the guideline on Good Pharmacovigilance Practice (GVP) for all medications trial participants are taking during the course of the trial.

7.1 Device Deficiencies

Device deficiencies are defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. Device deficiencies include malfunctions, use errors and inadequacy in the software supplied by the manufacturer.

Should any device deficiencies become apparent by the Sponsor during the trial, these will be assessed and reported to the regulators immediately in all the participating countries, and the sites will be informed accordingly.

Any potential device deficiencies which are identified by site investigators can be reported by the corresponding form in the CRF.

If a device deficiency is considered to have an impact on prescribing behaviour such that a participant experiences a safety event due to study participation, then the definitions and reporting mechanisms described below will apply:

7.2 Definitions for safety reporting in medical device trials

In medical device trials, relatedness should be assessed in relation to both the medical device and to the procedures which are associated with the device function (e.g. software malfunction).

(i) Adverse Device Effects (ADE)

An ADE is defined as an AE related to the use of the medical device and includes any AEs resulting from insufficient or inadequate instructions for use, deployment, installation or operation, or any malfunction of the medical device (device deficiency). It also includes any AE resulting from user error or from intentional misuse of the medical device.

(ii) Serious Adverse Device Effect (SADE)

A SADE is an ADE that results in any of the consequences characteristic of an SAE.

(iii)Unanticipated Serious Adverse Device Effect (USADE)

Those SADEs which by nature, incidence, severity or outcome have not been identified in the current IB, protocol or device brochure are considered an Unanticipated Serious Adverse Device Effect (USADE)

(iv)Anticipated Serious Adverse Device Effect (ASADE)

An ASADE is an effect which by nature, incidence, severity or outcome has been identified in the current IB, protocol or device brochure.

7.3 Causality

The assignment of causality for adverse events should be made by the investigator responsible for the care of the participant using the definitions in the table below.

If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigator. The pharmaceutical companies and/or other clinicians may be asked to advise in some cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA will be informed of both points of view.

Since participants should be receiving standard of care, safety events will be recorded only if causality to the device is deemed definite.

Unrelated:	No evidence of any causal relationship
Unlikely:	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible:	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (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.

7.4 Severity

Mild: Awareness of event but easily tolerated

Moderate: Discomfort enough to cause some interference with usual activity

Severe: Inability to carry out usual activity

7.5 Recording

For the purposes of the study, ADEs will be followed up according to local practice until the event has stabilised or resolved. SADEs will be recorded throughout the study.

7.6 Reporting of SADEs

All SADEs occurring during the study must be reported to the Sponsor within 24 hours via zodiac.study@imperial.ac.uk AND RGIT@imperial.ac.uk as detailed in the study-specific procedure manual, and only if causality to the device is deemed definite.

All SADEs will be reviewed by the Chief Investigator or a designated medically qualified representative to confirm expectedness and causality. Reporting of SADEs and review by the CI/medical monitor will be via the electronic CRF.

In addition, in the UK all reportable SADE's must be emailed to the MHRA at aic@mhra.gov.uk, using either the MEDDEV 2.7/3 SAE reporting table, or the MDCG 2020-10/2 SAE reporting table.

Events which indicate an imminent risk of death, serious injury or serious illness and require prompt remedial action for other patients, users or other persons or a new finding to it, must be reported to the MHRA by the ICTU Study Manager immediately but not later than 2 calendar days following the date the Sponsor is made aware.

Any other reportable events should be reported immediately but not later than 7 calendar days following the date the Sponsor is made aware.

In the UK, for USADEs, reports should be made to the REC within 15 days according to HRA website (via Investigator using specific form on website – non-CTIMP trials).

The Study Manager should also notify the Device Manufacturer and Investigators at all sites of the USADE.

In Spain and Italy, local ethical and regulatory requirements should be adhered to.

7.7 Developmental Safety Update Reports / Annual Safety Reports / Quarterly Reports

Developmental Safety Update Reports (DSUR) / Annual Safety will be submitted to the Sponsor, the Ethics Committee and Regulatory Authority in accordance with local / national regulatory requirements.

In the UK, quarterly summary reports of all SADE's must also be submitted to the MHRA via aic@mhra.gov.uk in the format detailed in the study-specific procedure manual.

In Spain and Italy, local regulatory requirements should be adhered to.

7.8 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the regulatory authority and the relevant REC of the measures taken and the circumstances giving rise to those measures.

8. STATISTICAL ANALYSES

8.1 Sample Size and power considerations

It is estimated that in the standard of care arm, we expect 7% of participants to be on combined therapy at 24 weeks. This estimate is based on published data in Koskinas et al.[24] using the ELIPS study cohort which included exclusively ACS patients. A slightly lower proportion of patients, 5%, may be expected to be on combined 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 participants 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.[25], 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[26]. 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 prudent we have assumed an ICC of 0.1.

Based on our experience working in this setting we don't expect any loss of clusters. However, drop out may occur within clusters. As data is extracted from routinely collected electronic healthcare records, we expect missing data to be low as it will only be participants who actively request data collection to stop that will have missing outcome data. Considering a conservative approach[27] 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[28] and applying a method of "Tests for Two Proportions in a Cluster-Randomised Design".

8.2 Planned recruitment rate

The targeted number of patients to be enrolled is approximately 33 for each site. The enrolment period is planned to be 9 months.

8.3 Statistical Analysis

A detailed Statistical Analysis Plan (SAP) will be developed and signed off prior to data extraction for final data analysis. Trial results will be reported according to the Consolidated Reporting Trials (CONSORT) extension for Cluster Trials updated in 2012 [29].
The trial characteristics including the number of participants and clusters randomised in each group, the number completing the trial, and lost to follow-up, will be described using a CONSORT Flow Diagram- for cluster randomised trials.
Baseline participant characteristics will be summarised using means, standard deviations, medians, and/or 25th, 75th percentiles, minimum and maximum for continuous variables, and counts and percentages for categorical variables. 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.

(i) Primary Endpoint Analysis:

The primary outcome of the study is 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). Combination therapy is defined as two or more drug combination regimens using commercially available licenced LLTs, including

- Statins,
- Selective cholesterol-absorption inhibitors,
- Adenosine triphosphate-citrate lyase (ACL) inhibitors,
- Bile acid sequestrants,
- PCSK9 monoclonal inhibitors
- PCSK9 siRNA therapy

Escalated therapy includes increase in statin potency, 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.

The primary analysis will be the Intention-to-treat population and will include all eligible and randomised participants through use of multiple imputation. Patients in the ITT population will be analysed according to the randomised group allocated to the cluster (site) in which they are followed, either SoC or DSS.

In cluster randomised trials, clustering effect must be considered in the analysis. There are two common individual-level analyses approaches: generalised estimating equations (GEEs) or marginal model and mixed effects or conditional models that typically lead to higher power and allow adjustment for covariates.

The choice of the model will depend on the question under study. However, whether a marginal (GEE) or a conditional model (Mixed effects) is more appropriate for a specific research question has not been answered in general. A simulation study that compared the power of two approaches showed that the difference between the two approaches diminished as the number of clusters increased. In particular, the difference was negligible if the total number of clusters was at least 30 [30, 31].
Although there are differences in the interpretation of the resulting parameter estimates based on marginal (GEE) and conditional (Mixed effects) approaches, if we assume the log link function, such as the log-binomial model, the parameters coincide apart from the intercept[32].

For this trial as the primary outcome is binary and we are interested in estimation of risk ratio (RR). As there will be a large number of clusters (>40) we will use a generalised linear mixed model (GLMM) with a binomial distribution, log link function and with fixed effect for country and site type (secondary/ tertiary care) 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.