Statistical Analysis Plan

Study name:	SECURE
Study title:	Secondary Prevention of Cardiovascular Disease in the Elderly
Study type:	A prospective, multicentre, open-label, randomized controlled clinical trial comparing a polypill versus standard of care treatment strategies in post MI elderly patients
Investigational Medical Product:	Cardiovascular Combination Polypill AAR (acetylsalicylic acid 100 mg, atorvastatin 40 mg or 20 mg, and ramipril 10, 5 and 2.5 mg).
ClinicalTrials.gov ID:	NCT02596126
EudraCT Number:	2015-002868-17
Protocol Number/Version	633765/Version 5.0 25/09/2019
Statistical Analysis Plan (SAP) Author	[redacted]
SAP Date and Version	1.0, 31 August 2021
SAP Reviewers	[redacted]

Table of content

Signature page

We, the undersigned, have reviewed this statistical analysis plan and we approve and agree on its content.

List of abbreviations and definition of terms

AAR	Acetylsalicylic acid 100 mg, Atorvastatin 40 mg or 20 mg, Ramipril 10, 5 and 2.5 mg
AE	Adverse Event
ANCOVA	Analysis of covariance
BARC	Bleeding Academic Research Consortium
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CEC	Clinical Events Committee
CI	Confidence Interval
CKD	Chronic kidney disease
Cox PH	Cox Proportional Hazards
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CV	Cardiovascular
DBP	Diastolic blood pressure
HR	Hazard ratio
ITT	Intention-to-treat
LDL	Low-density lipoprotein
LVEF	Left ventricular ejection fraction
MI	Myocardial Infarction
ITT	Intention-to-treat
MMAS-8	Morisky-Medication Adherence Scale (8 item)
PCI	Percutaneous Coronary Intervention
PP	Per Protocol
QALY	Quality adjusted life years
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
TSQM	Treatment Satisfaction Questionnaire for Medication

SAP modification history

SAP Version	Date of SAP Version	Author	Changes from Previous Version
1.0	31-08-2021	T Collier	NA

1. Introduction

1.1 Preface

The main aim of SECURE is to evaluate the efficacy of a polypill strategy containing aspirin (100 mg), ramipril (2.5, 5 or 10 mgs), and atorvastatin (40 or 20 mgs) compared with the standard of care (usual care according to the local clinical practices at each participating country) in secondary prevention of major cardiovascular events. The hypothesis of SECURE is that the use of a polypill strategy including three components with proven efficacy as well as demonstrated positive impact on adherence will reduce major cardiovascular events in patients with myocardial infarction (MI) by reducing treatment complexity, lack of adherence and achieving better risk factor control, reducing the risk of recurrent disease and death in elderly patients with CVD, and thereby reducing the burden of CVD in Europe.

1.2 Purpose of the statistical analysis plan (SAP)

The purpose of this SAP is to set out in detail the statistical principles and methods that will be used to analyse the primary and secondary endpoints in SECURE.

This document has been prepared in conjunction with the study protocol, version 5.0 and the electronic Case Report Forms (CRFs), version 3.4.

Any deviation(s) from the original statistical plan will be described and justified in a protocol amendment and/or in the final report, as appropriate. The SAP will be finalised and approved by the relevant parties prior to the final database lock.

2. Study objectives and endpoints

SECURE will test the efficacy of a polypill containing aspirin (100 mg), ramipril (2.5, 5, or 10 mg), and atorvastatin (40mg or 20mg), for secondary cardiovascular prevention in the elderly patients (≥65 years old) with a recent (within 6 months) myocardial infarction (MI).

2.1 Primary objective and endpoint

The primary objective of SECURE is to evaluate the efficacy of a polypill strategy containing aspirin (100 mg), ramipril (2.5, 5 or 10 mgs), and atorvastatin (40 or 20 mgs) compared with the standard of care (usual care according to the local clinical practices at each participating country) in secondary prevention of major cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, and urgent revascularization).

2.2 Secondary objectives and endpoints

The secondary objectives are to evaluate a polypill strategy as compared with standard of care for secondary cardiovascular prevention after MI in an elderly population in:

- reducing other clinical endpoints
- improving baseline adherence

- improving quality of life
- controlling cardiovascular risk factors (LDL cholesterol, systolic and diastolic blood pressure)
- cost-effectiveness
- safety and tolerability
- patient satisfaction
- performance across the different socioeconomic and health settings.

3. Study methods

3.1 General study design

SECURE is a randomized, multicenter, open-label, prospective, adaptive, parallel two arms study comparing the efficacy of a polypill strategy with the standard of care (usual care according to the local clinical practices at each participating country) in secondary prevention of major cardiovascular events in elderly patients with a recent MI.

A total number of 2514 patients will be randomized (1:1) to Cardiovascular Combination Pill AAR or Usual Care. Patients will be recruited across seven countries in Europe (Spain, Italy, Germany, France, Hungary, Poland, and Czech Republic). Patients will be ≥65 years old and diagnosed with a type 1 myocardial infarction within 6 months prior to study enrolment.

Patients will be followed up for a minimum of 2 years and a maximum of 5 years. There will be 3 follow up visits at month 6, 12 and 24 and telephone follow up calls at month 18, 36, 48 and 60. The study outline is represented in Figure 1.

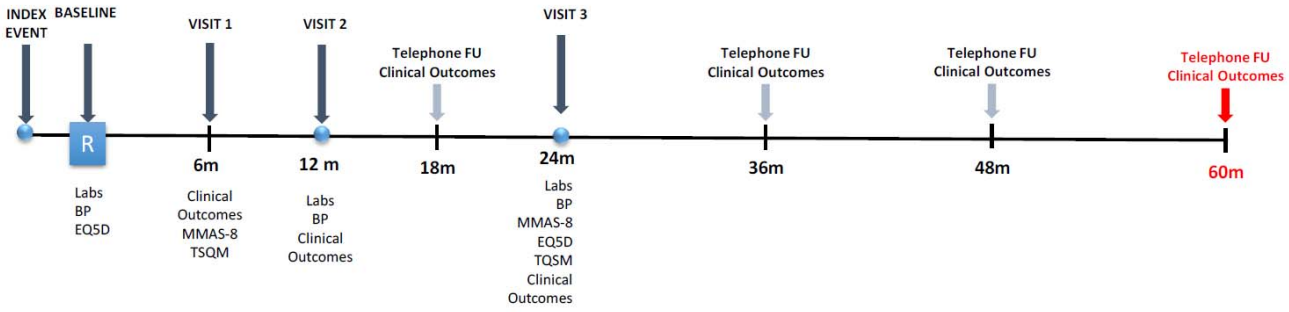

Figure 1: Study outline

3.2 Inclusion and exclusion criteria

To determine whether an individual is eligible to be randomized to SECURE the following inclusion and exclusion criteria have been set out.

3.2.1 Inclusion criteria

1. Patients diagnosed with a type 1 myocardial infarction within the previous 6 months.

2. Subjects must be ≥65 years old, presenting with at least one of the following additional conditions:
    - Documented diabetes mellitus or previous treatment with oral hypoglycemic drugs or insulin.
    - Mild to moderate renal dysfunction: creatinine clearance 60-30 mL/min/1.73 m2.
    - Prior myocardial infarction: defined as an AMI occurring before the index event documented in a medical report.
    - Prior coronary revascularization: coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI).
    - Prior stroke: history of a documented stroke, defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue, not resulting in death.
    - Age ≥ 75 years.
3. Signed informed consent.

3.2.2 Exclusion criteria

1. Unable to sign informed consent.
2. Contraindications to any of the components of the polypill.
3. Living in a nursing home.
4. Mental illness limiting the capacity of self-care.
5. Participating in another clinical trial.
6. Severe congestive heart failure (NYHA III-IV).
7. Severe renal disease (Creatinine Clearance (CrCl) <30ml/min/1.73 m2).
8. Need for oral anticoagulation at the time of randomization or planned in the future months.
9. Any condition limiting life expectancy <2 years, including but not limited to active malignancy.
10. Significant arrhythmias (including unresolved ventricular arrhythmias or atrial fibrillation).
11. Scheduled coronary revascularization (patients can be randomized after final revascularization is completed within the prespecified timeframe).
12. Do not agree to the filing, forwarding and use of his/ her pseudonymised data.

3.3 Randomisation and blinding

Randomization will occur within 6 months of the index event (AMI) in a 1:1 ratio to either Cardiovascular Combination Polypill AAR 40 or Usual care. Randomization will be stratified by center using a centralized online system. Patients randomized to the Polypill arm will begin treatment within 6 months of the index event at the discretion of the physician.

Study treatments are not blinded. The main objective of SECURE is to test the efficacy of simple treatment strategy of bioequivalent active principals in an easy to use, once daily capsule versus the multi-pill treatment regimen. In order to test this hypothesis, the design does not allow for blinding

the treatments. Study endpoints will be adjudicated by an independent Clinical Events Committee (CEC) who are blind to the treatment allocation.

3.4 Study variables

The frequency and timing of all the relevant variable observations and assessments is described in Table 1.

Table 1: Study visits and assessments

Assessments[1]	Study Visits							
	Screening and baseline	Visit 1 (6m ± 2 w)	Visit 2 (12m ± 2 w)	Phone 1 (18m ± 2 w)	V3 (24m ± 2 w)	Phone 2 (36m ± 4 w)	Phone 3 (48m ± 4 w)	Phone 4 (60m ± 4 w)
Informed Consent	x							
Inclusion/exclusion criteria	x							
Randomization (R)	x							
Demographic data	x							
Medical history	x							
Physical examination including body weight	x							
Vital signs and blood pressure[2]	x	x	x		x			
Previous/concomitant medications	x	x	x	x	x	x	x	x
Non-fasting blood analysis	x		x		x			
Adherence		x			x			
Quality of Life	x				x			
TSQM		x			x			
Resources Utilization		x	x		x			
Outcomes		x	x	x	x	x	x	x
Adverse Event Reporting		←	—	—	—	—	—	→

[1]Medication supply will be done every 3-6 months; [2] Blood pressure and heart rate, a mean of two readings after 5 min sitting rest.

3.5 Sample size

The planned total sample size in this study is 2514 patients (1257 per group). The initial assumptions for the determination of sample size are as following:

- A composite primary endpoint event rate of 7.7% per year in the population to be recruited
- A true hazard ratio of 1
- A planned accrual period for the study of 3 years
- A minimum follow-up and treatment period of 2 years
- An estimated loss to follow-up of 1%

Based on these assumptions, it is anticipated that 420 composite primary events will be accrued during the follow-up period. A non-inferiority margin of 1.373 for the upper limit of the 95% confidence interval for the hazard ratio is set for this study. With the total sample size of 2514 patients (1257 per group) a noninferiority test at 0.025 one-sided significance level with have a 90% power to reject the null hypothesis of inferiority.

With this sample size, the study will have 78% power at a two-sided alpha of 0.05 to demonstrate a relative risk reduction of 21%, which corresponds to a hazard ratio 0.79.

4. Analysis populations

The following analysis populations have been defined. All these analysis populations will be strictly determined on a per-patient basis before data base lock and unblinding.

4.1 Intention-to-treat (ITT) population

All randomised patients, analysed according to the group to which they were randomised. This will be the population for the primary analysis.

4.2 Per protocol (PP) population

All randomised patients who received at least one dose of IMP, and have no major protocol deviations, analysed according to the group to which they were randomised. Patients with major protocol deviations will be identified before database lock and unblinding.

4.3 As treated population

All randomised patients who received at least one dose of IMP, analysed according to the treatment group which they received.

5. General considerations for statistical analysis

The following sections describe the general statistical principles that will be used in the analysis of SECURE.

5.1 Covariate adjustment

The primary analysis for the primary and any secondary time-to-event endpoints will be stratified by country but will not be adjusted for any baseline covariates. Sensitivity analysis for the primary and secondary outcomes will be conducted adjusting for the following baseline covariates: gender, age (<75, 75+), diabetes, CKD, previous vascular event. Continuous endpoints e.g. between group differences in SBP will be analysed using analysis of covariance (ANCOVA) adjusting for baseline.

5.2 Missing data

Missing outcome data will not be imputed for the main analysis of the primary and secondary endpoints. Imputation of missing outcome data will be carried out as a sensitivity analysis for the primary endpoint.

5.3 Adjustment for multiplicity

No adjustments will be made for multiplicity. A test for superiority for the primary outcome will be carried out only if non-inferiority has been demonstrated. A test for superiority for the key secondary endpoint will be carried out only if superiority has been demontstrated for the primary endpoint. All other secondary outcomes will be considered as exploratory.

5.4 Descriptive statistics

Descriptive summaries will be provided where appropriate for each variable of interest.

Summaries for continuous variables will include the number of non-missing values (N), number of patients with missing data (missing), mean, standard deviation, median, ranges (minimum and maximum) and first and third quartile.

Summaries for categorical variables will include the number (N) and percentage (%) of patients who are in each particular category. Percentages will be calculated out of the total number of patients with available information. The number of patients with missing data for each categorical variable will also be reported.

For time-to-event endpoints the number and percentage of patients with the event will be reported. Cumulative event curves and cumulative percentages will be obtained through the Kaplan-Meier method.

5.5 Inferential statistics

All statistical tests will use an alpha level of 5%, with the exception of the one-sided non-inferiority test on the primary endpoint where the alpha level will be set to 2.5%. All statistical analyses will use 95% confidence intervals (CI).

For the comparison of categorical variables, statistical differences will be assessed by a chi-square test or a Fisher's exact test as appropriate. For binary categorical variables risk ratios and 95% CIs will be estimated using standard methods for two-by-two tables.

For continuous variables comparison, the Student *t*-test or analysis of covariance (ANCOVA) adjusting for baseline values, will be used where appropriate. For non-normal distributed data or where normalization is not possible, non-parametric test will be used (e.g. Mann-Whitney) as appropriate.

All time-to-event endpoints consist of right-censored variables as patients can be lost to follow-up, withdraw from the study, die before the endpoint occurs or be administratively censored. Time to the first event will be investigated using Cox proportional hazards (Cox PH) regression. Hazard ratios and 95% CIs will be obtained from the Cox PH model. P-values will be obtained using the log-rank test. The valididity of the proportional hazards' assumption will be assessed.

6. Patient disposition

6.1 Disposition of patients and discontinuations

The flow of patients from screening (if available), randomization, through each visit to the final visit will be summarized in a CONSORT flowchart. This will include:

- Number of patients screened
- Number of screened patients not randomized along with reasons for not being randomized (if available)
- Number of patients randomized to each treatment group
- Number of patients withdrawn from the study with reason for withdrawal
- Number of patients lost to follow-up
- Number of patients with available data at each visit
- Number of patients died
- Number of patients with data on the primary endpoint in the ITT and PP populations

Length of follow-up will be summarized overall and by treatment group: the minimum, maximum, median, 25^{th} and 75^{th} percentiles of person-years of follow-up will be reported.

A subject will be considered lost to follow-up only after patient has not been confirmed alive or dead in more than 18 months AND all means of all subsequent contact have been exhausted.

Discontinuation of the study treatment will be summarized by treatment group at each visit. The following criteria will be used:

- *Brief Temporary Discontinuation of polypill*: discontinuation for a period of 1 to 5 days
- *Temporary Discontinuation of polypill*: discontinuation for a period of 6 to 30 days
- *Permanent Discontinuation of polypill*: discontinuation for a period longer than 30 days

After brief temporary and temporary discontinuation, patients can continue treatment with Cardiovascular Combination Polypill AAR, if advised by investigator. After permanent discontinuation patients will be followed up according to regular protocol until the end of the follow up period.

6.2 Protocol deviations

All deviations from the study protocol will be documented in the Protocol Deviation Log and will be reviewed by the Chief Investigator to assess whether participant safety or study integrity has been affected. Protocol deviations will be summarized by treatment group; for each type of deviation, the number of occurences of the deviation and the number of patients with at least one occurrence of the deviation will be reported. Deviations which have been classified as serious will be reported separately.

Patients with a major deviation will be identified and agreed prior to data base lock and unblinding for exclusion from the PP population.

7. Demographics and other baseline characteristics

The following variables will be summarized overall and by treatment group:

- Demographics: age, sex, country, ethnicity, education, employment, height, weight, and body mass index (BMI)
- Lifestyle: smoking history
- Vital signs: systolic blood pressure, diastolic blood pressure, heart rate
- Prior disease history and comorbidities: diabetes mellitus, hypertension, hyperlipidaemia, angina, previous MI, coronary artery disease (CAD), previous PCI, previous CABG, stroke, congestive heart failure, peripheral arterial occlusive disease, COPD/asthma, cancer
- Baseline medications: ACE inhibitor, statin
- Other diagnostic information: type of MI, undergone revascularization, revascularization type, left ventricular ejection fraction (LVEF), Killip class, evidence of CAD
- Other baseline characteristics collected in the eCRF will be summarized as appropriate.

No statistical hypothesis testing of demographic or baseline data will be performed.

Concomitant medications taken during the study will be summarized.

8. Endpoint evaluation

The following section describes the definition, statistical method of analysis and reporting for the primary and secondary endpoints.

8.1 Primary endpoint

The primary endpoint is defined as the time to first occurrence of any component of the following composite endpoint, as adjudicated by the CEC:

- Cardiovascular (CV) death
- Nonfatal type 1 myocardial infarction (MI)
- Nonfatal ischemic stroke
- Urgent coronary revascularization

CV death: includes any death resulting from acute MI, sudden cardiac death, heart failure, stroke, or any other CV causes

Nonfatal type 1 MI: defined by the presence of electrocardiographic changes or at least 1 elevated biomarker measurement of a troponin T level ≥ 0.1 ng/mL

Nonfatal ischemic stroke: Acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue, not resulting in death.

Urgent coronary revascularization: Episode/s of persisting or increasing chest pain (with or without ST-T changes or elevated biomarkers) requiring urgent hospitalization and urgent coronary revascularization (PCI or CABG), during the same hospitalization.

Patients who are lost to follow-up, withdrew consent or died of non-CV causes without experiencing the primary composite endpoint will be censored at the date at which they were lost, withdrew or died.

For the primary endpoint, first, the non-inferiority hypothesis will be tested using a univariable Cox PH regression model including treatment group (pollypill versus standard of care) as the only covariate and stratified by country. The pre-specified non-inferiority margin is a hazard ratio (HR) =1.373. If the upper limit of a two-sided 95% confidence interval for the HR is less than 1.373, non-inferiority will be confirmed.

If the non-inferiority hypothesis is confirmed, it will be followed with a test of superiority using a log-rank test.

The cumulative incidence of the primary endpoint will be calculated using the Kaplan-Meier method and displayed using a Kaplan-Meier plot.

8.2 Key secondary endpoint analysis

Time to first occurrence of the composite endpoint:

- CV death
- Nonfatal type 1 MI
- Nonfatal ischemic stroke.

This endpoint will be analysed using the methods described in 5.5 for time-to-event endpoints.

8.3 Secondary endpoints analysis

1. Time to first occurrence of each component of the primary composite endpoint: (i) CV death (ii) nonfatal type 1 MI (iii) nonfatal ischemic stroke.

These endpoints will be analysed using the methods described in 5.5 for time-to-event endpoints.

2. Treatment adherence at 6 months and 24 months.

Treatment adherence is measured at visit 1 (6 months) and visit 3 (24 months) using the Morisky-Medication Adherence Scale (8 item) Questionnaire (MMAS-8). The number and percentage of

patients with low (0-5), medium (6-7) and high (8) adherence will be reported by treatment group. The distributions of the MMAS-8 score at 6 months and 24 months will be compared between treatment groups using an ordinal logistic regression model. If the assumption of proportional odds is badly violated, a Mann-Whitney test will be used. The proportion of patients with high adherence at 6 months and 24 months will be compared between treatment groups using a risk ratio and 95% CI estimated using standard methods for a two-by-two table. A p-value will be obtained using a chi squared test.

3. Patient satisfaction at 6 months and 24 months.

Patient satisfaction is measured at visit 1 (6 months) and visit 3 (2 years) using the Treatment Satisfaction Questionnaire for Medication (TSQM) version 1.4 a 14-item psychometric instrument comprising of four domains: effectiveness (questions 1 to 3), side effects (questions 4 to 8), convenience (questions 9 to 11) and global satisfaction (questions 12 to 14). Scaled scores for each domain range from 0 to 100.

Effectiveness score: (items 1-4)

- If all 3 items complete: $ES = ([item\ 1 + item\ 2 + item\ 3 - 3]/18) \times 100$
- If 1 item is missing: $ES = ([item\ 1? + item\ 2? + item\ 3? - 2]/12) \times 100$
- If more that 1 item is missing then the effectiveness score should be assigned as missing

Side effects score: (items 5-8)

- If all 3 items complete: $SES = ([item\ 5 + item\ 6 + item\ 7 + item\ 8 - 4]/16) \times 100$
- If 1 item is missing: $SES = ([item\ 5? + item\ 6? + item\ 7? + item\ 8? - 3]/12) \times 100$
- If more that 1 item is missing then the side effect score should be assigned as missing

Convenience score: (items 9-11)

- If all 3 items complete: $CS = ([item\ 9 + item\ 10 + item\ 11 - 3]/18) \times 100$
- If 1 item is missing: $CS = ([item\ 9? + item\ 10? + item\ 11? - 2]/12) \times 100$
- If more that 1 item is missing then the convenience score should be assigned as missing

Global satisfaction score (GSS): (items 12-14)

- First rescale item 14: $item14R = [item\ 14 - 1] \times 5/6$
- If all 3 items complete: $GSS = ([item\ 12 + item\ 12 + item\ 14R - 3]/12) \times 100$
- If 1 item is missing: $GSS = ([item\ 12? + item\ 13? + item\ 14R? - 2]/8) \times 100$
- If more that 1 item is missing then the global satisfaction score should be assigned as missing

Mean and standard devation for each score will be reported by treatment group at 6 months and 2 years. Comparison of mean scores between treatment groups at 6 months and 2 years will be made using a two-sample t-test. The difference in mean score and 95% CI will be reported.

4. Risk factor control.

The following three CV risk factors, systolic blood pressure (SBP), diastolic blood pressure (DBP) and low-density lipoprotein (LDL) cholesterol levels are measured at baseline, visit 1 (6 months), visit 2 (12 months) and visit 3 (24 months). For each of the three risk factors the frequency, mean and standard deviation at each visit will be reported by treatment group. The difference in mean change from

baseline between groups will be compared using ANCOVA (adjusting for baseline levels) at 6 months, 12 months and 24 months. The difference in mean change adjusting for baseline and 95% CI will be reported.

8.4 Subgroups

The following pre-specified subgroup analyses will be carried out for the primary efficacy endpoint:

- Country
- Age (<75, 75+)
- Sex
- Diabetes
- CKD
- Previous vascular event.

HRs and 95% CIs for the estimated treatment effect within each subgroup will be estimated using Cox PH regression. Statistical significance of the interaction term (treatment group and subgroup) will be evaluated using a likelihood ratio test. The results will be presented in the form of a forest plot figure.

8.5 Safety endpoints

1. All-cause mortality

Time to all-cause mortality will be analysed using the statistical methods described above in section 5.5 for time-to-event endpoints.

2. Adverse events (AE)

The following AE are defined :

- Bleeding – as defined by the Bleeding Academic Research Consortium (BARC) Definition. See Annex 5 of SECURE Protocol.
- Renal dysfunction (increase in creatinine by 0.5 mg/dl or more) or hyperkalemia (K 5.5 mEq/L) reported by physician in charge and leading to a change in doses or drug interruption.
- Drug allergies.
- Refractory cough leading to drug discontinuation.

These endpoints will be analysed using the statistical methods described above in section 5.5 for binary endpoints.

8.6 Health economic endpoints

Quality of Life will be assessed with the validated EuroQol EQ-5D (3L) scale measured at visit 3 (24 months). EQ-5D scores will be transformed into quality adjusted life years (QALYs). See Annex 10 of SECURE Protocol.

Cost differences and Incremental Cost-Effectiveness Ratio (ICER), expressed as the costs per QALY gained, of the Cardiovascular Combination Polypill AAR versus usual care.

Occurrence of the following events:

- Scheduled Revascularization (non-urgent)
- Angina
- Atherosclerosis
- Other Cardiovascular Hospitalizations or Interventions
- Emergency Room Visits

The methods of analysis for the health economic endpoints will be described in detail in a separate analysis plan.

9. Technical considerations

9.1 Rounding conventions

Percentages will be rounded to one decimal place. Mean, standard deviation, median, Q1 and Q3 will be presented to one more decimal place than the raw data; minimum and maximum will be presented with the same number of decimal places as the raw data. All *p*-values should be rounded to 3 decimal places. If a rounded *p*-value is 0.000 (*i.e.*, the actual *p*-value is less than 0.0005), then this *p*-value will be presented as '<0.001'.

10. References

Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ; CONSORT Group. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. JAMA. 2006 Mar 8;295(10):1152-60. doi: 10.1001/jama.295.10.1152. Erratum in: JAMA. 2006 Oct 18;296(15):1842. PMID: 16522836.

11. Listings of Tables, Figures and Listings

11.1 Tables

Table 1 Baseline patient characteristics: demographics, lifestyle, anthropometrics, vital signs, comorbidities, laboratory results, and previous medical history

Table 2 Details of the index event

Table 3 Primary and secondary outcomes

Table 4 Safety outcomes and adverse events

Table 5 Protocol deviations

11.2 Figures

Figure 1: CONSORT flow chart

Figure 2: Kaplan-Meier for primary endpoint

Figure 3: Kaplan-Meir plot for key secondary endpoint

Figure 4: Kaplan-Meier plot for components of primary endpoint