$$log(\pi_{ij}) = \beta_0 + \beta_1 ASCDSS_{ij} + \beta_2\, COUNTRY1_{ij} + \beta_3\, COUNTRY2_{ij} + \cdots + \beta_4\, COUNTRY3_{ij} + \beta_5 Site\ type + U_j$$

π_{ij}: probability of combination therapy for the i[th] participant in j[th] site

$ASCDSS_{ij}$: dummy variable for intervention ($ASCDSS_{ij} = 0\ or\ 1$) for participant i in j[th] site

$COUNTRY1_{ij}, COUNTRY2_{ij}, and\ COUNTRY3_{ij}$: dummy variable for COUNTRY ($COUNTRY_{ij} = 0\ or\ 1$) for participant i in j[th] site

U_j: random effect for site j $\sim N(0, \sigma_u^2)$

For primary analysis hypotheses will be tested as two-sided with a significance level of 0.05.

We will also undertake a sensitivity analysis on those with complete cases.

(ii) Handling missing outcomes:

Missing data will be examined and quantified; this will include the time of withdrawal and tabulation for withdrawal reasons 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.

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. The multilevel multiple imputation model will be detailed in the statistical analysis plan and will include all primary model covariates as well and other predictors of outcomes that are thought to be associated with the outcome.

(iii)Analysis of secondary endpoints:

For time to event outcome, analysis will include all randomised participants. Kaplan-Meier plots will be used to estimate and display time to event outcomes such as time to initiation of 2 or more drug combination regimens 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.

All analysis for other secondary endpoints will be based on Intention to Treat population.

For continuous outcomes (e.g. LDL-C by Week 16) 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) and a random effect for study site (as a random intercept). We will report adjusted mean difference and 95% confidence interval with p-value.

For binary outcomes (e.g. target LDL-C level (<1.4 mmol/L (<55 mg/dL) by Week 16) 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) 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[33] and Rubin[34] no adjustments for multiple testing will be used but a precise, focused interpretation of the individual results for secondary outcomes will be reported. Further analysis of sub-groups and exploratory analysis will be undertaken, and these will all be described and defined in the statistical analysis plan that will be written and signed off prior to data download.

(iv) Modelling and Simulation Based Analyses

The key aim of the simulation-based analysis is to provide estimates of LLT utilisation, LDL-C goal achievement, and CV outcomes due to guidelines-based treatment intensification. Figure 2, captured in the appendix, provides an overall workflow for this analysis. In the simulation, for each patient in the study population, treatment with LLT will be initiated or intensified, if required, depending on LDL-C goal achievement in a sequential manner. Reduction in LDL-C with a given LLT will be probabilistically estimated based on methodology similar to prior investigations [35, 36]. Baseline risk, representing risk without LLT will estimated via the SMART risk calculator (or an alternate method) from patient's demographic and clinical characteristics. The treatment benefit model will be utilized to estimate the risk-reduction based on the LLT type, magnitude of LDL-C lowering, and time on therapy [37].

The simulation will be based on a Monte-Carlo approach and will proceed by sampling patients one at a time from the study population with replacement (bootstrap approach). If the study population size is N, the Monte Carlo simulation will be based on a sample size of N. Several iterations (e.g., 100) of the Monte Carlo model will be conducted to generate the distribution of summary measures (e.g., $X_1, X_2, \ldots X_{100}$). Each iteration of the simulation will also sample from uncertainties in the parameters such as those in the baseline risk model and reduction in LDL-C with an LLT. The final measures will be based on the median and uncertainty interval from these iterations. A patient and a clone (one patient at baseline and one cloned patient with treatment) will undergo simulation through the course of the model horizon. For each day in the simulation, risk will be assessed to probabilistically determine occurrence of an event. Once LLT, LDL-C, and CV outcomes have been determined for each patient over time, results will be aggregated and summarized in a manner described in Tables 1-4 in appendices.

9. REGULATORY, ETHICAL AND LEGAL ISSUES

9.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the 7th revision of the 1964 Declaration of Helsinki.

9.2 Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines).

9.3 Research Ethics Committee (REC) Approval

(i) Initial Approval

Prior to the enrolment of participants, the REC must provide written approval of the conduct of the trial at named sites, the protocol and any amendments, the Participant Information Sheet and Consent Form, any other written information that will be provided to the participants, any advertisements that will be used and details of any participant compensation.

(ii) Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the REC for approval as instructed by the Sponsor. Amendments requiring REC approval may be implemented only after a copy of the REC's approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to participants may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation.

The study team, in collaboration with the Sponsor will assess whether a proposed amendment is substantial or non-substantial. For each proposed amendment, a revised version of the protocol will be prepared using tracked changes, a new version number assigned and the revised document will be reviewed and approved by the Trial Executive Committee and Sponsor prior to submission to the REC and Health Research Authority (HRA). The amended protocol will be sent to participating sites for local approval to be granted and the approved version will be shared with all staff involved in the trial.

(iii)Annual Progress Reports

Annual Progress Reports will be submitted to the Research Ethics Committee (REC) and the Sponsor in accordance with local / national requirements. The Annual Progress Report will also detail all SAEs recorded.

(iv) End of Trial Notification

The REC will be informed about the end of the trial, within the required timelines.

The end of trial notification will be submitted within 90 days of the end of trial definition being met.

9.4 HRA approval

In the UK, Health Research Authority (HRA) approval will be obtained prior to starting the study. Each participating site will confirm capacity and capability prior to commencing.

The HRA and all participating sites also need to be notified of all protocol amendments to assess whether the amendment affects the institutional approval for each site.

In Italy and Spain, appropriate ethical approvals will be gained.

9.5 Regulatory Authority Approval

The study will be performed in compliance with each country regulatory requirements. Clinical Trial Authorisation from the appropriate Regulatory Authority(ies) must be sought/obtained (as applicable to local country regulations) prior to the start of the study. In addition, the Regulatory Authority(ies) must receive all safety updates as required, approve amendments prior to their implementation (as instructed by the Sponsor), and be notified of the end of the trial.

9.6 Non-Compliance and Serious Breaches

All protocol deviations and protocol violations will be reported via the eCRF/CRF and reviewed by the Chief Investigator and reported to the ICTU QA manager on a monthly basis. Protocol violations will be reported to the Sponsor.

An assessment of whether the protocol deviation/violation constitutes a serious breach will be made.

A serious breach is defined as:

A breach of the conditions and principles of GCP in connection with a trial or the trial protocol, which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the UK trial participants; or
- The overall scientific value of the trial

The Sponsor will be notified within 24 hours of identifying a likely Serious Breach. If a decision is made that the incident constitutes a Serious Breach, this will be reported to the REC within 7 days of becoming aware of the serious breach.

9.7 Insurance and Indemnity and Sponsor

The Sponsor has civil liability insurance, which covers this study in all participating countries: the UK, Spain and Italy.

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

Imperial College London will act as the main Sponsor for this trial. Delegated responsibilities will be assigned to the NHS trusts (and other sites) taking part in the trial.

9.8 Trial Registration

The study will be registered on a trial database in accordance with requirements of the International Committee of Medical Journal Editors (ICMJE) regulations.

9.9 Informed Consent

Potential patients will be offered a patient information sheet at a clinic visit or during assessment at the study site. Additional permissions will not be required to approach