2.4 Secondary Endpoint

1. Time to initiation of combination therapy or escalation of Lipid lowering therapy as defined in the primary endpoint.

2. LDL-C by Week 16

3. Proportion of patients reaching target LDL-C level (<1.4 mmol/L (<55 mg/dL) by Week 16.

2.5. Exploratory analysis

We will do some prespecified exploratory analyses including:

1. Proportion of patients achieving a decrease from baseline LDL-C level of more than 50% by Week 16 for LLT naïve patients
2. Percent change from baseline in LDL-C by Week 16 for LLT naïve patients
3. Percent change from baseline in non-HDL-C by Week 16 for LLT naïve patients
4. Percent change from baseline in HDL-C by Week 16 for LLT naïve patients
5. Percent change from baseline in triglycerides by Week 16 for LLT naïve patients
6. Percent change from baseline in total cholesterol by Week 16 for LLT naïve patients
7. Proportion of patients on combination therapy at Week 16 (for at least 4 weeks) achieving target LDL-C level <1.4 mmol/L (<55 mg/dL) and a decrease of baseline in LDL-C level of at least 50% by Week 16 for LLT naïve patients
8. Proportion of all patients achieving target LDL-C level <1.8 mmol/L (<70 mg/dL) by Week 16
9. Proportion of patients on combination therapies with three oral LLTs or 1 injectable therapy plus an oral LLT
10. Proportion of patients with all-cause and CV mortality by Week 16
11. Proportion of patients with myocardial infarction, stroke/TIA, admission for CV reasons and revascularisations (CABG and/or angioplasty) by Week 16
12. Proportion of patients with goal achievement (LDL-C <1.4mmol/L by Week 16 or 55mg/dl) in each trial arm stratified by institution setting (secondary/tertiary/mixed), country (UK/Spain/Italy) and by subpopulations defined by whether patients had experienced one or more CV events in the 2 years prior to admission.
13. LDL-C levels by 16 weeks among LLT naïve (at ACS), monotherapy and combination therapy patients, within the DSS arm.
14. Quantitative evaluation as evaluated by the DSS Evaluation Questionnaire of the DSS by the clinicians at DSS sites

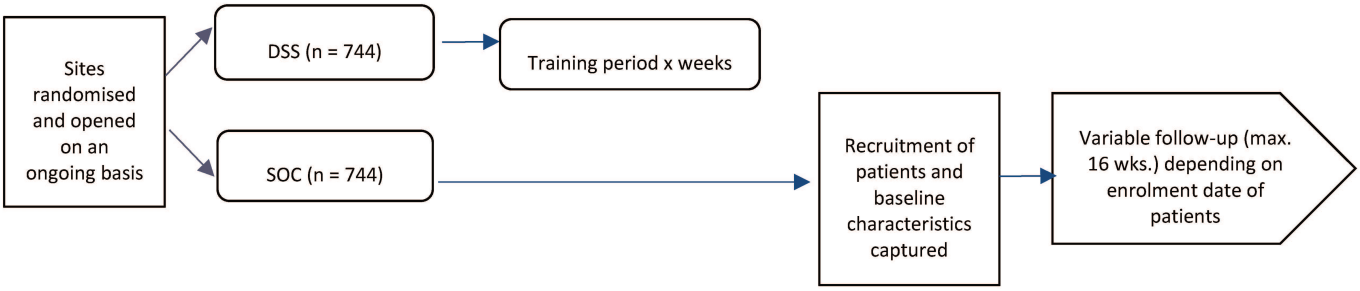
3. STUDY DESIGN

3.1 Design

An international, multi-centre, randomised, parallel study design with a maximum of 48 sites randomised to Standard of Care (SoC) (24 sites) or DSS (24 sites) across 3 countries: the UK, Spain and Italy. We plan to recruit 16 sites per country; 8 DSS sites; 8 SoC sites. In the

event of under-recruitment of sites in Italy or Spain, up to 6 replacement sites may be recruited from the UK. DSS sites will receive a standardised period of training prior to commencing patient recruitment. Patients will be followed up for a maximum of 16 weeks.

Figure 1 Study Flow



4. PARTICIPANT ENTRY

4.1 Study setting and population

Adults admitted with ACS event to hospital sites and where subsequent follow up of the patients is carried out.

(i) Inclusion criteria:

Sites:

1. Manage ACS patients as defined by: Symptoms of myocardial ischemia with an unstable pattern, occurring at rest or with minimal exertion, within 72 hours of an unscheduled hospital admission due to presumed or proven obstructive coronary disease and at least one of the following:
   - Elevated cardiac biomarkers
   - Resting electrocardiographic changes consistent with ischemia or infarction, plus additional evidence of obstructive coronary disease from regional wall motion or perfusion abnormality, 70% or more epicardial coronary stenosis by angiography, or need for coronary revascularization procedure
2. Mange post ACS follow up care of patients including risk factor control
3. Ability to provide follow up information on patient care for a maximum of 16 weeks including blood tests
4. Willing/ able to access and undertake training for the DSS
5. Adequate internet connection at site and the ability to access the DSS
6. No restrictions on use of LLTs (within national guidelines/ reimbursement)
7. Patient information essential for DSS input on all of the following:
   - LDL-C, TC, HDL-C measurements.
   - Record of corresponding lipid-lowering therapy at the time the LDL-C is measured.
   - Estimated GFR (eGFR), e.g. available or derived using MDRD, or its component, the serum creatinine.

   Patient demographics (age, gender), prior clinical history (ASCVD, coronary artery disease, cerebrovascular disease, abdominal aortic aneurysm, peripheral artery disease, Diabetes Mellitus), systolic blood pressure, smoking status.

Participants:

1. Aged ≥18 to < 80 years old
2. Provide written informed consent
3. Presenting to a study site with ACS as LLT naïve, monotherapy or combination therapy (defined as more than one LLT agent)
4. Willing to take lipid lowering treatments for the secondary prevention of cardiovascular disease
5. Attending the same study site (or same clinical team) for ACS follow up to ensure follow up data can be collected; or ensure that follow up data can be collected from other clinical institutions as part of the clinical pathway.

(ii) Exclusion criteria:

Sites:

1. Unable to capture/ provide data on patients with ACS during admission and follow up
2. Unable or unwilling to use treatments other than statins for ACS care

Participants:

1. Unable to provide written informed consent
2. LDL-C measurement < 1.8 mmol/L at admission

5. PROCEDURES AND MEASUREMENTS

5.1 Randomisation of sites and Blinding

The 48 sites will be randomly assigned to DSS or SoC using permuted block randomisation stratified by country and site type (secondary/ tertiary/ mixed care). A randomisation list will be created by a statistician and data manager, and allocation concealment will be achieved using a secure web-based system.

Sites and the study team will only be made aware of their randomisation allocation after being recruited and assigned to a pre-randomised numeric key.

Patients will not know the site allocation (DSS or SoC) until after the study has ended.

5.2 Identification and recruitment of participants

Patients will be identified at hospitals that routinely manage and care for adults with ACS. Study sites will be spread across the UK, Italy and Spain. As the study sites will be selected based on their ACS patient management pathway, local Participant Identification Centres will not be needed/utilised. Selected participating and initiated sites will be randomised to the DSS or SoC alone. For DSS randomised sites, staff will be involved in multiple stages of the care pathway for ACS patients. Sites that are randomised to the DSS will be trained extensively on the practical use of the DSS and its clinical utility to quantify relative and absolute benefits and will implement the DSS when caring for different lipid lowering regimens, for those patients who have consented to the trial. This will allow better informed, shared decision making. In parallel we will undertake public engagement.

At the end of the study, the sites in the SoC group will be offered the provision of the DSS and training manuals to use. No data will be collected.

The trial will be registered on any relevant local portfolio systems in the UK, Spain and Italy.

5.3 Screening and Baseline evaluations

Written informed consent will be obtained before participant data is captured in the study database or DSS system (if DSS site). The patient will be informed that the site is participating in a trial of personalised risk assessment to guide optimal care. If the patient declines to participate, care will be offered based on the health care professionals' knowledge/ opinions/ routine practice without the use of the DSS to guide precision estimates of baseline risk and therapeutic benefit. Research/ clinical staff at the study site will identify eligible patients during the index ACS admission to the site and who will be followed up for continuing care at the site.

At a DSS site, patients who consent may have their care guided at any stage of the care pathway, for instance during the index hospitalisation, during follow up (at attendance of cardiac rehabilitation, during out-patient visits). Patients recruited in the SoC sites will undergo an identical process with the difference being that health care physicians guiding their care will not be using the DSS to guide care.

No specific tests are required before the patient can enter the trial; the patient must meet the inclusion criteria including provide written informed consent.

Data from the following routine clinical assessments will be captured at the Baseline timepoint: participant Informed Consent; inclusion/exclusion checked; Medical History, Blood pressure, LDL-C measurement, demographics, concomitant medications and lifestyle factors such as smoking cessation, frequency of regular exercise.

5.4 Visit Schedule

	Baseline	**All other visits as per routine care up to 16 weeks**
Visit	**1**	**2 onwards**
Informed consent	X	
Inclusion & exclusion criteria	X	X
DSS variables	X	X*
Demography	X	
Medical history	X	
Vital Signs	X	X
Full Lipid Profile	X	X
Medications / LLT	X	X
Lifestyle (smoking, exercise & diet)	X	X
CV events	X	X

***DSS use optional after Baseline visit**

5.5 Follow-up

Follow-up clinic visits will take place as per routine clinical practice. In general these vary but are expected to occur within 3 months for patients accessing cardiac rehabilitation services or at approximately 12 weeks and 16 weeks post index ACS event after discharge in general (1-2 visits). We have not mandated additional visits and the follow up is intended to reflect routine care pathways although the exact timing may vary (maximum 16 weeks). These visits will consist of standard routine care in both randomised groups, with the exception that at DSS sites, staff will be asked to utilise the DSS to assess whether LLT should be further optimised for consented patients.

Routine clinical care includes blood tests for lipids and blood pressure evaluation, evaluation of lifestyle factors such as smoking, exercise and diet. In the scenario that a cholesterol measurement is unavailable at the time of follow up, patients will be required for have blood tests after the routine follow up. This situation is not specific to this trial and reflects real world clinical practice.

5.6 Incidental findings

Any clinical incidental findings related to the participant which are identified during the course of the study will be followed up with the clinical team at the study sites as per routine care requirements.

6. WITHDRAWAL

6.1 Withdrawal from Study

Failure to attend clinic visits is not considered study discontinuation or withdrawal of consent. Patients will be asked to consent to information on vital status being obtained from national records or from their GP. Withdrawal could occur for the following reasons:

- At the request of the participant for any reason.

As patients are not receiving any investigational treatment the above scenario is unlikely. Furthermore, physicians may choose to de-escalate therapies on clinical grounds. This will be captured within the context of the randomised groups and de-escalation of therapies is not a reason to discontinue a study participant.

6.2 Procedures for Withdrawal from Study

If a participant withdraws from the trial, the decision to withdraw from further trial procedures will be documented on the electronic case report form (eCRF) and in the medical notes. If the participant does not agree for data collected to be retained, the data must be excluded from the analyses.

Participants who have discontinued the trial and/or have withdrawn from the trial will not be replaced, as the sample size allows for potential loss to follow-up.

7. SAFETY REPORTING

As this trial is utilising a non-patient intervention, and because all participants will be treated only in line with standard of care, the treating physicians at study sites will report any Adverse Drug Reactions (ADRs)/ Adverse Events (AEs) in routine ways in accordance with