Statistical Analysis Plan (SAP)

Short Study title / Acronym: OptimiZation Of lipid lowering therapies using a Decision support system In patients with Acute Coronary syndrome (ZODIAC).

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Protocol V3.0

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1. Abbreviations

ACS	Acute Coronary Syndromes
ADR	Adverse Drug Reaction
AE	Adverse Event
ASCVD	Atherosclerotic Cardiovascular Disease
CI	Chief Investigator
CV	Cardiovascular
CVD	Cardiovascular Disease
CRF	Case Report Form
DSS	Decision Support System
eCRF	Electronic Case Report Form
EAS	European Atherosclerosis Society
ESC	European Society of Cardiology
HRA	Health Research Authority
GPvP	Good Pharmacovigilance Practice
ICMJE	International Committee of Medical Journal Editors
ICTU	Imperial Clinical Trials Unit
ITT	Intention to Treat
LDL-C	Low-density lipoprotein cholesterol
LLT	Lipid Lowering Therapy
LMT	Lipid Modifying Treatment
MCMC	Markov chain Monte Carlo
MI	Myocardial Infarction
NSTEMI	Non-ST segment elevation myocardial infarction
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
SAP	Statistical Analysis Plan
SoC	Standard of Care
SOP	Standard Operating Procedure
STEMI	ST segment elevation myocardial infarction
TEC	Trial Executive Committee
UA	Unstable Angina

2. Background

2.1. Study Summary

The ZODIAC trial is an international, multicentre, cluster randomised, parallel arm trial. Its aim is to assess whether the availability and use of a Decision Support System (DSS) is more likely to result in implementation and achievement of European Atherosclerosis Society (EAS)/ European Society of Cardiology (ESC) lipid lowering goals, focusing on the early optimisation of lipid lowering therapy (LLT), in patients with Acute Coronary Syndromes (ACS).[1] ACS represent conditions compatible with acute myocardial ischemia and/or infarction. The study will be performed at approximately 48 investigational sites in the United Kingdom, Italy and Spain. DSS will be added to routine care and will be compared to routine care alone. Patients will be followed up for a maximum of 16 weeks.

2.2. Study Flowchart

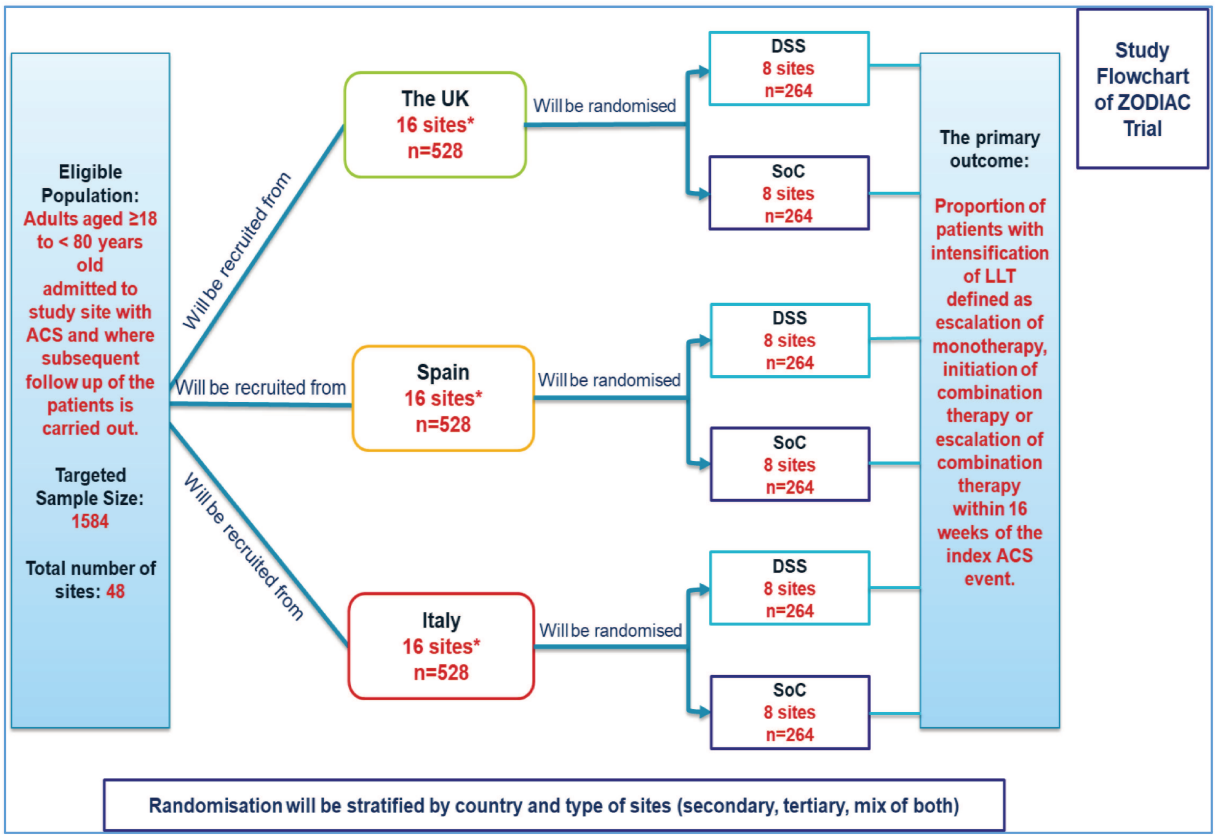

Figure 1: Study flowchart

* In the event of under-recruitment of sites in Italy or Spain, up to 6 replacement sites may be recruited from UK.

3. Study Objectives

3.1. Primary Objectives

To compare implementation of a DSS (aligned to the 2019 EAS/ESC Guidelines[1]) added to routine clinical care as compared with routine care without a DSS, to assess whether the addition of a DSS system to current practice increases the likelihood of intensification of LLT defined as escalation of monotherapy, initiation of combination therapy or escalation of combination therapy within a 16-week period.

3.2. Secondary Objectives

1. To compare the time to intensification of LLT in DSS versus routine care.
2. To compare the mean low-density lipoprotein cholesterol (LDL-C) and other key lipid variables by Week 16 in DSS versus routine care.
3. To compare the proportion of patients reaching target LDL-C level (<1.4 mmol/L (<55 mg/dL) by Week 16 in DSS versus routine care.
4. To compare the proportions of patients who receive different types of intensification of LLT: combination therapy by Week 16, escalated monotherapy by Week 16 and escalated combination therapy by Week 16 in DSS versus routine care.

3.3. Exploratory Objectives

<u>For all patients, by treatment arm:</u>

1. To determine the proportion of patients achieving target LDL-C level <1.8 mmol/L (<70 mg/dL) by Week 16
2. To determine the proportion of all cause and CV mortality by Week 16
3. To determine the proportion of patients experiencing myocardial infarction, stroke/TIA, admission for CV reasons and revascularization by week 16
4. To determine the proportion of patients prescribed combination therapies consisting of three oral LLT or 1 injectable therapy plus one or more oral LLT by Week 16
5. To determine whether the effect of the DSS on goal achievement (LDL-C < 1.4mmol/L by Week 16 or 55mg/dl) varies by institution setting, country, or subpopulations of interest (patients with a prior CV event in the 2 years prior to admission).

For LLT-naïve patients, by treatment arm:

6. To determine the proportion of patients achieving a decrease from baseline in LDL-C level of more than 50% by Week 16
7. To determine the percent change from baseline by Week 16 for:
    - LDL-C
    - non-high density lipoprotein cholesterol (non-HDL-C)
    - high-density lipoprotein cholesterol (HDL-C)
    - triglycerides
    - total cholesterol (TC)

In the DSS arm only:

8. To summarise LDL-C levels by Week 16 among patients who, on admission, are a) LLT naïve b) receiving monotherapy and c) receiving combination therapy
9. To carry out a qualitative evaluation of the DSS by the clinicians at DSS sites

In patients who are LLT-naïve on admission and who are prescribed combination therapy for at least 4 weeks by Week 16:

10. To determine the proportion of patients 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 stratifying, where feasible, by different types of combination therapies e.g. oral combination therapies only, oral plus injectable combination therapy.

3.4. Simulation Study Objectives

The simulation study is beyond the scope of this SAP. It will be carried out by an external partner, Axtria. They will define their own statistical analysis.

4. Design

4.1. Study Design

An international, multicentre, cluster randomised, parallel arm trial with a total of 48 sites randomised to Standard of Care (SoC) [24 sites] or DSS [24 sites] across 3 countries: the United Kingdom (UK), Spain and Italy. There will be 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 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. As there are no defined study visits after the patient's baseline visit all outcomes will be assessed as close to 16 weeks as possible.

4.2. Treatment Groups

Study sites will be allocated to either SoC group or the DSS group. Both groups will be following routine clinical care including local/national prescribing guidelines during the course of the study.

For those sites randomised to the DSS, there will be no patient intervention, but those sites will be trained on a DSS tool. The DSS is available in a web application that can be accessed on the Internet using the most common Web browsers, namely Google Chrome, Safari, Internet Explorer, Microsoft Edge, or Mozilla Firefox intended for clinicians to estimate the clinical benefit of any LLT regimen, whether monotherapy or combination therapies. The DSS does not recommend treatments but shows the expected ASCVD risk, absolute and relative ASCVD risk reductions and number needed to treat for the various treatments selected by the clinical user on the potential value of initiation of an add-on therapy for reducing the risk of recurrent cardiovascular (CV) events. Implementing the patient-specific recommendation remains at the clinicians' discretion. The DSS will be protected from unwanted use by asking its users to enter their OpenClinica credentials.

4.3. Study Population

Patients will be identified at hospitals that routinely manage and care for adults with ACS. Adults admitted with ACS to hospital sites where subsequent follow up of the patients is also carried out.

4.4. Eligibility Criteria

4.4.1. Inclusion Criteria

Sites which:

- 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
- Manage post ACS follow up care of patients including risk factor control
- Can provide follow up information on patient care for a maximum of 16 weeks including blood tests
- Are willing/ able to access and undertake training for the DSS
- Have adequate internet connection at site and the ability to access the DSS
- Have no restrictions on use of LLT (within national guidelines/ reimbursement)
- Collect 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 glomerular filtration rate (eGFR), e.g. available or derived using Modification of Diet in Renal Disease (MDRD)[2], or its component, the serum creatinine.
    - Patient's demographics (age, gender), clinical history (ASCVD, coronary artery disease, cerebrovascular disease, abdominal aortic aneurysm, peripheral artery disease, diabetes melitus), systolic blood pressure, smoking status.

Patients who:

- Are aged ≥18 to < 80 years old
- Can provide written informed consent
- Present to a study site with ACS as LLT naïve, monotherapy or combination therapy (defined as more than one LLT agent)
- Are willing to take LLT for the secondary prevention of CV disease
    - 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 (patients are required to provide consent for the site to contact other health providers such as the patient's GP to collect relevant follow up information for the purposes of the study).

4.4.2. Exclusion Criteria:

Sites which:

- Are unable to capture/provide data on patients with ACS during admission and follow up (or are unable to facilitate follow up with e.g. the patient's GP where required for the purposes of the study)
- Are unable or unwilling to use LLT other than statins for ACS care

Patients who:

- Cannot provide written informed consent
- Have LDL-C measurement < 1.8 mmol/L at admission

4.5. Sample Size

It is estimated that in the SoC arm, we expect 7% of patients to be on combined therapy at 24 weeks. This estimate is based on published data (Koskinas et al[3]) using the ELIPS study cohort which included exclusively ACS patients. A slightly lower proportion of patients (5%) may be expected to be on combination therapy at 16 weeks.

To detect a meaningful difference in proportions from the SoC group of 0.05 to 0.15 in the DSS with 90% power, we require 744 patients in 24 clusters within each arm.

This calculation assumes a two-sided statistical test at the 5% significance level, ICC of 0.1 and clusters of a similar size (31 for each site).

Justification for ICC of 0.1: Based on the article by Campbell et al.[4], it would be reasonable for a guideline implementation study within primary care to assume an ICC of the order of 0.1 for process variables and an ICC of less than 0.05 for the outcome variable. This is also in line with empirical estimates obtained from an online database with ICC reported for cluster studies that aimed to change practice.[5] In the database we examined the hypertension guideline interventions, these varied from 0.048 to 0.064. In addition, we have to consider clustering within country; to be conservative we have assumed an ICC of 0.1.

Based on our experience working in this setting we do not expect any loss of clusters. However, drop out may occur within clusters. As data are extracted from routinely collected electronic healthcare records, we expect missing data to be low as it will only be patients who actively request data collection to stop that will have missing outcome data. Considering a conservative approach[6] and assuming a loss to follow-up rate of 5%, we need a minimum total sample size of 1568. Considering adjusted numbers per cluster we aim to recruit 792 over 24 clusters per arm (a total sample size of 1584).

All calculations were done using PASS 2022 software[7] and applying a method of "Tests for Two Proportions in a Cluster-Randomised Design".

4.6. Randomisation

The 48 sites will be randomly assigned to DSS or SoC using permuted block randomisation stratified by country and site type (secondary/ tertiary care/mix of both). A randomisation list will be created by the Data Manager, and allocation concealment will be achieved using a secure local system.

Sites will only be randomised after being recruited by linking sites to a pre-randomised numeric list and stored in a secure web-based system.

The randomisation list is concealed from members of the team who are involved in recruitment. Concealment from the operational staff after randomisation has occurred is not possible but intervention allocation will be blinded to the patient.

The process in summarised in Figure 2.

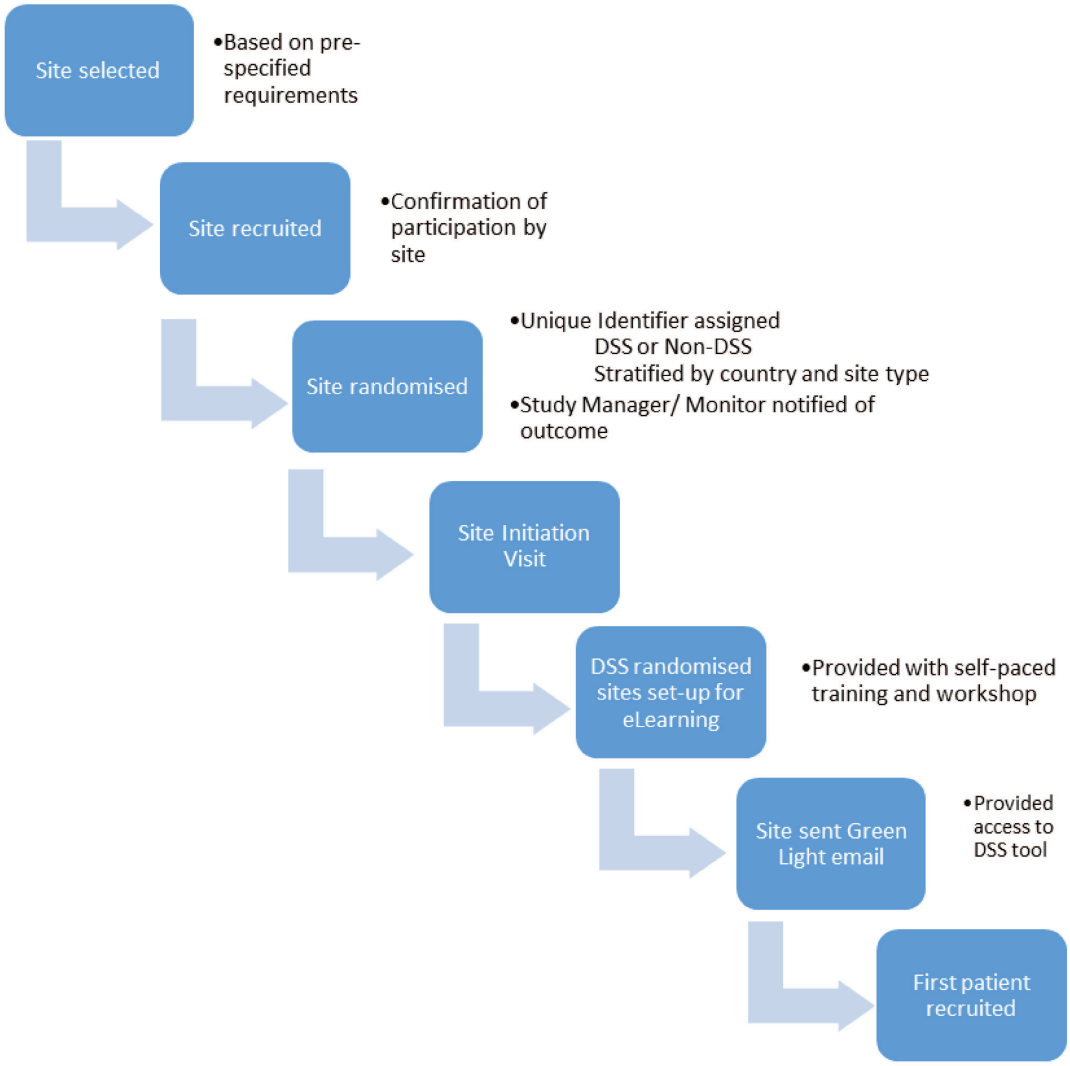

Figure 2: Randomisation workflow

4.7. Blinding

Study patients and the analysing statistician will be blinded to the treatment group. Due to the nature of the intervention the study team delivering the intervention will not be blinded.

4.8. 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 to have blood tests after the routine follow up. This situation is not specific to this trial and reflects real world clinical practice.

Every effort will be made to ensure follow up data are collected by sites. Where follow up visits have not been attended by Week 16, sites will access the patient's local medical record and/or contact the patient's GP to determine the outcome data status at Week 16. In the event that the local medical record is not available or the GP does not respond, then the patient will be regarded as lost to follow up from the date of the last visit attended or last known prescription from the patient's record for the purposes of censoring.

Note that, for operational reasons, some patients may have data reported at 24 weeks only. These data may be used, where appropriate, to derive or impute the LLT medication status at 16 weeks.

The schedule of events is shown in **Error! Reference source not found.**.

Table 1: Schedule of Time and Events

	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[a]
Demography	X	
CV Medical history	X	
Vital Signs[b]	X	X
Full Lipid Profile	X	X
Medications / LLT	X	X
Lifestyle (smoking, exercise & diet)	X	X
CV events	X	X

[a] DSS use optional after Baseline visit

[b] Includes height, weight, body mass index, temperature, diastolic and systolic blood pressure, and blood pressure position

5. Variables of Analysis

5.1. Baseline Variables

The important demographic variables

1. Age
2. Gender
3. Sex at birth
4. Ethnicity

Lifestyle variables

1. Smoking status (and type of tobacco)
2. Exercise
3. Dietary advice (and if this has been followed)
4. Weight, height and body mass index

Medical/medication history of the patients

1. Cardiovascular History
2. Concomitant medication
3. Lipid lowering therapies and their doses

5.2. Primary Efficacy Variable

Proportion of patients with intensification of LLT relative to baseline, regardless of adherence to the DSS, within 16 weeks of index ACS event.

Intensification includes:

- escalation of monotherapy OR
- initiation of combination therapy OR
- escalation of combination therapy

Only commercially available licensed LLT will be considered.

Patients will be considered LLT-naïve on admission if no LLT medications (statins, ezetimibe, bempedoic acid, bile acid sequestrants, evolocumab, alirocumab and inclisiran) are listed on the LLT 'prior to admission' form which captures LLT therapy in the month prior to admission. Patients who are admitted on medicines such as fish oils, nicotinic acid derivatives and fibrates will be considered to be a subgroup of LLT-naïve patients since these agents do not have a clinically significant effect on LDL levels.

Patients who are LLT-naïve on admission will be expected to start on statin monotherapy prior to discharge or an alternative monotherapy prior to discharge, and rarely post-discharge i.e. during follow up. For patients initiated on monotherapy as their first LLT, intensification of therapy in these patients can only occur after starting monotherapy. Therefore, the primary outcome will be met in these patients if they subsequently receive escalation of their monotherapy or start combination therapy during follow up. It is also possible that some LLT-naïve patients may be started on combination therapy at discharge. In this case the primary outcome will be met at discharge.

For patients who are already prescribed LLT prior to admission, they will meet the primary outcome if intensification occurs between admission and discharge or after discharge.

Table 2: Primary outcome defintion

Baseline therapy patients recruited with	**Meets primary outcome at 16 weeks if the patients is now on**
<2 LLT drugs (i.e. 0 to 1)	Combination therapy (2 or more drugs) OR
	Escalated monotherapy (one drug increase in dose, or switch to more potent single drug)

>=2 LLT drugs	Escalated combination therapy (e.g. 3 drugs, increase in the potency of one of the drugs if the total number of drugs remains unchanged)

Combination therapy is defined as being on two or more commercially available licensed LLT where treatments overlap by at least one day including:

- Statins (WHO ATC subclass A10AA),
    - Rosuvastatin
    - Atorvastatin
    - Simvastatin
    - Fluvastatin
    - Lovastatin
    - Pravastatin
    - Pitavastatin
- Ezetimibe (Selective cholesterol-absorption inhibitor),
- Bempedoic Acid (Adenosine triphosphate-citrate lyase (ACL) inhibitor),
- Bile acid sequestrant,
- PCSK9 monoclonal inhibitors,
    - Alirocumab
    - Evolocumab
- PCSK9 siRNA therapy (inclisiran)

Escalated therapy includes increase in statin dose or potency (e.g. another statin at a dose which is predicted to have a greater reduction in LDL-C), switching to a more potent combination regimen e.g. statin plus ezetimibe to statin plus PCSK9 Mab, or two drug combination therapy increased to triple therapy.

A bespoke algorithm will be developed to assign primary outcome status by comparing LLT therapy on the 'prior to admission', 'discharge' and 'follow-up' forms. Changes in LLT will be classified as 'escalated monotherapy', 'initiated combination therapy' or 'escalated combination therapy' or 'unchanged/de-intensified' (Appendix A). This classification will be informed by published LDL-lowering potencies of different drugs, different doses and their combinations.[8-12] The primary outcome is a binary outcome and will be classified as 'Yes' in patients who are classified as receiving 'escalated monotherapy', 'initiated combination therapy' or 'escalated combination therapy' at any time and 'No' if they are classified as 'unchanged/de-intensified' throughout follow up. The algorithm will take into account the most likely foreseen treatment change scenarios. A 10% sample of LLT naïve and non-naïve patients will be checked by blinded clinical review to validate the algorithm. If any unclassified treatment changes are identified that are not captured by the algorithm e.g. due to unforeseen or ambiguous scenarios, these will be reviewed on a case-by-case basis by blinded clinical review to determine whether the change is considered an intensification. Where

appropriate, the algorithm will be updated to capture these scenarios. A validation check will be performed on a data extract after 25% of patients are recruited. These checks will be performed separately by country.

5.3. Secondary Efficacy Variables

1. Time to intensification of LLT by week 16
2. LDL-C level closest to 16 weeks
3. Non-HDL-C level closest to 16 weeks
4. HDL-C level closest to 16 weeks
5. TC level closest to 16 weeks
6. Triglycerides level closest to 16 weeks
7. Proportion of patients' reaching target LDL-C levels, <1.4 mmol/L (<55 mg/dL) by week 16
8. Proportion of patients who receive combination therapy by Week 16
9. Proportion of patients who receive escalated monotherapy by Week 16
10. Proportion of patients who receive escalated combination therapy by Week 16

5.4. Safety Variables

This trial is using the DSS system that is classified as a device. Therefore we will provide safety reporting on the following for the DSS arm only:

1. Adverse Device Effects (ADE): Any untoward and unintended response to a medical device.
    - This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device.
2. Serious Adverse Device Effects (SADE): Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.
    - Unanticipated Serious Adverse Device Effect (USADE): Any serious adverse device effect which, by its nature, incidence, severity or outcome, has not been identified in the anticipated AE's
    - Anticipated Serious Adverse Device Effects (ASADE): is an effect which by its nature, incidence, severity or outcome has been identified in the anticipated AE's. No ASADEs have been identified in this case.

The assignment of causality and severity for adverse device effects should be made by the investigator responsible for the care of the patient using the definitions in the tables below (**Error! Reference source not found.** and **Error! Reference source not found.**).

Table 3: Causality definitions of adverse device effects

Causality	Definition
Unrelated	No evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the effect did not occur within a reasonable time after use of the device . There is another reasonable explanation for the effect(e.g. the patient's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the effect occurs within a reasonable time after use of the device). However, the influence of other factors may have contributed to the effect (e.g. the patient's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out

Table 4: Severity definitions of adverse device effect

Severity	Definition
Mild	Awareness of effect but easily tolerated
Moderate	Discomfort enough to cause some interference with usual activity
Severe	Inability to carry out usual activity

5.5. Exploratory Variables

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 from 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 LLT or 1 injectable therapy plus one or more 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 or 55mg/dl by Week 16) 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

6. Estimands

6.1. Primary Estimand

In randomised trials there can be post-randomisation events that may have an impact on the outcome and thus the estimation of the effect of the intervention may be ambiguous if we do not consider these events. Therefore, we use the ICH E9 (R1) addendum on estimands and sensitivity analysis[13] to define the primary estimand with its five attributes: treatment, population, variable, population-level summary, and handling intercurrent events.

The primary objective of the trial is to compare implementation of a DSS added to routine clinical care as compared with routine care without a DSS, to assess whether the availability of a DSS system in current practice increases the likelihood of initiation of combination therapy or escalation of LLT over a 16-week period. This is a pragmatic clinical trial and the primary estimand will be a treatment policy estimand that will answer the question whether DSS added to routine clinical care increases the likelihood of initiation of combination therapy or escalation of LLT over a 16-week period compared with routine care regardless of whether the prescriber uses the DSS for decision making.

The following attributes can describe the primary estimand (**Error! Reference source not found.**):

Table 5: Primary estimand attributes for the primary outcome

Estimand Attributes	**Definition**
Population	Adults admitted with ACS to hospital sites where subsequent study data follow up of the patients is carried out defined by ZODIAC inclusion and exclusion criteria
Treatment conditions	Experimental (DSS and SoC) versus control (SoC alone)
Outcome variables	Patients treated with combination therapy, or who receive escalated monotherapy, or escalated combination therapy, within 16 weeks of the index ACS (regardless of adherence i.e. use of the DSS by the prescribing physician for decision making)
Intercurrent events (and strategies to handle them)	Adherence to the DSS system (at participant level i.e. physician in DSS site does not use DSS) – treatment policy[1] Patients who die are excluded from the analysis – principal stratum[2]
Population Summary measure	Risk ratio adjusted for stratification variables (country and type of site)
Rationale for choosing estimand	The aim is to estimate the benefit of DSS vs SoC for patients with ACS if adopted as part of routine clinical care regardless of adherence to the DSS (as this reflects the pragmatic nature of the trial and real-world use). The outcome of patients who die during follow up is unknown. These patients are excluded from the analysis because the mortality rate is anticipated to be low in this population.

[1]A treatment policy strategy considers the occurrence of the associated event as irrelevant, and participant data are analysed regardless.

[2] Principal stratum strategy includes only those subjects without the intercurrent event

6.2. Supplementary Estimand

A supplementary estimand (**Error! Reference source not found.**) using a principal stratum s trategy will be used to assess whether the DSS added to routine clinical care increases the likelihood of initiation of combination therapy or escalation of LLT over a 16-week period compared with routine care in patients in whom the DSS is used by the prescribing physician for decision making.

A second, unblinded, statistician wil perform this analysis using programming code prepared by the primary blinded study statistician.

Table 6: Supplementary estimand attributes for the primary outcome

Estimand Attributes	**Definition**
Population	Adults admitted with ACS to hospital sites where subsequent study data follow up of the patients is carried out defined by ZODIAC inclusion and exclusion criteria
Treatment conditions	Experimental (DSS and SoC) versus control (SoC alone)
Outcome variables	Patients treated with combination therapy, or who receive escalated monotherapy, or escalated combination therapy, within 16 weeks of the index ACS
Intercurrent events (and strategies to handle them)	Adherence to the DSS system (at participant level i.e. physician in DSS site does not use DSS) – principal stratum[1] Patients who die are excluded from the analysis – principal stratum[1]
Population Summary measure	Risk ratio adjusted for stratification variables (country and type of site)
Rationale for choosing estimand	The aim is to estimate the benefit of DSS vs standard care for patients with ACS if adopted as part of routine clinical care in patients for whom the prescribing physician uses the DSS for descion making. The outcome of patients who die during follow up is unknown. These patients are excluded from the analysis because the mortality rate is anticipated to be low in this population.

[1] Principal stratum strategy includes only those subjects without the intercurrent event

7. Analysis Populations

7.1. Intention To Treat Population

As we considered principal stratum strategy to handle death, the primary analysis will be undertaken on an 'modifed intention-to-treat' (mITT) basis. This will allow for the inclusion of all eligible and included patients through use of multiple imputation (Section 9.1 and 9.2) after excluding patints who died. Patients in the mITT population will be analysed according to the randomised group allocated to the cluster (site) in which they are followed, either SoC or DSS, irrespective of noncompliance.

We will also undertake two sensitivity analyses on full ITT population and on those with complete cases (i.e. complete outcome data).

7.2. Safety Population

As in this trial all patients will be treated only in line with SoC, the treating physicians at study sites will report any Adverse Drug Reactions (ADRs)/ Adverse Events (AEs) in routine ways in accordance with the guideline on Good Pharmacovigilance Practice (GVP) for all medications trial patients are taking during the course of the trial. This is not a Clinical Trials of Investigational Medicinal Product (CTIMP), therefore no Serious Adverse Events in relation to the licensed medicines are being collected.

Device deficiencies will be captured in those patients who are at a study site using DSS only. Device deficiencies include malfunctions, user errors and inadequacy in the software supplied by the manufacturer.

8. Statistical Analysis

8.1. General Methodology

Trial results will be reported according to the Consolidated Standards or Reporting Trials (CONSORT) and the consort extension for Cluster Trials.[14]

There is one planned final analysis that will be completed approximately 8-12 weeks after the final patient has completed the trial, allowing for an appropriate time for the data to be collected, cleaned, and prepared for the final analysis. All patients will be included up until they are no longer observed (i.e. end of study form completed).

In secondary outcome analyses no adjustments for multiple testing will be used but a precise, focused interpretation of the individual results for secondary outcomes will be reported. Significance levels used will be 0.05 and 95% confidence intervals will be reported. No formal interim analysis or predefined early stopping rules are planned for this trial.

Descriptive data on recruitment, baseline characteristics and study retention will be presented for the whole trial population and separately by country.

8.2. Patient Flow (CONSORT Diagram)

The flow of centres and patients through the trial stages will be reported in accordance with the CONSORT extension statement for cluster randomised trials (Figure 3).[14] The flow diagram will include the number of patients screened, eligible and entered into the trial at each site, receiving the allocated treatment and included in the primary analysis. This will include the number of clusters randomised and followed up to be in the analysis of the primary outcome and number of patients within these as well. Reasons for ineligibility, non-completion of study (where available), and exclusion from the primary analysis will be summarised.

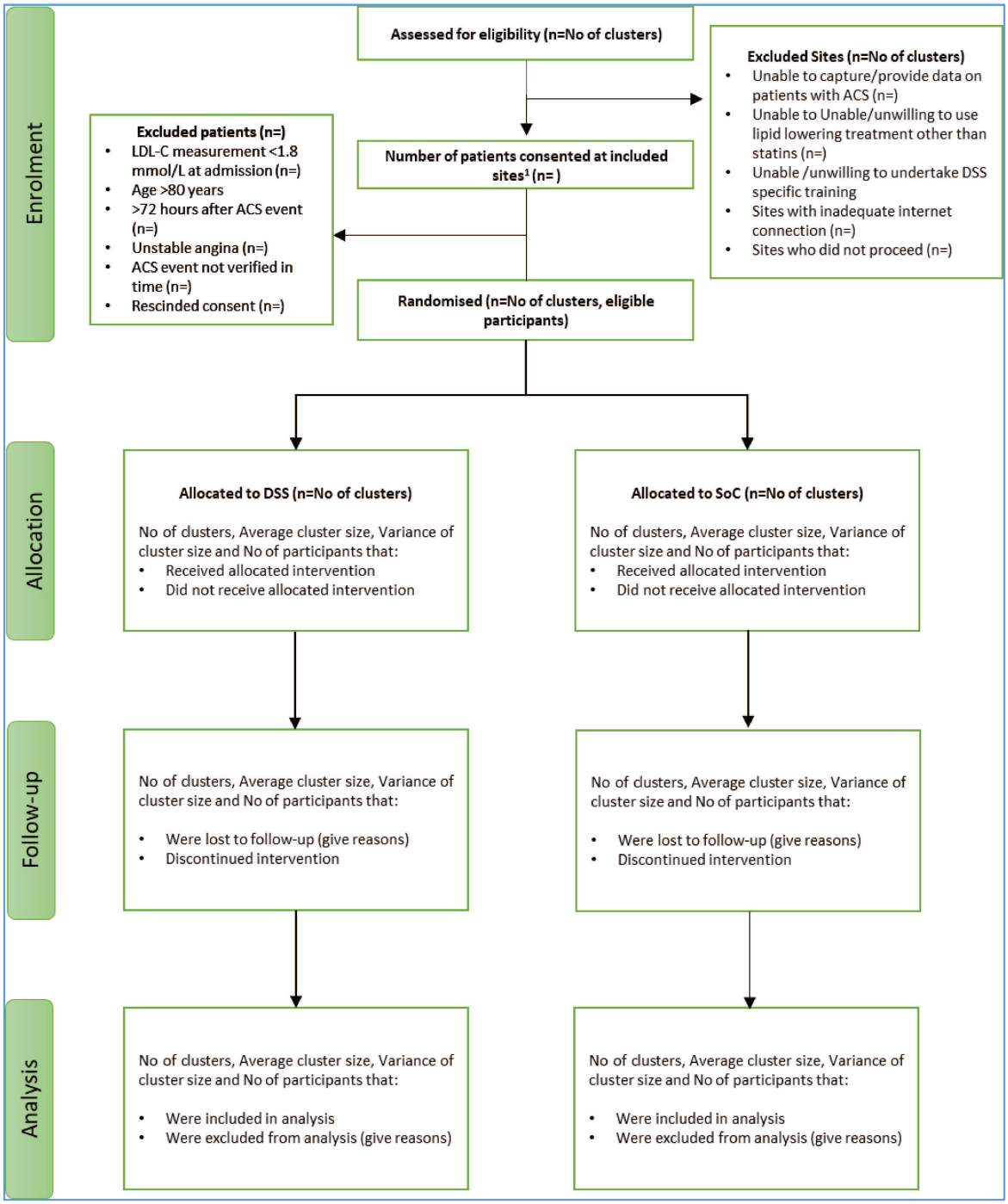

Figure 3: CONSORT chart

[1] Total no. of eligible patients and the number of patients assessed for eligibility not recorded for practical purposes.

8.3. Baseline Demographics

Baseline patient characteristics will be cross tabulated according to the randomised group to check for appropriate balance and to provide an overview of the study population. They will be summarised using means and standard deviations or medians and 25th, 75th percentiles for continuous variables, and counts and percentages for categorical variables.

As described in Section 5.2, baseline LLT is defined as LLT prior to admission and will be categorised as none, LLT monotherapy and LLT combination therapy. Combinations will be further classified by number of LLT drugs. In addition, we will present LLT classified by intensity based on expected percentage reduction in LDL-C as categorised in the 2019 ESC/EAS guidelines for the management of dyslipidaemias.[1] An additional category of 'very high intensity' is included starting at 65% LDL-C reduction.This is just above the 64% LDL-C reduction of evolocumab 140/420mg, the highest expected LDL-C reduction associated with a monotherapy medication in the ZODIAC study. Combination therapies typically are classified as moderate intensity or higher.

For lipid levels, the baseline value will be defined as the last value recorded before or at the day of hospital admission for ACS whichever is the closest to the day of hospital admission.

No hypothesis testing will be performed to test for differences in baseline characteristics by arm.

We will also examine balance between trial arms for the stratification variables at the cluster level.

8.4. Primary Efficacy Analysis

The primary outcome measure, the proportion of patients treated with combination therapy, or who receive escalated monotherapy, or escalated combination therapy, within 16 weeks of the index ACS (regardless of adherence at 16 weeks) will be modelled using a generalised linear mixed model. This model will use a binomial distribution, log link function and with fixed effect for country and site type (secondary/tertiary care/mixed) and a random effect for study site (as a random intercept). If there is a convergence problem with the log-binomial model, Poisson regression with robust standard errors (modified Poisson regression) will be used. The intervention effect will be reported as a Risk Ratio with a 95% confidence interval. For primary analysis hypotheses will be tested as two-sided with a significance level of 0.05.

$$log(\pi_{ij}) = \beta_0 + \beta_1 ACSDSS_{ij} + \beta_2\, COUNTRY1_{ij} + \beta_3\, COUNTRY2_{ij} + \beta_4 Site\ type_{ij} + \beta_5 Site\ type_{ij} + U_j$$

Where:

- π_{ij}: probability of combination therapy for the i[th] patient in j[th] site
- $ACSDSS_{ij}$: dummy variable for intervention ($ACSDSS_{ij} = 0\ or\ 1$) for patient i in j[th] site
- $COUNTRY1_{ij}, COUNTRY2_{ij}$: dummy variable for COUNTRY ($COUNTRY_{ij} = 0\ or\ 1$) for patient i in j[th] site
- $Site\ type1_{ij}, Site\ type2_{ij}$: dummy variable for Site Type ($Site\ type_{ij} = 0\ or\ 1$) for patient i in j[th] site type
- U_j: random effect for site j $\sim N(0, \sigma_u^2)$

This model will use the modified intention-to-treat population and will include all eligible and randomised patients through use of multi-level multiple imputation. If any particpants die within 16 weeks they will be excluded from this primary analysis and any similar secondary outcome analysis but will be included in the time to event outcomes (until censored). We will tabulate mortality by intervention arm.

We define the primary outcome as missing for anyone who does not have full 16 week follow up, unless they have met the primary outcome prior to the time they are lost to follow up. All patients will be followed up and the primary outcome data will be collected unless the participant requests to withdraw from data collection. Missing data will be examined and quantified; this will include the time of withdrawal and tabulation for reasons for non-completion of study by country, site, and arms. Patterns of missingness and relationship between variables and outcome will be explored. The proportion of clusters (sites) with a missing individual outcome will be calculated and reported as the number of entire clusters with a missing outcome divided by the number of clusters randomised.

As mentioned in Section 4.8, some patients may have data reported at 24 weeks only. These data may be used, where appropriate, to derive or impute the LLT medication status at 16 weeks.

Although mixed models are valid under the missing at random (MAR) assumption, we will use the multilevel multiple imputation (MMI) method to impute values for individuals who have missing outcome data. Missing data can be related to the cluster level or at patient level. We define level 1 variables as those relating to the patient as X and Y and Z, and level 2 variables as those relating to the site as A and B.

Using the *JOMO package* in R with missing outcome data we can use an imputation model which is the same as the analysis model. The JOMO package allows imputation on a mix of multilevel continuous and categorical data.[15] This method uses Markov chain Monte Carlo (MCMC) methods to impute missing values. We will run N imputations and combine the estimates using the mitools package. We will impute N datasets based on the percentage of participants with incomplete outcomes, where N is rounded to the nearest 10. A minimum of 5 imputation datasets will be used. We will include at patient level, intervention, outcome,

age, sex, and comorbidities (diabetes, time since first CV diagnosis) and at site level, type of site and country in the imputation model. We do not anticipate cluster-level variables to be missing. The appropriateness of the assumption of approximate normality of the random effect of this model will be assessed graphically.

8.5. Secondary Efficacy Analysis

Analysis of the time to event outcomes will include all randomised patients. All analysis for other secondary endpoints will be based on 'intention to treat' population.

8.5.1. Time to event outcome

- Time to initiation of combination therapy: the start defined as date the participant entered the trial (consent date) and end defined as date of initiation of combination therapy or escalation of therapy. We will censor for loss to follow up, withdrawals and death.

Kaplan-Meier plots will be used to estimate and display time to event outcomes such as time to intensification of LLT by study arms. A **Cox proportional hazards model with shared frailty** will be used to account for clustering and to assess the effect of DSS or SoC after adjusting for stratification factors. We will report adjusted hazard ratio (HR) and 95% confidence interval with p-value.

$$log\left(\frac{h(t)}{h_0(t)}\right) = \beta_1 ACSDSS_{ij} + \beta_2\, COUNTRY1_{ij} + \beta_3\, COUNTRY2_{ij} + \beta_4 Site\ type_{ij} + \beta_5 Site\ type_{ij} + U_j$$

Where:

- $log\left(\frac{h(t)}{h_0(t)}\right) =$: log hazard ratio
- $ACSDSS_{ij}$: dummy variable for intervention ($ASCDSS_{ij} = 0\ or\ 1$) for patient i in j[th] site
- $COUNTRY1_{ij}, COUNTRY2_{ij}$: dummy variable for COUNTRY ($COUNTRY_{ij} = 0\ or\ 1$) for patient i in j[th] site
- $Site\ type1_{ij}, Site\ type2_{ij}$: dummy variable for Site Type ($Site\ type_{ij} = 0\ or\ 1$) for patient i in j[th] site type
- U_j: random effect for site j $\sim N(0, \sigma_u^2)$

8.5.2. Continuous outcome

- LDL-C level (or other lipid measure) closest to 16 weeks between intervention arms.

A linear mixed model with a normal distribution, identity link function will be used with a fixed effect for country and site type (secondary/ tertiary care/mix of both) and a random effect for study site (as a random intercept). We will report adjusted mean difference and 95% confidence interval with p-value. In the case of missing data, multiple imputations will be used to impute the outcome at 16 weeks. Baseline measurements and those taken before 16 weeks will be used for the imputation process

$$y = \beta_0 + \beta_1 ACSDSS_{ij} + \beta_2\, COUNTRY1_{ij} + \beta_3\, COUNTRY2_{ij} + \beta_4 Site\ type_{ij} + \beta_5 Site\ type_{ij} + \beta_6 BaselineLDL_{ij} + U_j$$

Where:

- y: mean LDL-C (or other lipid measure) in mmol/L
- $ACSDSS_{ij}$: dummy variable for intervention ($ACSDSS_{ij} = 0\ or\ 1$) for patient i in j[th] site
- $COUNTRY1_{ij}, COUNTRY2_{ij}$: dummy variable for COUNTRY ($COUNTRY_{ij} = 0\ or\ 1$) for patient i in j[th] site
- $Site\ type1_{ij}, Site\ type2_{ij}$: dummy variable for Site Type ($Site\ type_{ij} = 0\ or\ 1$) for patient i in j[th] site type
- $BaselineLDL_{ij}$: continuous measure in mmol/L for patient i in j[th] site
- U_j: random effect for site j $\sim N(0, \sigma_u^2)$

8.5.3. Binary outcomes

- Proportion of patients' reaching target LDL-C levels, <1.4 mmol/L (<55 mg/dL) by Week 16, proportion of patients who receive combination therapy, proportion of patients who receive escalated monotherapy and proportion of patients who receive escalated combination therapy

This analysis will be for all people with Week 16 follow-up.

We will follow the same approach as described for primary outcome and use log-binomial model or modified Poisson regression with a fixed effect for country and site type (secondary/ tertiary care/mix of both) and a random effect for study site (as a random intercept) to estimate an adjusted Risk Ratio with a 95% confidence interval and p-value.

Model assumptions for all models will be examined using residual analysis. Following the recommendations by Parker[16] and Rubin[17] no adjustments for multiple testing will be used but a precise, focused interpretation of the individual results for secondary outcomes will be reported.

$$log(\pi_{ij}) = \beta_0 + \beta_1 ACSDSS_{ij} + \beta_2 COUNTRY1_{ij} + \beta_3 COUNTRY2_{ij} + \beta_4 Site\ type_{ij} + \beta_5 Site\ type_{ij} + U_j$$

Where:

- π_{ij}: probability of combination therapy (or other binary outcome) for the ith patient in jth site
- $ACSDSS_{ij}$: dummy variable for intervention ($ACSDSS_{ij} = 0\ or\ 1$) for patient i in jth site
- $COUNTRY1_{ij}, COUNTRY2_{ij}$: dummy variable for COUNTRY ($COUNTRY_{ij} = 0\ or\ 1$) for patient i in jth site
- $Site\ type1_{ij}, Site\ type2_{ij}$: dummy variable for Site Type ($Site\ type_{ij} = 0\ or\ 1$) for patient i in jth site type
- U_j: random effect for site j $\sim N(0, \sigma_u^2)$

8.6. Safety Analysis

Information on adverse device effects (ADEs) that are considered to be definitely related to the DSS will be collected. These ADEs will be tabulated for the DSS arm only and stratified by severity. Data will be presented as the number of patients with at least one ADE, and as the number of ADEs reported.

8.7. Interim Analysis

The Trial Executive Committee will review safety data at the timepoints of their choosing. No statistical hypothesis testing will be completed for the TEC.

The statistician will analyse the interim data at the request of the TEC meeting and act as a data manager, in raising and resolving data queries with participating sites, via the Trial Manager. Closed TEC reports will include recruitment, randomisation balance and stratification effectiveness, baseline characteristics, withdrawals, concomitant medicationsand adverse device events. Open TEC reports will be provided without outcome or arm information. Interim analyses do not involve formal statistical hypothesis testing; as a result, no adjustment for interim analyses has been made.

In addition, as described in Section 5.2, we will complete periodic blinded validation checks on the algorithm used to assign the trial's primary outcome.

8.8. Subgroup Analysis (of Primary Outcome)

Subgroup analysis will follow the same analysis of the primary outcome with the addition of an interaction term between the treatment and the subgroup analysis variables. These will be summarised by forest plots.

The variables investgated in the subgroup analyses are (at patient level):

- gender (men vs women)
- age (below vs above or equal to median age)
- diabetes (yes vs no)
- LLT naïve (yes vs no)
- patients experiencing one or more CV event in the 2 years prior to admission

Below is an example model for an interaction between intervention and gender added.

$$log(\pi_{ij}) = \beta_0 + \beta_1 ACSDSS_{ij} + \beta_2\, COUNTRY1_{ij} + \beta_3\, COUNTRY2_{ij} + \beta_4 Site\ type_{ij} + \beta_5 Site\ type_{ij} + \beta_6 Gender_{ij} + \beta_7 ACSDSS_{ij} * Gender + U_j$$

Where:

- π_{ij}: probability of combination therapy for the i[th] patient in j[th] site
- $ACSDSS_{ij}$: dummy variable for intervention ($ACSDSS_{ij} = 0\ or\ 1$) for patient i in j[th] site
- $COUNTRY1_{ij}, COUNTRY2_{ij}$: dummy variable for COUNTRY ($COUNTRY_{ij} = 0\ or\ 1$) for patient i in j[th] site
- $Site\ type1_{ij}, Site\ type2_{ij}$: dummy variable for Site Type ($Site\ type_{ij} = 0\ or\ 1$) for patient i in j[th] site type
- U_j: random effect for site j $\sim N(0, \sigma_u^2)$
- $Gender_{ij}$: dummy variable for gender of patient i in jth site

Subgroup analyses at cluster level by site type is not planned as the number of sites is anticipated to be small for some strata.

8.9. Exploratory Analysis

Proportions of those patients achieving the binary outcomes described in Section 5.5 will be described by frequencies and percentages by trial arm and for the overall population and by prespecified subgroups. No statistical significance testing will be performed for these analyses.

Mean (SD) and median (IQR) percentage change from baseline will be tabulated for each lipid measure.

The DSS Evaluation Questionnaire consists of 11 questions (see Table 43). Questions 1 to 10 are Likert responses scored from 1 (strongly disagree) to 5 (strongly agree) adapted from a previously published system usablility scale (SUS).[18] Question 11 is an additional question to capture overall user-friendliness of the DSS tool scored from six options from 'worst imaginable' to 'best imaginable'. Responses to the DSS Evaluation Questionnaire by the clinicians at DSS sites will be summarised descriptively using:

- mean (and range) score for each question (negative items (in italics in Table 43) will be reverse coded
- proportion of patients agreeing and disagreeing with each question (Questions 1 to 10)
- proportion who rated the DSS poor or worse in terms of overall user-friendliness (Question 11)
- proportion who deemed the DSS good or better in terms of overall user-friendliness (Question 11).

An overall usabilty score scaled from 0 to 100 will be computed from responses to Questions 1 to 10 only.[18] A value of 1 is subtracted from the score of odd-numbered questions and the respondent's score is subtracted from 5 for even-numbered questions. These new values are summed and multiplied by 2.5 to give a score ranging from 0 to 100. Higher scores indicated greater usability.

Two additional open-ended questions (not included in the published SUS) have been included to capture suggestions for improvement of the DSS in terms of usability and examples of where the tool has been impactful in clinical practice. Responses to this question will be evaluated separately and are outside the scope of this SAP.

8.10. Sensitivity Analysis

Two sensitivity analyses are planned for this study as below:

- A complete case analysis of the primary outcome will be undertaken as a sensitivity analyses. This will include all eligible and randomised patients whose outcomes are

available by 16 weeks. Patients in population will be analysed according to the randomised group allocated to the cluster (site) in which they are followed, either SoC or DSS.

- Full ITT analysis including patients who died and incorporating multiple imputation.

8.11. Modelling and Simulation Based Analyses

The modelling and simulation based analyses will be conducted by Axtria. Axtria will develop their own statistical analysis plan which can be read in conjunction with this SAP.

9. Statistical Considerations

9.1. Missing Baseline Data

Every effort will be taken to minimise missing data. If baseline values are missing, to avoid a loss of power within the analyses which adjust for baseline values, these values will be imputed with the mean baseline value calculated from the non-missing values using pooled data from both treatment groups.

9.2. Multiple Comparisons

No multiplicity adjustments will be performed for the analysis of secondary outcomes, and results will be viewed as hypothesis-generating.

10. Software

All analyses will be conducted in Stata version 17, with the exception of the multi level multiple imputation that will be conducted in R version 4.2.1 or higher.

11. Appendix A: Primary Outcome Algorithm

Study%20Specific%20Procedure%20Manu

12. Appendix B: Tables to Present

12.1. Recruitment

Table 7: Randomisation stratification variables

		Number of Sites		
		DSS	**Control**	**Overall**
Sites, N (%)	United Kingdom			
	Italy			
	Spain			
	Total			
Clinic Type, N (%)	Secondary care			
	Tertiary care			
	Mix of both			
	Total			

Table 8: Number of patients per site per country

		Total N
Total Patients		
Centre	**Name of site**	N (%)
United Kingdom	…	
	…	
	…	
Italy	…	
	…	
	…	
Spain	…	
	…	
	…	

Table 9: Reasons for exclusion of sites

Exclusion reason (patients)	**N (%)**
Unable to capture/ provide data on patients with ACS during admission and follow up	
Unable or unwilling to use lipid lowering treatments other than statins for ACS care	
Unable or unwilling to access and undertake training for the DSS	
Inadequate internet connection at site and the ability to access the DSS	
Site did not proceed	

Table 10: Reasons for exclusion of participants from enrolled sites

Exclusion reason (patients)	**N (%)**
Aged <18 to ≥ 80 years old	
Unable to provide written informed consent	
Patient rescinded consent (changed mind before any data collected)	
LDL-C measurement < 1.8 mmol/L at admission	
Unstable angina	
ACS event not verified in time	
>72 hours after ACS event	

12.2. Baseline Characteristics

Table 11: Baseline demographics of randomised patients at screening

		DSS	Control	Overall
Age (years)				
	N (Missing)			
	Mean, SD			
	Median, IQR			
	Min, Max			
Sex (assigned at birth), n (%)				
	N (Missing)			
	Female			
	Male			
Ethnicity, n (%)				
	N (Missing)			
	White			
	Black			
	Asian			
	Mixed Race			
	North African			
	Other			

Table 12: Type of index event experienced by randomised patients

		DSS	Control	Overall
Index Acute Coronary Syndrome (ACS) Event, n (%)				
	N (Missing)			
	STEMI			
	NSTEMI			

Table 13: Cardiovascular risk factor history of randomised patients PRIOR to index event admission

		DSS	Control	Overall
Diabetes Mellitus Diagnosis, n (%)				
	N (Missing)			
	Yes			
	No			
If yes*	Prediabetes			
	Type-1			
	Type-2			
	Gestational			
Coronary Artery Disease Diagnosis, n (%)				
	N (Missing)			
	Yes			
	No			
If yes*	Myocardial Infarction			
	Coronary Artery Bypass Surgery			
	Angioplasty/PCI			
Cerebrovascular Disease Diagnosis, n (%)				
	N (Missing)			
	Yes			
	No			
If yes*	Stroke/TIA			
	Carotid artery stenosis			
	Aneurysms			
Peripheral Artery Disease Diagnosis, n (%)				
	N (Missing)			
	Yes			
	No			
If yes*	Arteriosclerosis Obliterans			
	Arterial Insufficiency of the Legs			
	Claudication			
Abdominal Aortic Aneurysm Diagnosis, n (%)				
	N (Missing)			
	Yes			
	No			
Time since first ASCVD Diagnosis (years)				

	N (Missing)			
	Mean, SD			
	Median, IQR			
	Min, Max			
Smoking status	N (Missing)			
	Current regular			
	Current occasional			
	Former regular			
	Never			

*patient may answer yes to one of more of the specific categories

Table 14: Baseline laboratory measurements and observations of randomised patients

		DSS	Control	Overall
eGRF (mL/min/1.73m^2)				
	N (Missing)			
	Mean, SD			
	Median, IQR			
	Min, Max			
hs-CRP (mg/dL)				
	N (Missing)			
	Mean, SD			
	Median, IQR			
	Min, Max			
Systolic blood pressure (mmHg)				
	N (Missing)			
	Mean, SD			
	Median, IQR			
	Min, Max			

Table 15: Concomitant medications of randomised patients at screening

		DSS	Control	Overall
Antiplatelet medication				
	N (Missing)			
	Yes			
	No			
If yes*	Aspirin			
	Clopidogrel			
	Prasugel			
	Ticagrelor			
	Other			
Anticoagulant medication				
	N (Missing)			
	Yes			
	No			
Blood pressure medication				
	N (Missing)			
	Yes			
	No			
If yes*	Angiotensin-II receptor blocker			
	ACE inhibitor			
	Calcium channel blocker			
	Beta-blocker			
	Aspirin			
Diabetes related medication				
	N (Missing)			
	Yes			
	No			
If yes*	Insulin			
	Sulfonylurea			
	SGLT2 inhibitor			
Taking any aspirin (if not specified as antiplatelet)				
	N (Missing)			
	Yes			
	No			

Table 16: Lipid lowering therapy prior to admission

n (%)		DSS	Control	Overall
Prior to admission in the last month, was patient was taking any cholesterol lowering medication?				
	N (Missing)			
	No			
	Yes, monotherapy			
	Yes, combination therapy			
	Two drugs			
	≥Three drugs			
If yes, what class*	Statin			
	Ezetimibe			
	Bempedoic Acid			
	Bile sequestrants			
	PCSK9 Monoclonals			
	PCK9 siRNA			
	Other			
Patient compliant with LLT	Yes			
	No			
	Missing			
LLT intensity (expected LDL reduction), n(%)				
Monotherapy:				
	Low (<30%)			
	Moderate (≥30% to <50%)			
	High (≥50% to <65%)			
	Very high potency (≥65%)			
	Potency undefined			
Combination:				
	Low (<30%)			
	Moderate (≥30% to <50%)			
	High (≥50% to <65%)			
	Very high potency (≥65%)			
	Potency undefined			

Table 17: Lipid lowering therapy at discharge

n (%)		DSS	Control	Overall
At discharge, was patient was taking any cholesterol lowering medication?				
	N (Missing)			
	No			
	Yes, monotherapy			
	Yes, combination therapy			
	Two drugs			
	≥ Three drugs			
If yes, what class*	Statin			
	Ezetimibe			
	Bempedoic Acid			

	Bile sequestrants			
	PCSK9 Monoclonals			
	PCK9 siRNA			
	Other			
LLT potency				
Monotherapy:				
	Low (<30%)			
	Moderate (≥30% to <50%)			
	High (≥50% to <65%)			
	Very high potency (≥65%)			
	Potency undefined			
Combination:				
	Low (<30%)			
	Moderate (≥30% to <50%)			
	High (≥50% to <65%)			
	Very high potency (≥65%)			
	Potency undefined			

Table 18: Lipid profile at baseline (closest measure prior to or during admission): all patients

Measure		**DSS**	**Control**	**Overall**
LDL-C (mmol/L)				
	N (Missing)			
	Mean, SD			
	Median, IQR			
	Min, Max			
Non HDL-C (mmol/L)				
	N (Missing)			
	Mean, SD			
	Median, IQR			
	Min, Max			
HDL-C (mmol/L)				
	N (Missing)			
	Mean, SD			
	Median, IQR			
	Min, Max			
Total Cholesterol (mmol/L)				
	N (Missing)			
	Mean, SD			
	Median, IQR			
	Min, Max			
Triglycerides (mmol/L)				
	N (Missing)			
	Mean, SD			

	Median, IQR			
	Min, Max			

Table 19: Lipid profile at baseline (closest measure prior to or during admission): LLT naïve patients

Measure		DSS	Control	Overall
LDL-C (mmol/L)				
	N (Missing)			
	Mean, SD			
	Median, IQR			
	Min, Max			
Non HDL-C (mmol/L)				
	N (Missing)			
	Mean, SD			
	Median, IQR			
	Min, Max			
HDL-C (mmol/L)				
	N (Missing)			
	Mean, SD			
	Median, IQR			
	Min, Max			
Total Cholesterol (mmol/L)				
	N (Missing)			
	Mean, SD			
	Median, IQR			
	Min, Max			
Triglycerides (mmol/L)				
	N (Missing)			
	Mean, SD			
	Median, IQR			
	Min, Max			

Table 20: Lipid profile at baseline (closest measure prior to or during admission): non-LLT naïve patients

Measure		DSS	Control	Overall
LDL-C (mmol/L)				
	N (Missing)			
	Mean, SD			
	Median, IQR			
	Min, Max			
Non HDL-C (mmol/L)				
	N (Missing)			

	Mean, SD			
	Median, IQR			
	Min, Max			
HDL-C (mmol/L)				
	N (Missing)			
	Mean, SD			
	Median, IQR			
	Min, Max			
Total Cholesterol (mmol/L)				
	N (Missing)			
	Mean, SD			
	Median, IQR			
	Min, Max			
Triglycerides (mmol/L)				
	N (Missing)			
	Mean, SD			
	Median, IQR			
	Min, Max			

12.3. Study withdrawals

Table 21: Study completion and reason for non-completion

Completion status	**No. of patients (%)**		
	DSS	**Control**	**Overall**
Completed Study			
Completed study with outcome data at 16 weeks			
Did Not Complete Study			
Patient withdrew consent			
Death			
Lost to follow-up			
No longer meets eligibility criteria			
Adverse event			
Investigator decision			
Other			
…….			

Table 22: Timing of study withdrawals

Time of withdrawal On or before:	No. of patients (%)		
	DSS	Control	Overall
Week 4			
Week 8			
Week 12			
Week 16			
Total			

12.4. Primary Efficacy Analysis

12.4.1. Primary estimand

Table 23: Effect of DSS on proportion of patients initiated on combination therapy, escalation of monotherapy or escalation of combination therapy, regardless of prescriber use of the DSS

Patients with primary outcome at 16 weeks	Trial arm		Adjusted Risk Ratio*	95% confidence interval
	DSS	Control		
N			x.xx	x.xx to x.xx
n (%)				

*adjusted for country, site type (secondary/tertiary care/mix of both) and study site

12.4.2. Supplementary estimand

Table 24: Effect of DSS on proportion of patients initiated on combination therapy, escalation of monotherapy or escalation of combination therapy in patients for whom the prescribing physician used the DSS

Patients with primary outcome at 16 weeks	Trial arm		Adjusted Risk Ratio*	95% confidence interval
	DSS	Control		
N			x.xx	x.xx to x.xx
n (%)				

*adjusted for country, site type (secondary/tertiary care/mix of both) and study site

12.5. Secondary Efficacy Analysis

12.5.1. Time to event outcomes

Table 25: Effect of DSS on time to initiation of LLT combination therapy or escalation of LLT monotherapy or escalation of LLT combination therapy

Patients with primary outcome	Trial arm		Adjusted Hazard Ratio*	95% confidence interval
	DSS	Control		
N			x.xx	x.xx to x.xx
n (%)				
Median survival (weeks) (95% CI)				

*adjusted for country, site type (secondary/tertiary care/mix of both) and study site

12.5.2. Continuous outcomes

Table 26: Effect of DSS on lipid profile at Week 16

Trial arm	DSS	Control	Adjusted mean difference at Week 16*	95% confidence interval
LDL-C level (mmol/L)				
N (missing)			x.xx	x.xx to x.xx
Mean (SD)				
Median (IQR)				
Non-HDL-C level (mmol/L)				
N (missing)			x.xx	x.xx to x.xx
Mean (SD)				
Median (IQR)				
HDL-C level (mmol/L)				
N (missing)			x.xx	x.xx to x.xx
Mean (SD)				
Median (IQR)				
Total cholesterol (mmol/L)				
N (missing)			x.xx	x.xx to x.xx
Mean (SD)				
Median (IQR)				
Triglycerides (mmol/L)				
N (missing)			x.xx	x.xx to x.xx
Mean (SD)				
Median (IQR)				

*adjusted for country, site type (secondary/ tertiary care/mix of both) and study site

12.5.3. Binary outcomes

Table 27: Effect of DSS on proportion of patients receiving LLT combination therapy

Patients receiving LLT combination therapy	Trial arm		Adjusted Risk Ratio*	95% confidence interval
	DSS	Control		
N (missing)			x.xx	x.xx to x.xx
n (%)				

*adjusted for country, site type (secondary/ tertiary care/mix of both) and study site

Table 28: Effect of DSS on proportion of patients receiving escalated LLT monotherapy

Patients receiving escalated LLT monotherapy	Trial arm		Adjusted Risk Ratio*	95% confidence interval
	DSS	Control		
N (missing)			x.xx	x.xx to x.xx
n (%)				

*adjusted for country, site type (secondary/ tertiary care/mix of both) and study site

Table 29: Effect of DSS on proportion of patients receiving escalated LLT combination therapy

Patients receiving escalated LLT combination therapy	Trial arm		Adjusted Risk Ratio*	95% confidence interval
	DSS	Control		
N (missing)			x.xx	x.xx to x.xx
n (%)				

*adjusted for country, site type (secondary/ tertiary care/mix of both) and study site

Table 30: Effect of DSS on reaching target LDL-C levels

Patients with target LDL-C levels, <1.4 mmol/L (<55 mg/dL) by week 16	Trial arm		Adjusted Risk Ratio*	95% confidence interval
	DSS	Control		
N (missing)			x.xx	x.xx to x.xx
n (%)				

*adjusted for country, site type (secondary/ tertiary care/mix of both) and study site

12.6. Safety Analysis

Table 31: Adverse Device Effects by trial arm

	DSS arm only	
	No. of patients (%)	**No. of events**
ADE		
SADE		
USADE		
ASADE		

Table 32: Severity of Adverse Device Effects by trial arm

	DSS arm only	
	No. of patients (%)	**No. of events**
ADE		
Mild		
Moderate		
Severe		

Table 33: Relatedness of Adverse Device Effects by trial arm

	DSS arm only	
	No. of patients (%)	**No. of events**
ADE		
Related		
Serious and Related		
Serious, Related and Unanticipated		

Table 34: Type of Adverse Device Effects by trial arm

	DSS arm only	
	No. of patients (%)	**No. of events**
System Organ Class		
Preferred Term		
……		

12.7. Subgroup Analysis

Forest plots will be presented for subgroup of interested listed in Section 8.8.

12.8. Exploratory Analysis

Table 35: Exploratory endpoints by Week 16 (all patients)

Endpoint	Trial arm		
	DSS	**Control**	**Overall**
Patients achieving target LDL-C level <1.8 mmol/L (<70 mg/dL) by Week 16			
N (missing)			
n (%)			
Patients on combination therapies with three oral LLT or 1 injectable therapy plus one or more oral LLT			
N (missing)			
n (%)			
Mortality before Week 16			
N (missing)			
All-cause, n (%)			
Cardiovascular cause , n (%)			
Cardiovascular outcomes occurring during follow up (i.e. after baseline and before Week 16)			
N (missing)			
Coronary artery disease outcome, n (%)			
Myocardial infarction, n (%)			
Coronary Artery Bypass Graft, n (%)			
Angioplasty, n (%)			
Cerebrovascular disease, n (%)			
Aneurysms, n(%)			
Stroke/TIA, n (%)			
Vascular malformations, n (%)			
Carotid stenosis, n (%)			
Peripheral artery disease, n (%)			
Arteriosclerosis obliterans, n (%)			
Arterial insufficiency of the legs, n (%)			
Claudification, n (%)			
Abdominal aortic aneurysm, n (%)			

Table 36: LDL-C lowering in LLT-naïve patients by Week 16

Endpoint	Trial arm		
	DSS	**Control**	**Overall**
Patients achieving a decrease of baseline in LDL-C level of more than 50% by Week 16			
N (missing)			
n (%)			

Table 37: Percentage change in lipid profile in LLT-naïve patients by Week 16

Endpoint	Trial arm		
	DSS	**Control**	**Overall**
Percent change from baseline in LDL-C by Week 16			
N (missing)			
Mean (SD)			
Median (SD)			
Percent change from baseline in HDL-C by Week 16			
N (missing)			
Mean (SD)			
Median (SD)			
Percent change from baseline in non-HDL-C by Week 16			
N (missing)			
Mean (SD)			
Median (SD)			
Percent change from baseline in triglycerides by Week 16			
N (missing)			
Mean (SD)			
Median (SD)			
Percent change from baseline in total cholesterol by Week 16			
N (missing)			
Mean (SD)			
Median (SD)			

Table 38: LDL-C lowering in LLT-naïve patients receiving combination therapy (for at least 4 weeks) by Week 16

Endpoint	Trial arm		
	DSS	**Control**	**Overall**
Patients 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			
N (missing)			
All combination therapies, n (%)			
Oral combination therapies only, n (%)			
Oral plus injectable combination therapy, n (%)			

Table 39: LDL-C levels by Week 16 according to LLT therapy at baseline in DSS arm

Endpoint	LLT therapy at baseline		
	None	**Monotherapy**	**Combination**
LDL-C level			
N (missing)			
Mean (SD)			
Median (SD)			

Table 40: LDL-C goal achievement (LDL-C < 1.4mmol/L or 55mg/dl)by Week 16 by site type

Site type	Trial arm		
	DSS	**Control**	**Overall**
Secondary			
N (missing)			
n (%)			
Tertiary			
N (missing)			
n (%)			
Mixed			
N (missing)			
n (%)			

Table 41: LDL-C goal achievement (LDL-C < 1.4mmol/L or 55mg/dl)by Week 16 by country

Country	Trial arm		
	DSS	**Control**	**Overall**
UK			
N (missing)			
n (%)			
Italy			
N (missing)			
n (%)			
Spain			
N (missing)			
n (%)			

Table 42: LDL-C goal achievement (LDL-C < 1.4mmol/L or 55mg/dl) by Week 16 by CV event history

≥1 CV event in 2 years prior to admission	Trial arm		
	DSS	**Control**	**Overall**
Yes			
N (missing)			
n (%)			
No			
N (missing)			
Mean (SD)			

Table 43: Qualitative evaluation of DSS

Statement	**Rating, mean (SD, range)[a]**	**Agreement with statement, n (%)**	**Disgreement with statement, n (%)**
1.I think that I would like to use this tool frequently.			
2.*I found the tool unnecessarily complex.*			
3.I thought the tool was easy to use.			
4.*I think that I would need the support of a technical person to be able to use this tool.*			
5.I found the various functions in the tool were well integrated.			
6.*I thought there was too much inconsistency in this tool.*			
7.I imagine that most people would learn to use this tool very quickly.			
8.*I found the tool very awkward to use.*			
9.I felt very confident using the tool.			
10.*I needed to learn a lot of things before I could get going with this tool.*			
Statement	**Rating, mean (SD, range)[b]**	**Poor or worse, n(%)**	**Good or better, n (%)**
11.Overall, I would rate the user-friendliness of this tool as			

[a] Score from 1 to 5 [b] Score from 1 to 6

Table 44: Qualitative evaluation of DSS – Standardised overall usability score (computed from Questions 1 to 10)

	Overall Usablity Score (ranging from 0 to 100)
N (n missing)	
Mean (SD, range)	
Median (IQR)	

12.10. Sensitivity Analysis

Table 45: Effect of DSS on proportion of patients initiated on LLT combination therapy, escalation of LLT monotherapy or escalation of LLT combination therapy in patients with complete outcome data

Patients with primary outcome at 16 weeks	Trial arm		Adjusted Risk Ratio*	95% confidence interval
	DSS	Control		
N (missing)			x.xx	x.xx to x.xx
n (%)				

*adjusted for country, site type (secondary/ tertiary care/mix of both) and study site

Table 46: Effect of DSS on proportion of patients initiated on LLT combination therapy, escalation of LLT monotherapy or escalation of LLT combination therapy inclusive of patients who died (full ITT)

Patients with primary outcome at 16 weeks	Trial arm		Adjusted Risk Ratio*	95% confidence interval
	DSS	Control		
N (missing)			x.xx	x.xx to x.xx
n (%)				

*adjusted for country, site type (secondary/ tertiary care/mix of both) and study site

13. Appendix C: Figures to Present

A CONSORT diagram will be used to summarise participant flow as appropriate for cluster trials.

Bar charts with 95% confidence intervals will be used to present proportions of patients meeting the primary outcome and secondary binary outcomes.

Kaplan-Meier plots will be presented for time to event outcomes (i.e. time to intenstification of LLT).

Forest plots of adjusted risk ratios will be used to summarise the primary outcome and subgroup analyses described in Section 8.8.

14. Appendix D: Example Code for analysis

14.1. Primary Outcome

```
// Load the data
use "datafile.dta", clear

// Set the maximum number of iterations
set maxiter 1000

// Fit the mixed log-binomial regression model
glm outcome intervention country site_type, family(binomial) link(log) vce(cluster site)
robust

// Display the results
estimates table
```

14.2. Secondary Outcomes

14.2.1. Time to event

```
// Load the data
use "datafile.dta", clear

// Set up date as survival data
stset outcome_date , failure(outcome=1) origin(date of consent)

// Fit the Cox proportional hazards model with shared frailty
stcox intervention country site_type, shared(site) frailty(site)

// Summarize the model results
estat phtest
```

14.2.2. Continuous outcomes

```
// Load the data
use "datafile.dta", clear

// Fit the mixed multi-level regression model
xtmixed outcome intervention country site_type baseline|| site : , covariance(unstructured)

// Display the results
estimates table
```

14.2.3. Binary Outcomes

```
// Load the data
use "datafile.dta", clear

// Set the maximum number of iterations
set maxiter 1000

// Fit the mixed log-binomial regression model
glm outcome intervention country site_type, family(binomial) link(log) vce(cluster site)
robust

// Display the results
estimates table
```

14.3. Multiple Imputation

```
> library(jomo)

# Define cluster/group indicator
> clus <- data$site

# Define the data.frame with outcomes of the imputation model
> data <- within(data, outcome <- factor(outcome))
> Y <- data[, c("outcome")]

# Define the data frame with covariates of the imputation model
> X <- data[, c("intervention", "example1", " example2")]

# Perform multilevel imputation:
> set.seed(1997)
> imp <- jomo(Y = Y, X = X, clus = clus, nburn = 2000, nbetween = 1000, nimp = 5)
> imp.list <- imputationList(split(imp, imp$Imputation)[-1])

# Fit model to each of the 5 imputed data sets
> fit.imp <- with(data = imp.list, lmer(outcome ~ intervention + example1 + example2
(1|clus)))

# Extract coefficients and variances
> coefs <- MIextract(fit.imp, fun = fixef)
> vars <- MIextract(fit.imp, fun = function(x) diag(vcov(x)))

# Pool results with Rubin's rules
```

```
> results <- MIcombine(coefs, vars)
> summary(results)

# Run jomo.MCMCchain
> imp <- jomo.MCMCchain(Y = Y, X = X, nburn = 5000)
> plot(imp$collectbeta[1, 1, 1:5000], type = "l", ylab = expression(beta["e,0"]), xlab =
"Iteration number")
```

15. Amendments to Version 1.0

16. References

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