small persistent short-term 3-month risk of rebound stent thrombosis and myocardial infarction following the transition from dual to monotherapy.

1.2 BLEEDING AND TOTAL MORTALITY

Large registries and trials have shown that major bleeding is associated with an increase in mortality that could potentially negate the benefits of acute coronary syndrome treatment [Moscucci et al, 2003; Yusuf et al 2006; Stone et al, 2008; Budaj et al 2009]. Importantly, these bleeding risks are not confined to the initial hospitalization phase but are seen beyond hospitalisation [Yusuf et al, 2006; Rao et al, 2006; Stone et al, 2007].

The association between bleeding and mortality has been a consistent feature of acute coronary syndrome trials irrespective of the intervention being assessed. Moreover, improvements in outcome are seen with interventions that are associated with a lower bleeding risk. For example, in the OASIS-5 trial [Yusuf et al, 2006], fondaparinux had similar antithrombotic benefits to enoxaparin but was associated with lower rates of major bleeding and marked reductions in all-cause mortality. Similar benefits have also been reported for randomised controlled trials of arterial access sites in patients treated with an invasive strategy for either ST-segment [Karrowni et al, 2013] or non-ST-segment [Valgimigli et al, 2015] myocardial infarction. Again, because radial artery access was associated with less bleeding, overall all-cause mortality was lower [Karrowni et al, 2013; Valgimigli et al, 2015]. There have been various mechanisms proposed for the link between bleeding and mortality that include rebound hypercoagulability, discontinuation of anti-thrombotic treatments, inflammation and ischaemia [Steg et al, 2011]. The European Society of Cardiology Working Group on Thrombosis has called for clinical trials to address bleeding in acute coronary syndrome including the exploration of the duration of dual anti-platelet therapy [Steg et al, 2011].

1.3 REDUCING ATHEROTHROMBOTIC EVENTS

In patients with acute coronary syndrome, the risk of a recurrent adverse cardiac event is related to the burden of coronary artery disease. Coronary intervention by either percutaneous coronary intervention or coronary artery bypass graft surgery effectively reduces this risk by relief of obstructive coronary disease. Coronary artery bypass graft surgery generally provides complete revascularization because

the bypass grafts are placed in distal locations 'bypassing' the more proximal disease. By contrast, percutaneous coronary intervention provides a focal treatment to individual lesions, and treatment may be incomplete because not all of the lesions may be treated by stents. Audit of the British Cardiovascular Society Intervention (BCIS) database indicates that in 2013 to 2014, 49% of all percutaneous coronary intervention procedures were associated with residual disease (≥1 stenosis >50% severity), fulfilling the criteria for incomplete revascularisation. Patients with acute coronary syndrome and incomplete revascularisation have a residual burden of coronary disease that is a substrate for recurrent plaque rupture, coronary thrombosis and future cardiac events. Prolonged dual antiplatelet therapy may mitigate this risk and prolonged therapy may benefit those patients with incomplete revascularisation following the index procedure to a greater extent than patients with complete revascularisation.

1.4 PILOT DATA: ONE-YEAR MORTALITY FOLLOWING MYOCARDIAL INFARCTION

Clinical trial populations tend to be highly selected and hence do not reflect real world clinical practice. Using our national datasets, we have explored one-year mortality following acute coronary syndrome (Table 2). Perhaps as anticipated, all event rates are much higher in real world populations. Although cardiovascular death is 4-fold higher, the proportion of non-cardiovascular death is 8-fold higher and includes >3-fold higher rates of fatal bleeding. This reinforces the need to address this question in the population that will be treated in routine clinical practice.

Table 2.
Comparative Event Rates Following Acute Coronary Syndrome

	CURE (Clopidogrel)	**TRITON** (Prasugrel)	**TRILOGY** (Prasugrel)	**PLATO** (Ticagrelor)	**Randomised Controlled Trial Average**	**Scotland** (Clopidogrel) **2006-2010 (one-year event rates)**
All-cause Mortality	5.8%	3.0%	8.3%	4.5%	5.40%	25.4%
Cardiovascular Death	5.1%	2.1%	6.6%	4.0%	4.45%	17.8%
Non-cardiovascular Death	0.7%	0.9%	1.7%	0.5%	0.95%	7.6%
Fatal Bleeding	0.2%	0.4%	0.2%	0.3%	0.28%	0.9%

1.5 ELECTRONIC HEALTH RECORDS FOR MAJOR CLINICAL TRIALS

We have previously demonstrated our ability to undertake large clinical trials and to exploit electronic health records to describe the diagnosis, investigation, treatment and clinical outcomes of patients with coronary heart disease [Pell et al, 2008; Mills et al, 2011; Mills et al, 2012; Shah et al, 2015a; SCOT-HEART, 2015; Shah et al, 2015b; Williams et al, 2016]. In particular, we have used electronic health records to describe the implementation of sensitive [Mills et al, 2011; Mills et al, 2012] and high-sensitivity [Shah et al, 2015a; Shah et al, 2015b] cardiac troponin I assays in patients presenting with suspected acute coronary syndrome. We were able to report utilisation of healthcare resources including invasive coronary angiography, changing patterns of clinical diagnosis, and alterations in therapeutic interventions. Furthermore, we were able to follow-up patients for recurrent hospitalisations and survival, and reported many major findings that have informed current clinical practice and international guidelines. This laid the foundation for the ongoing British Heart Foundation-funded multicentre High-Sensitivity Troponin in the Evaluation of Patients With Acute Coronary Syndrome (High-STEACS) trial (NCT1852123) of over 20,000 patients presenting with suspected acute coronary syndrome.

We have recently reported the Scottish COmputed Tomography of the HEART (SCOT-HEART) trial that assessed the additive value of computed tomography coronary angiography (CTCA) in the rapid access chest pain clinic [SCOT-HEART, 2015]. This was conducted in 12 hospitals across Scotland and defined the influence of CTCA on the diagnosis, investigation, treatment and outcome of over 4,000 patients with suspected angina pectoris due to coronary heart disease. Using national electronic health record datasets, we described numerous clinical outcomes including rates of invasive coronary angiography, coronary revascularisation, recurrent myocardial infarction, and cardiac and all-cause death [SCOT-HEART, 2015]. In subsequent post-hoc analyses, we were also able to obtain community prescribing data and identify the timing and changes in preventative and anti-anginal therapy consequent on the recommendations of the treating clinician in the light of the CTCA findings [Williams et al, 2016]. This has proven extremely powerful and demonstrates the feasibility and uniqueness of our

proposed approach.

The use of electronic health records, routinely collected data and pragmatic trials is increasingly being recognised as the most appropriate approach to address many of the outstanding questions we face today [Ford & Norrie, 2016].

1.6 IMPORTANCE

Determining the default strategy for the duration of dual anti-platelet therapy is important because there is considerable heterogeneity in clinical practice and there are both harms and benefits from the intervention. For the public and patients, it is unclear what is the best duration of treatment to maximize the benefit (prevention of myocardial infarction) and minimize the harm (major bleeding) as well as to establish the effect on overall mortality. Patients prefer not to take medication unless it is necessary and are particularly concerned about the risks and harms of treatments. Dual anti-platelet therapy causes excessive minor and major bleeding (up to 1 in 6 patients) that can be very problematic for patients and occasionally fatal. However, patients also want the reassurance that they will not suffer another heart attack, require further invasive procedures or develop additional potentially life threatening disease.

For clinicians and health care providers, there remains much uncertainty regarding the length of therapy after acute coronary syndrome. Duration of therapy is seen as a major priority for future research by numerous national and international guideline committees as well as having financial implications in terms of drug costs and therapy management in primary care. Currently there is equipoise with significant variations in local and regional practice that are confusing for patients, primary care physicians and cardiologists. Indeed, the Scottish Intercollegiate Guideline Network has varied between 3 and 6 months in its recommendations, and the European and North American guidelines recommend up to 12 months but acknowledge that shorter durations may be appropriate. All would welcome having clear evidence and guidance [Steg et al, 2011; Sharma et al, 2016].

There are considerable cost implications for duration of therapy, especially for the latest generation of P2Y12 receptor antagonists with prasugrel and ticagrelor costing £50-60 per month. Major pharmaceutical companies have to date not funded trials comparing shorter (<12 months) durations of dual anti-platelet therapy, and arguably it is not in their commercial interest to do so. In addition, many patients were excluded from the major trials because of potential bleeding concerns. There is therefore a major concern that the evidence to date has been extrapolated to a broader population with a higher risk of adverse outcomes from bleeding. This has the potential for unnecessary harm that could attenuate or nullify any benefit from reducing cardiovascular events.

1.7 SCIENTIFIC PRINCIPLES UNDERLYING THE PROPOSED RESEARCH

We propose a novel approach to assess the strategy for the duration of dual anti-platelet therapy in type 1 myocardial infarction using routinely collected electronic health records linked to an international randomised controlled trial [Ford & Norrie, 2016]. We will compare the proportion of patients with different baseline

characteristics (in terms of bleeding and atherothrombotic risks) among those included and not included in the trial (those who are not approached or refuse to participate) and within countries, where possible.. This design (i) facilitates a large adequately powered trial, (ii) represents 'real world' clinical practice and includes all patients who, in the opinion of the treating physician, should be managed with dual anti-platelet therapy, (iii) will allow valid extrapolation of results to patients who would otherwise not participate in clinical trials and who arguably have the greatest potential to incur benefits and risks, (iv) makes for a highly efficient and cost-effective method of research delivery, (v) ensures optimal comparability and avoidance of bias, and (vi) generates adequate statistical power to address these pressing clinical questions.

1.8 RATIONALE FOR THE TRIAL

Although several major trials have consistently demonstrated the benefits of dual anti-platelet therapy in patients with acute coronary syndrome, the optimal duration of therapy is unresolved, and the benefit of prolonged therapy may not outweigh the bleeding hazards. There are increasing calls for randomised controlled trials to assess duration of therapy following acute coronary syndrome [Steg et al, 2011; Sharma et al, 2016]. Current European Society of Cardiology guidelines [Roffi et al, 2015] recommend 12 months of dual antiplatelet therapy despite this lack of clear definitive evidence and the real concern that major bleeding exceeds the modest benefits of reducing atherothrombotic events beyond 3 months.

We will test the hypothesis that compared to 12 months, 3 months of dual anti-platelet therapy is safer for patients with type 1 myocardial infarction.

2. STUDY OBJECTIVES

Our principal question is: should the default strategy for the duration of dual anti-platelet therapy be 3 or 12 months after type 1 myocardial infarction? Given the opposing long-term harms and short-term benefits of dual antiplatelet therapy from recent meta-analyses, we propose to focus on the primary end-point of all-cause mortality. All-cause mortality is felt to be the only single outcome which could reliably capture the trade off in benefit from avoiding recurrent cardiovascular events in the acute term (part of which benefit should lead to fewer deaths) and the harms from bleeding over the longer term (part of which will lead to more deaths). All-cause mortality is also a simple outcome to measure and is highly complete and accurate in routine datasets, and any difference or similarity seen in all-cause mortality should be convincing as to which is overall the better duration of therapy for both patients and clinicians.

Of course, secondary outcomes such as cardiovascular death, myocardial infarction, non-cardiovascular death and major bleeding will also be of major interest. We may also be able to identify subgroups of patients who experience substantially greater benefits or on the other hand have much greater hazards, which will allow a more nuanced recommendation for a treatment policy than simply one size fits all.

2.1 STUDY ENDPOINTS

Table 3.
Study Endpoints

	Safety	Efficacy
Primary Endpoint	All-cause mortality	All-cause mortality
Secondary Endpoints	Non-cardiovascular death (including fatal bleeding) and major non-fatal bleeding	Cardiovascular death or non-fatal myocardial infarction
	Non-cardiovascular death (including fatal bleeding)	Cardiovascular mortality (cardiac and non-cardiac)
	Major fatal and non-fatal bleeding	Myocardial infarction (fatal and non-fatal)
	Hospitalisation for bleeding	Stent thrombosis
	Intracranial haemorrhage	Coronary revascularisation
	Gastrointestinal bleeding	Thrombotic stroke
Other endpoints*	Blood Transfusion	
	Haemoglobin	
	Iron Therapy	

*Other endpoints will be collected where possible, but this will be country specific.

3 STUDY DESIGN

This will be a prospective multicentre international open-label randomised controlled trial assessing the duration of dual antiplatelet therapy in patients with type 1 myocardial infarction.

4. STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

We plan to recruit 18,318 patients with type 1 myocardial infarction from both UK hospitals and international hospitals. The international sites will use a separate country-specific protocol.

Recruitment in the UK was halted after 4,576 patients because the funder felt the trial was no longer deliverable due to the current challenging environment. The statistical analysis will include the 4,576 patients recruited in the UK and as many international patients who have completed follow-up at the time of analysis.

4.2 INCLUSION CRITERIA

For inclusion in the study, participants will fulfil the following criteria:

- Aged ≥18 years
- Clinical diagnosis of type 1 myocardial infarction within 12 weeks
- In the opinion of the attending clinician requires dual anti-platelet therapy with aspirin and a P2Y12 receptor antagonist.
- Resident in the country of recruitment with their unique health identifier
- The attending clinician has equipoise regarding the duration of therapy
- Provision of informed consent

4.3 EXCLUSION CRITERIA

Participants will not enter the study if any of the following exclusion criteria are fulfilled:

- Clear indication for specific duration of dual anti-platelet therapy
- Type 2 myocardial infarction
- Contraindication to aspirin or P2Y12 receptor antagonist.
- Non-resident in the country of recruitment
- Previous recruitment into the trial
- Inability or unwilling to give informed consent

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 the majority of patients except where this would undermine the primary end-points of the trials. Co-enrolment in observational studies will be permitted. Co-enrolment in interventional trials 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

Patients will be identified and recruited from the cardiology and general medical hospital wards. All patients will be approached for study recruitment by their usual care team including appropriately trained members of the research team to whom this task has been delegated (this is not restricted to clinicians). Patients will be provided with a Patient Information Sheet and given an opportunity to ask questions about participation in the trial.

5.2 CONSENTING PARTICIPANTS

After an appropriate period of time, patients willing to participate in the study will be asked to provide written informed consent by the patient's usual care team or appropriately trained members of the research team to whom this task has been delegated (this is not restricted to clinicians). Written informed consent will be obtained before any study related procedures are performed.

5.3 SCREENING FOR ELIGIBILITY

The patient's usual care team or appropriately trained members of the research team to whom this task has been delegated (this is not restricted to clinicians) will identify potential participants and confirm and document eligibility. This will be based on routinely collected clinical data and review of clinical records.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Ineligible and non-recruited patients will receive standard medical care. Characteristics and profile of these patients will be determined from routinely collected electronic health record data so a screening log will not be required.

5.5 RANDOMISATION

5.5.1 Randomisation Procedures

A web-based computer-generated randomisation process will be used to ensure allocation concealment and reduce bias. The randomisation system will be provided by ECTU and patients will be randomised using their unique health identifier to prevent inadvertent duplicate randomisation. International sites will use their own randomisation system which will be described in their country specific protocol. Randomisation will be by permuted-block with a level of stratification for

each of the following groups of patients: (i) conservative non-invasive strategy (invasive coronary angiography is not planned), (ii) invasive coronary angiography is planned but has not yet occurred, (iii) an invasive coronary angiogram has been performed and the patient has been referred or undergone CABG surgery, (iv) an invasive coronary angiogram has been performed and the patient has had at least one drug eluting stent implanted, (v) an invasive coronary angiogram has been performed and the patient has had only bare metal stents implanted (this group will also include patients who have had balloon angioplasty only performed without stent implantation), (vi) an invasive coronary angiogram has been performed and the patient is to receive medical management only.

Block size will be randomly determined, and each block will contain both treatments in a 1:1 ratio.

5.5.2 Treatment Allocation

Patients will be randomised 1:1 to 3 or 12 months of dual anti-platelet therapy. Dual anti-platelet therapy will consist of aspirin plus a P2Y12 receptor antagonist (clopidogrel, ticagrelor or prasugrel) chosen by the attending clinician. The participant will be provided with a study card detailing the duration of therapy that they have been randomised to.

5.5.3 Methods to Ensure Blinding

This is an open-label trial and there will be no masking of treatment allocation or need for unblinding.

5.5.4 Discontinuation of the Investigational Medicinal Product

Changes to the duration of therapy will be discouraged but can be changed at the discretion of the attending clinician. Given that discontinuation of dual anti-platelet therapy can be inconsistent [Bueno et al, 2016], the patient's General Practitioner and Consultant Cardiologist will be contacted with a prompt to discontinue the dual antiplatelet therapy before the randomised duration of therapy ends.

5.6 WITHDRAWAL OF STUDY PARTICIPANTS

Participants are free to withdraw from the study at any point or a participant may be withdrawn by the attending clinician. If a participant wishes to withdraw they will need to contact their local research team who will document the nature and primary reason for withdrawal, if possible. The contact details for the local site will be provided on a study card. Unless the participant specifically withdraws consent any data collected up to the point of withdrawal will be retained and analysed and data will continue to be collected remotely from the participant's medical notes and via data linkage.

Participants who withdraw or are withdrawn from the study will not be replaced.

6 INVESTIGATIONAL MEDICINAL PRODUCTS

6.1. STUDY DRUGS

There are four IMPs being used in the study: aspirin (75 mg tablet), clopidogrel (75 mg tablet), ticagrelor (90 mg tablet) and prasugrel (10 mg tablet or 5 mg tablet if participant is over 75 years or weight <60 kg).

All IMPs have marketing authorisations for the condition (acute coronary syndrome) under investigation here. As several brands of both clopidogrel and aspirin are marketed in the UK, the IMPs are defined by the active substance only. All authorised brands may be used and pharmacies may provide the brand of drug which is available to them.

All drugs will be stored, used and prescribed by an authorised healthcare professional according to local clinical practice guidelines.

The Summary of Product Characteristics (SPCs) for all 4 IMPs are provided in a separate document which has been signed and verified by the CI and the Sponsor.

6.2. PARTICIPANT COMPLIANCE

Compliance with the randomised duration of therapy will be assessed using routine collected prescribing data, where possible, for the purposes of the study outcomes. Non-compliance will not be recorded or reported to the Sponsor.

6.3. OTHER MEDICATIONS

6.3.1 Prohibited Medications

There are no prohibited medications in this study. Patients will be treated as per standard care.

7 STUDY ASSESSMENTS

7.1 DATA COLLECTION AND OUTCOME ASSESSMENTS

Baseline patient characteristics, past medical history and medication use will be obtained from the randomisation database and data linkage from the participant's electronic health records.

Outcome measures for patients recruited in Scotland will be obtained through the Farr Institute in collaboration with 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] and HighSTEACS [Shah et al, 2015a; Shah et al, 2015b] trials (Tables 2 and 3). We will capture all hospital admission events and will have access to clinical records and imaging as required through NHS Safe Havens. Outcome measures for patients recruited in England will be obtained through NHS Digital. We will record the following safety endpoints: all-cause death, non-cardiovascular death, fatal bleeding, major bleeding (including gastrointestinal and intracranial haemorrhage), hospitalization for bleeding (all ICD-10 coded), as well as blood transfusions, where possible). The bleeding data will be used to classify bleeding events using the standardized bleeding definition for cardiovascular clinical trials as defined by the Bleeding Academic Research Consortium (BARC) [Mehran et al, 2011]. We will record the following efficacy endpoints: all-cause death, cardiovascular (cardiac and non-cardiac) death, myocardial infarction (non-fatal and fatal) [Thygesen et al, 2012], stroke (non-fatal and fatal; thrombotic and haemorrhagic), coronary revascularisation (percutaneous coronary intervention and coronary artery bypass graft surgery), and stent thrombosis.

7.2 COMPLIANCE

Compliance with the duration of therapy will be undertaken by record linkage with community-dispensed prescriptions and/or national registries, where possible.

8. DATA COLLECTION

Study data will be entered into an eCRF developed by Edinburgh Clinical Trials Unit. 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 either be entered directly into the eCRF or held in a trusted research environment. International sites will use their own data collection system to record the study data and the electronic health record data.

8.1 DATA MANAGEMENT

8.1.1 Personal Data

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

Participant's name, address, date of birth, GP contact details, health information and unique health identifier (Community Health Index (CHI) number or National Health Service (NHS) number will be collected. Personal data will be stored securely in the eCRF and by the research team at each site for a minimum of 5 years after the study has finished. The location and duration of storage of personal data at the international sites will be documented in their country specific protocol.

8.1.2 Transfer of Data

Data collected or generated by the study may be transferred to external individuals or organisations outside of the Sponsoring organisation(s). It may be provided to researchers running other research studies outwith NHS Lothian/University of Edinburgh. Following publication of the primary paper, a de-identified individual participant data set will be submitted to a data archive for sharing purposes. Participant information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research**.** Where this information includes identifiable information, it will be held securely with strict arrangements about who can access the information.

In order to perform data linkage, participant's personal details including their unique health number will be transferred to central health care and government data services bodies.

8.1.3 Data Processor

The data processor is the Edinburgh Clinical Trials Unit, Usher Institute, University of Edinburgh.

8.1.4 Data Controller

The data controller is the University of Edinburgh and NHS Lothian who are the co-sponsors of this study.

9. STATISTICS AND DATA ANALYSIS

9.1 PROPOSED SAMPLE SIZE

We plan to recruit 18,318 patients over 3 years across all participating countries. Of these, based on contemporary practice data for Scotland just under 7.5% will be treated with either coronary artery bypass graft surgery or percutaneous coronary intervention with a bare metal stent, giving a minimum sample size (excluding this 7.5%) for the main analysis of 16,944. If there is no substantial heterogeneity in outcome between these two groups, then they can be included in the analysis and further increase the power.

Recruitment in the UK was halted after 4,576 patients because the funder felt the trial was no longer deliverable due to the current challenging environment. The

statistical analysis will include the 4,576 patients recruited in the UK and as many international patients who have completed follow-up at the time of analysis.

9.2 SAMPLE SIZE CALCULATION

No clinical trials have been published comparing duration of therapy for unselected patients with type 1 myocardial infarction. However, most patients with type 1 myocardial infarction now undergo early percutaneous coronary intervention. From meta-analysis of stent trials comparing ≤6 months with 12 months of dual antiplatelet therapy [Palmerini et al, 2015] (among whom a large proportion of patients had acute coronary syndrome), the point estimates of the hazard ratios for all-cause mortality, non-cardiac mortality and bleeding were 0.87, 0.83 and 0.58 respectively. Over a 5-year period (2006-2010) in Scotland 25.4% of patients died within one year of acute coronary syndrome of whom 7.6% died from a non-cardiovascular cause, and 0.92% had a fatal bleed.

The study has been powered to assess the primary endpoint of all-cause mortality across the combined medical therapy and percutaneous coronary intervention with drug-eluting stent arms (92.5% of the study population). Assuming a more conservative relative risk reduction of 10% (risk ratio 0.9), and that patients who consent to participate in the study have a one-third lower overall risk of mortality than unselected patients, shorter durations of therapy would lead to an absolute difference of 1.69% (0.1 x 0.254 x 0.667) from the 12-month duration of treatment rate of 16.9%. A sample size of 8,472 patients per group (16,944 overall) would provide 85% power to detect this difference at two-sided P<0.05 (Stata 15.1 procedure ‘power two-prop’ without continuity correction). Given that this is an outcome ascertained by record linkage for geographically highly stable populations, we anticipate close to zero loss to follow up. To achieve the 16,944 across combined medical therapy and percutaneous coronary intervention with drug-eluting stent arms (92.5% of the study population) we need to randomise 16,944/0.925 = 18,318 participants. In addition, the study will have slightly increased power by using not just the occurrence of the event but also incorporating the time-to-event using log-rank statistics (and Cox proportional hazards models to adjust for baseline covariates).

An initial check of the data linkage procedures will be performed at approximately 10% of recruitment. The independent Trial Steering Committee will monitor all the assumptions behind the sample size calculations in aggregated data as the trial progresses. The full sample size of 16,944 would also allow us to detect an absolute risk reduction of 1% (from 6% to 5%) in non-cardiovascular mortality with 81% power and an absolute risk reduction of 0.3% (from 0.6% to 0.3%) in bleeding death, with 83% power and two-sided P<0.05, with event rates being one-third lower in consented than in unselected patients. We do not expect to have power to estimate the treatment effect in coronary artery bypass graft surgery or percutaneous coronary intervention with bare metal stent groups.

9.3 PROPOSED ANALYSES

For the primary outcome (all-cause mortality) we will compare time-to-event in a Cox regression model, stratifying by country and centre to account for clustering of

participants, and adjusting for cardiac history (stratification factor in randomisation). For secondary outcomes of non-cardiovascular mortality and bleeding death, we will similarly estimate cause-specific hazard ratios, censoring for competing causes of death. All analyses will be by intention-to-treat.

It is highly likely that baseline characteristics will have a major influence on the overall clinical benefits and risks [Steg et al, 2011]. We will explore efficacy and safety outcomes in the 4 pre-specified and stratified cohorts nested within the trial: (i) medically managed, (ii) percutaneous coronary intervention with bare metal stent, (iii) percutaneous coronary intervention with drug-eluting stent, and (iv) coronary artery bypass graft surgery.

In a sensitivity analysis, we will consider a two-stage individual participant data (IPD) meta-analysis where the IPD from each country are analysed separately then combined by an appropriate fixed-effect or random effects meta-analysis model [Burke et al, 2017].

The statistical methods will be documented in full in a detailed statistical analysis plan. The methods used will take into account the early stopping of the trial, and the limited numbers of events that will be available for analysis. A composite outcome of non-fatal bleeding and all-cause mortality will be explored.

10. PHARMACOVIGILANCE

Full details of contraindications and side effects that have been reported following administration of the IMPs can be found in the relevant Summary of Product Characteristics (SPC). The safety reporting processes and regulatory requirements for the international sites will be detailed in their country specific protocol.

10.1 DEFINITIONS

An adverse event (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An adverse reaction (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

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

- results in death of the clinical trial participant;
- is life threatening*;
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

*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.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be caused by the IMP, that it is not consistent with the information about the IMP in the Summary of Product Characteristics (SPC).

10.2 RECORDING AND REPORTING AEs, ARs, SAEs AND SARs

Clinical observations, measurements and other data that have the potential to comprise Adverse Events will only be apparent to the investigators at the time of participant consent, or at times during subsequent participation when the investigators become aware of such observations, measurements or other data as part of their standard care activities.

As the IMPs being used in the study all have marketing authorisations and well known safety profiles, clinical observations, measurements and other data that comprise Adverse Events and are identified by the sites as such, will be recorded in the participant's health records but will not be recorded in an Adverse Event log, nor reported elsewhere. Clinical observations, measurements and other data that comprise Adverse Events will, however, be assessed for seriousness, causality, expectedness and severity as described below.

The study outcomes listed in Table 3, which will be collected through routinely collected data from electronic health records, will not be recorded as SAEs and will therefore not be reported to the Sponsor. The study outcome data from the electronic health records will, however, be sent to the DMC and TSC at pre-specified intervals throughout the trial. Due to recruitment being halted by the funder, the first pre-specified interval which will occur at approximately 25% mature data on the primary outcome, will coincide with final reporting.

10.2.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 10.1 for AEs identified at sites. All AEs identified by the site and assessed as Serious will not be recorded as SAEs, nor reported to the Sponsor, but the details of the events will be retained in the participants' health records.

10.2.2 Assessment of Causality

The Investigator will make an assessment of whether an SAE is likely to be related to the IMP according to the definitions below.

Unrelated: where an event is not considered to be related to the IMP.

Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the SAE has a causal relationship to the study drug. The assessment of causality will be made against the Reference Safety Information found in the Summary of Product Characteristics.

All SAEs identified by sites and assessed as possibly Related to the IMP will not be recorded as SARs, nor reported to the Sponsor, but the details of the events will be retained in the participant's health records.

10.2.3 Assessment of Expectedness

The evaluation of expectedness of SARs identified by sites will be made based on knowledge of the reaction and the relevant product information documented in the SPC

The event may be classed as either:

Expected: the SAR is consistent with the toxicity of the IMP listed in the SPC.

Unexpected: the SAR is not consistent with the toxicity in the SPC.

Only SARs which are identified by the sites, or by the Principal Investigator after the closure of sites, and considered unexpected (i.e. SUSARs) by the Principal Investigator (or another suitably qualified physician in the research team who has been delegated this role) will be recorded and reported to the Sponsor and Chief Investigator (CI) – see section 10.3. The Chief Investigator may not downgrade an event that has been assessed by an Investigator as a SUSAR.

Fatal and life threatening SARs should usually be considered unexpected. A fatal or life-threatening SAR can only be expected for an IMP when that specific SAR is explicitly listed as 'fatal' or 'life threatening' in the list of ARs (section 4.8 of the SPC) for that that IMP. An unexpected SAR comprises a SUSAR and should be recorded and reported as such.

10.2.4 Assessment of Severity

The Investigator will make an assessment of severity according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or

action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

10.3 REPORTING OF SUSARs

Once an Investigator becomes aware that a SUSAR 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 SUSAR, they should not wait for this additional information before notifying ACCORD. The SUSAR report form can be updated when the additional information is received.

The SUSAR will be recorded on a SAE form and the report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 10.2.2, Assessment of Causality and 10.2.3, Assessment of Expectedness.

The SAE form will be transmitted via email to safety@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be sent by fax to ACCORD on **+44 (0)131 242 9447** or may be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

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

10.4 REGULATORY REPORTING REQUIREMENTS

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

ACCORD has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD (or delegate) will inform Investigators at participating sites of all SUSARs and any other arising safety information.

ACCORD will be responsible for providing safety line listings and assistance; however, it is the responsibility of the Investigator to prepare the Development Safety Update Report. This annual report will list all SUSARs reported during that time period. The responsibility of submitting the Development Safety Update Report to the regulatory authority and RECs, lies with ACCORD.

10.5 FOLLOW UP PROCEDURES

After recording and reporting a SUSAR, the Investigator should make every effort to follow the event until a final outcome can be recorded or reported as necessary. Follow up information on a SUSAR will be reported to the ACCORD office.

10.6 PREGNANCY

Few patients will be of child-bearing potential in the trial. Such patients are advised against pregnancy following acute coronary syndrome because of the effect on the heart and the potential teratogenicity of the drugs prescribed. Pregnancy is not considered an AE or SAE. The IMPs being used in this study all have marketing authorisations and well known safety profiles so pregnancy information will not be recorded for any female participants or female partners of a male participant.

11 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

11.1 TRIAL MANAGEMENT GROUP

The trial will be managed and run by the Edinburgh Clinical Trials Unit which has full registration with the United Kingdom Clinical Research Collaboration. The study will be managed by a dedicated trial manager with support from a data programmer. The Clinical Trials Unit will also oversee the statistical and analytic aspects of the trial conduct.

11.2 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 with the applicants and 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.

11.3 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 of the follow-up data will be supplied at approximately 25%, 50%, 75% and 100% mature data on the primary outcome (all-cause mortality) to ensure there is no overwhelming evidence of safety or efficacy that would require early termination of the trial. Appropriate criteria cannot be specified precisely, but the DMC will work on the principle that a difference of at least 3 standard errors in an interim analysis of a major outcome event (e.g. the primary outcome) may be needed to justify halting, or modifying, a study before the planned completed recruitment or trial follow-up. The terms of reference of the Data Monitoring Committee and the names and contact details are detailed in the DMC charter.

Due to recruitment being halted by the funder the first interim analysis at approximately 25% mature data on the primary outcome will coincide with final reporting.

11.4 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 an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

11.5 RISK ASSESSMENT

A study specific risk assessment will be performed by representatives of the co-sponsors, ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs. Input will be sought from the Chief Investigator or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans. The risk assessment outcomes will also indicate which risk adaptions could be incorporated into the trial design.

11.6 BENEFIT and RISK BALANCE

The potential risks and hazards of dual anti-platelet therapy relate to the opposing benefits and risks of therapy. There is no doubt that dual anti-platelet therapy is associated with a reduction in atherothrombotic events with reductions in myocardial infarction and potentially cardiovascular death. However, this benefit comes at a cost of increasing bleeding complications that include major gastrointestinal and intracranial haemorrhage that can be fatal. The atherothrombotic risk is time varying (greatest in the first three months) whilst the bleeding risk is continuous. Thus, 3 months therapy may be too brief and an excess of atherothrombotic events will not be counterbalanced by reductions in bleeding complications. Conversely, 12 months therapy may lead to an excess of major bleeding complications with minimal reductions in atherothrombotic events. This risk-to-benefit balance is at the centre of the trial question.

The trial manager will liaise closely with all centres and encourage adherence to randomisation and the provision of promotional materials. There may be loss of equipoise during study conduct. We think this is unlikely since this question has remained unresolved for over 10 years with little new evidence anticipated to influence equipoise over the time course of the trial conduct. We will encourage all clinicians to contact the research team and discuss any potential issues as the trial progresses. We will be able to monitor trial prescription data throughout study conduct.

11.7 STUDY MONITORING AND AUDIT

ACCORD clinical trial monitors, or designees, will perform monitoring activities in accordance with the study monitoring plan. This will involve on-site visits and remote monitoring activities as necessary. ACCORD QA personnel, or designees, will perform study audits in accordance with the study audit plan. This will involve investigator site audits, study management audits and facility (including third parties) audits as necessary.

12 GOOD CLINICAL PRACTICE

12.1 ETHICAL CONDUCT

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

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

12.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended. The study will be risk adapted as this trial is assessing only the duration of therapy in IMPs that already have a marketing authorisation and approval for use in patients with acute coronary syndrome.

12.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff. Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

12.3.1 Informed Consent

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

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

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

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

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The original will be signed in the Investigator Site File (ISF). The participant will receive a copy of the signed consent form and a copy will be filed in the participant's medical notes. A copy of the consent form may also be transferred to the Edinburgh Clinical Trials Unit for monitoring. Monitoring of consent forms at international sites will be detailed in the country specific protocol.

12.3.2 Study Site Staff

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

12.3.3 Data Recording

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

12.3.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the ACCORD 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.
- ACCORD will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF) or Sponsor File, where required. The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs. Under certain circumstances the TMF responsibilities may be delegated to the research team by ACCORD.

12.3.5 GCP Training

The CI and Principal Investigators must hold evidence of appropriate GCP training. Targeted GCP training will be provided for all other members of the research team to whom study related responsibilities have been delegated.

12.3.6 Confidentiality

All laboratory specimens, 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.

12.3.7 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 and will uphold the Act's core principles. Access to collated participant data will be restricted to individuals from the research team treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

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

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

13. STUDY CONDUCT RESPONSIBILITIES

13.1 PROTOCOL AMENDMENTS

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

Proposed amendments will be submitted to the Sponsor for classification and authorisation. Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to implementation. The amendment submission process for international sites will be detailed in the country specific protocol.

13.2 PROTOCOL NON-COMPLIANCE

13.2.1 Definitions

Deviation - Any change, divergence, or departure from the study design, procedures defined in the protocol or GCP that does not significantly affect a subject's rights, safety, or well-being, or study outcomes.

Violation - A deviation that may potentially significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being

13.2.2 Protocol Waivers

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to

eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

13.2.3 Management of Deviations and Violations

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation.Deviation logs / violation forms will be transmitted via email to QA@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be sent by fax to ACCORD on **+44 (0)131 242 9447** or may be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

Non-compliance with the randomised allocation will not be recorded as a protocol deviation and/or violation.

13.3 URGENT SAFETY MEASURES

The Investigator may implement a deviation from or change to the protocol to eliminate an **immediate hazard** to trial participants without prior approval from the REC and the MHRA. This is defined as an urgent safety measure and the investigator must contact the Clinical Trial Unit at the MHRA and discuss the issue with a medical assessor immediately (+44 (0) 20 3080 6456).

The Investigator will then notify the MHRA (clintrialhelpline@mhra.gsi.gov.uk), the REC and ACCORD, in writing of the measures taken and the reason for the measures within 3 days by submitting a substantial amendment.

13.4 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 (QA@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 regulatory authorities and research ethics committees as necessary.

13.5 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol-defined end of study point. Patient identifiable information will be kept beyond 5 years to facilitate longer term follow up if necessary (this will be made explicit on

consent forms and patient information sheets). When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

13.6 END OF STUDY

It is anticipated that the study will last 4-5 years: three years for recruitment and 15 months of follow-up. The end of study is defined as 15 months after the last participant's last visit. However, longer term follow-up using record linkage may be performed at 5 and 10 years. The Investigators, trial management group 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, Regulatory Authority, R&D offices 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. In accordance with ACCORD SOP CR011, a Clinical Study Report (CSR) will be provided to the Sponsor (QA@accord.scot) and REC within 1 year of the end of the study. Upon completion of the study, the Chief Investigator will upload clinical trial results onto the EudraCT database on behalf of the Sponsor.

13.7 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 their 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 will have the benefit of NHS Indemnity.

The manufacturer of the IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug.

14. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

14.1 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 in accordance with ICH guidelines.

14.2 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 finalization. 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. The results of the study, together with other mandated information, will be uploaded to the European clinical trials database within 1 year of the end of the study.

14.3 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.

14.4 PEER REVIEW

The study protocol has undergone independent review by an Edinburgh Clinical Trials Unit statistician and by the British Heart Foundation. The protocol has been amended in accordance with their recommendations.

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