Randomized comparison of Evolut FX versus Sapien 3 Ultra Resilia: The COMPARE-TAVI 2 trial

STATISTICAL ANALYSIS PLAN (SAP) – Version 1.2

1. Administrative Information

Title:	COMPARE-TAVI 2: Evolut FX versus Edwards 3 Ultra Resilia
Trial registration number:	Clinicialtrials.gov ID: NCT06470022
SAP version:	*Version 1.2, 7.2.2025*
Protocol version:	Danish Ethical Committee: "Randomiseret sammenligning af TAVI-klapper (Randomized comparison of TAVI valves). The Compare-TAVI trial. V. 6.5.2024. J.no. 1-10-72-389-17" = Amendment 11, approved 16-5-2024. English version: "Randomized comparison of Evolut FX versus Sapien 3 Ultra Resilia. The Compare-TAVI trial. Protocol v. 28.5.2024 & 7.2.2025. Amendments have been approved for a Multi-Slice Computed Tomography (MSCT) substudy & a Cardiovascular Magnetic Resonance (CMR) substudy ("Amendment 12, approved 22-8-2024"). An amendment has been submitted for a hemodynamic substudy (Amendment 13, submitted 23.1.2025).

Roles and responsibility:

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1. Introduction

Background and rationale: Transcatheter Aortic Valve Implantation (TAVI) is a method in which an artificial heart valve is implanted through the femoral artery (the groin) or via an alternative access route (apical, transcaval, a.axillaris, direct aorta), instead of through conventional surgery. TAVI represents routine treatment for inoperable and high-risk surgical patients and is increasingly used in patients with low and intermediate surgical risk [1, 2]. Although a considerable number of TAVI valves have been introduced, there have been few direct comparisons of the valves. The purposes of the "COMPARE-TAVI" organization are to ensure continuous comparison of implanted TAVI valves, and to monitor long-term valve performance, through establishment of consecutive cohorts. The current Statistical Analysis Plan (SAP) relates to the comparison between the Evolut FX and the Edwards 3 Ultra Resilia valves.

Objective: To compare outcomes in patients randomized to treatment with Evolut FX versus Edwards 3 Ultra Resilia TAVI valves.

2. Study Methods

Trial design: Randomized controlled trial.

Randomization: Randomization 1:1 between Evolut FX and Sapien 3 Ultra Resilia valves, with stratification by center and sex.

Sample size for main study and substudies:

For the **main study** a sample size of 1346 was chosen, based on expected event rates of 12%, a non-inferiority margin of 4.5%, and an anticipated drop-out rate of 4% (Sealed Envelope | Power calculator for binary outcome non-inferiority trial). No interim analyses are planned. If the observed event rate differs significantly from the expected rate, the steering committee will consider adjusting sample size (preferable) or non-inferiority margin (Randomized comparison of TAVI valves: The Compare-TAVI trial - PubMed (nih.gov).

For the **CMR-substudy**, which will evaluate the hemodynamics (Effective Orifice Area (EOA) and aortic regurgitation fraction (ARF)), the expected EOA is 1.5 (SD 0.54) cm^2 and the expected ARF is 0.14 (with an expected SD of 0.09). A total of 148 patients are needed to document a difference of 0.25 cm^2 in EOA (1.5 to 1.25 cm^2) and 102 patients are needed to document a difference of 0.05 in the expected ARF (0.14 to 0.09). We aim to include 166 patients with an expected drop-out of 10%.

For the **MSCT-substudy**, the expected 12-month incidence of HypoAttenuated Leaflet Thickening (HALT) is approximately 24% based on the COMPARE-1 trial. With Beta=0.80 and alfa=0.05, a total of 778 patients are needed to document an 8% difference in HALT. With inclusion of 850 patients there is room for up to a 9% drop-out rate.

For the **invasive hemodynamic substudy**, a total of 396 patients are needed to document a 15% difference in EOA, if the mean EOA during stress is 2.31 and the standard deviation 1.24 (approximated from Johnson *et al.* by dividing the IQR by 1.35) [13]. To account for dropouts, we aim to include 440 patients in this substudy.

Framework: Non-inferiority testing of the primary outcome in the main study and superiority testing of secondary outcomes.

Statistical interim analyses and stopping guidance:
While no interim analyses are planned in the current trial, the **safety committee** will have access to all data for analysis of safety issues. Safety committee meetings are expected to be convened after inclusion of 1/3 and 2/3 of patients. The safety committee will write an assessment for the steering committee. The steering committee then will make the final decision whether to continue inclusion, change sample size, or change non-inferiority margins if event rates differ from expected rates. (See power calculation above.)

Timing of final analyses:
Primary outcome main trial: 15 months following inclusion of the last patient, to allow for I year of follow-up and 3 months for cleaning data.
Primary outcome hemodynamic trial: 3-months after last patient included.
Primary outcome CMR-substudy: 4 months after inclusion of the last patient, to allow for a CMR-scan at 1 month and 3 months plus 1 month for data cleaning and analysis.
Primary outcome of MSCT-substudy: 15 months after inclusion of the last patient, to allow for a MSCT-scan at 1 month and 12 months plus 3 months for data cleaning and analysis.
Secondary outcome of MSCT-substudy (including commissural and coronary alignment): 4 months after inclusion of the last patient to allow for a MSCT-scan at 1 month plus 3 months for data cleaning and analysis.

Secondary outcomes and exploratory outcomes: 30 days, 1 year, 3 years, 5 years, 10 years, with an expected 3-month delay for data cleaning at each time point of follow-up.

Timing of outcome assessments:
Primary outcome main trial: 1-year.
Secondary outcomes and exploratory outcomes: 30-day, 1-year, 3-year, 5-year, 10-year.
Primary outcome CMR-substudy: 30-day
Primary outcome Hemodynamic substudy: Inhospiital
Primary outcome MSCT-substudy: 30-day and 1-year.

3. Statistical Principles:

Descriptive statistics will be provided for continuous outcomes by treatment arm and will include mean (SD), median (IQR), and minimum and maximum, as appropriate. Categorical outcomes will be provided as counts (percentages). Continuous variables will be compared between treatment groups using a two-

sample t-test or the nonparametric Wilcoxon rank-sum test, as appropriate. Categorical variables will be compared between treatment groups using a Chi-square test or Fisher's exact test, as appropriate. Ordinal variables will be compared using the Cochran-Mantel-Haenszel test with row mean scores. For time-to-event outcomes (death), using Kaplan-Meier methods, the time points of 30 days, 1, 3, 5, and 10 years will be used. For other time-to-event outcomes, Aalen-Johansen analyses will be used to account for competing risk, such as death. For participants with an event, the event date will be based on the first event occurrence. For participants without an event, the date of censoring will be the time of outcome assessment (30 days, 1 year, 3 years, 5 years, 10 years) after TAVI unless the patient was withdrawn from the study earlier. In this case the date of withdrawal will be used. For each applicable time point, the event or event-free rate, the number of subjects at risk, the number of subjects with an event and the 95% confidence interval calculated using the Greenwood standard error will be reported. Log-rank will be used for comparisons. Cox regression will be used to compute HRs and to adjust for potential confounders. In general, two-sided testing will be performed with alfa=0.05 and provision of 95% CIs. However, special conditions apply to the primary outcome (one-sided testing) and secondary outcome analyses (multiple testing).

For the primary outcome, one-side non-inferiority testing will be performed. First, the risk of the primary outcome will be estimated in the two study arms. The risk differences and HR between the two treatment groups will be calculated for the primary outcome, as well as for each component of the primary outcome and the secondary outcomes. A one-sided 95% CI will be provided for the primary composite outcome, while two-sided 95% CIs will be provided for each component of the primary outcome, as well as for secondary and exploratory outcomes. For the primary outcome, a one-sided Farrington-Manning test will be employed to assess non-inferiority. For all other outcomes, including individual components of the primary outcome, a two-sided Wald test will be used. The non-inferiority assumption will be tested at a one-sided significance level with an α of 0.05 and power of 0.80. The non-inferiority margin is set to 4.5% at an expected event rate of 12%. If the cumulative event rate (blinded) is higher than 12%, either the sample size will need to be increased (preferable) or the non-inferiority margin will need to be adjusted. If the results of the trial are statistically significant, the null hypothesis can be rejected and the alternative hypothesis that the new treatment is non-inferior to standard treatment can be accepted. Non-inferiority would be shown if the upper limit of the one-sided 95% CI of the risk difference does not cross the prespecified noninferiority margin. The analysis of the primary composite outcome will be conducted according to the intention-to-treat principle, but per-protocol analyses will also be performed. Non-inferiority will be declared only if both analyses support the same conclusion. If non-inferiority is demonstrated for the primary composite outcome, a gate-keeping strategy with a split α will be used to test for superiority (H_0: RD = 0, H_A: RD $\neq$ 0) of the primary composite outcome (α = 0.025) and four secondary safety and efficacy outcomes (Bonferroni correction, α = 0.025/4 for each endpoint). All other secondary outcomes will be considered exploratory (hypothesis-generating) and will not be subject to Bonferroni correction. [13-15] If non-inferiority is not shown for the primary outcome, the four secondary safety and efficacy endpoints will still be presented but considered only exploratory. A complete case analysis of the primary composite outcome also will be performed, limited to patients who have paired 1-year and 1-month echocardiograms for evaluation of hemodynamic Transcatheter Heart Valve (THV)-deterioration, or who already have fulfilled one of the three other components of the composite endpoint

(death, stroke, or moderate or severe aortic regurgitation). Subgroup analyses will be performed as described below. Statistical analyses will be performed using Stata/SE or SAS.

The composite primary outcome and each component will be re-analysed at 3, 5, and 10 years of follow-up.

Adherence and protocol deviations:
If a patient is not treated with the intended valve (based on randomization), the operator will need to decide whether the deviation is due to 1) Lack of supply (chosen valve not available), 2) unsuccessful implantation attempt resulting in the operator's decision to implant another valve, 3) Complications during the procedure resulting in surgery or implantation of a second valve of other type, or 4) operator's choice to violate randomization and initially chose another valve.

Analysis of populations:
Intention-to-treat analyses will be used to assess primary and secondary outcomes. Per-protocol analyses will be provided in the supplement as well as as-treated analyses (cross-over). Complete case analyses will be prioritized.

The following rule will be used to ensure complete case analyses for the one-year primary outcome comprising death, stroke, moderate/severe aortic regurgitation, and moderate/severe valve deterioration:

1. Missing data are not expected for the death or stroke components unless a patient emigrated from the country. Patients who emigrated will be contacted (if consent has not been withdrawn) to evaluate whether they experienced one of these events.
2. For aortic regurgitation, the latest available echocardiogram will be used to determine degree of aortic regurgitation (1-year, 30-day, post-procedure).
3. THV deterioration can only be documented if both 30-day and 1-year echocardiograms are available. If not, the patient will be classified as having "no documented THV deterioration" and incorporated into the primary outcome analysis as having no THV deterioration at 1 year.

4. Trial Population

Screening data: For all sites, the proportion randomized among all patients treated with TAVI will be reported. Moreover, a screening log will be established to document patients who were found ineligible for randomization.

Eligibility: See Protocol. All patients eligible for treatment with both valves will be invited to participate.

Recruitment: See Protocol.

Withdrawal / local follow-up only / electronic health record follow-up & register-follow-up only: A patient who emigrates to another country will be lost to follow-up in electronic health records and

registries. Clinical follow-up by telephone will be attempted among patients who emigrated. If a patient considers withdrawing consent the site will contact the patient and clarify whether the patient just wants to have follow-up at the local hospital or prefer register-follow-up only, in which case the patient is not withdrawn. The various possibilities are as follows:

1. The patient does not want clinical follow-up at the center but accepts clinical follow-up at a local hospital and that data are collected from electronic health records and registries. This patient is NOT withdrawn from the study.
2. The patient does not want clinical follow-up at all but accepts follow-up based on electronic health records and registries and telephone follow-up. This patient is NOT withdrawn from the study.
3. The patient does not want clinical follow-up and telephone follow-up but accepts follow-up based on electronic health records and registries. This patient is NOT withdrawn from the study.
4. The patient wants to withdraw consent for a substudy but wants to stay in the main study. This patient is NOT withdrawn from the main study but is filed in the Electronic Case Report Form (ECRF) as withdrawn from the relevant substudy.
5. The patient wants complete withdrawal of consent: the patient will be followed until the date of consent withdrawal and will be filed in the ECRF as withdrawn from the study.

Baseline patient characteristics, clinical data, echocardiogram findings, and procedural and post-procedural characteristics: Previous medical history (PCI [Percutaneous Coronary Intervention], CABG [Coronary Artery Bypass Grafting], AMI [Acute Myocardial Infarction], stroke, hypertension, hyperlipidemia, diabetes, CHF [Congestive Heart Failure], COPD [Chronic Obstructive Pulmonary Disease], atrial fibrillation), family history of ischemic heart disease (IHD), previous pacemaker, peripheral vascular disease, height, weight, NYHA [New York Heart Association Class] and CCS [Canadian Cardiovascular Society] grading of angina pectoris, heart rate, blood pressure, pulmonary hypertension, ECG rhythm, conduction disturbances, biomarker levels (creatinin, Hgb, eGFR, BNP), FEV1, FVC, Euro-score 2, STS score, previous medications, valve morphology (valve-in-valve, bicuspid, tricuspid), timing (elective, subacute, acute), ST-junction dimension, distance from annulus to LM and RCA, access site dimensions, annulus dimensions (area, perimeter, short and long axis), level of calcium in annulus and access sites, level of tortuosity access sites, LVEF (Left Ventricle Ejection Fraction), AVA (aortic valve area), peak and mean gradients, procedural characteristics (predilatation, postdilatation, access, indication, closure devices, valve implanted, complications according to VARC-3 criteria, procedure time, fluroscopy time, radiation dose, contrast use, pacing modus, pacing during valve implantation, temporary leads before and/or after procedure), conduction disturbances before, during, and after procedure, simultaneous PCI or CPS (cardiopulmonary support), anticoagulation and thrombocyte inhibition after procedure, hospital length of stay. Analyses will be descriptive. (Please see statistical section.)

5. Analyses

Primary and secondary endpoints for the main study and for each predefined substudy are listed below.

A) Main study, N=1346

Primary composite endpoint (outcome): Mortality, stroke, moderate/severe aortic regurgitation, and moderate/severe THV deterioration at 1 year, using VARC-3 criteria [10].

Definitions of each component of the primary outcome:

Mortality: all-cause.

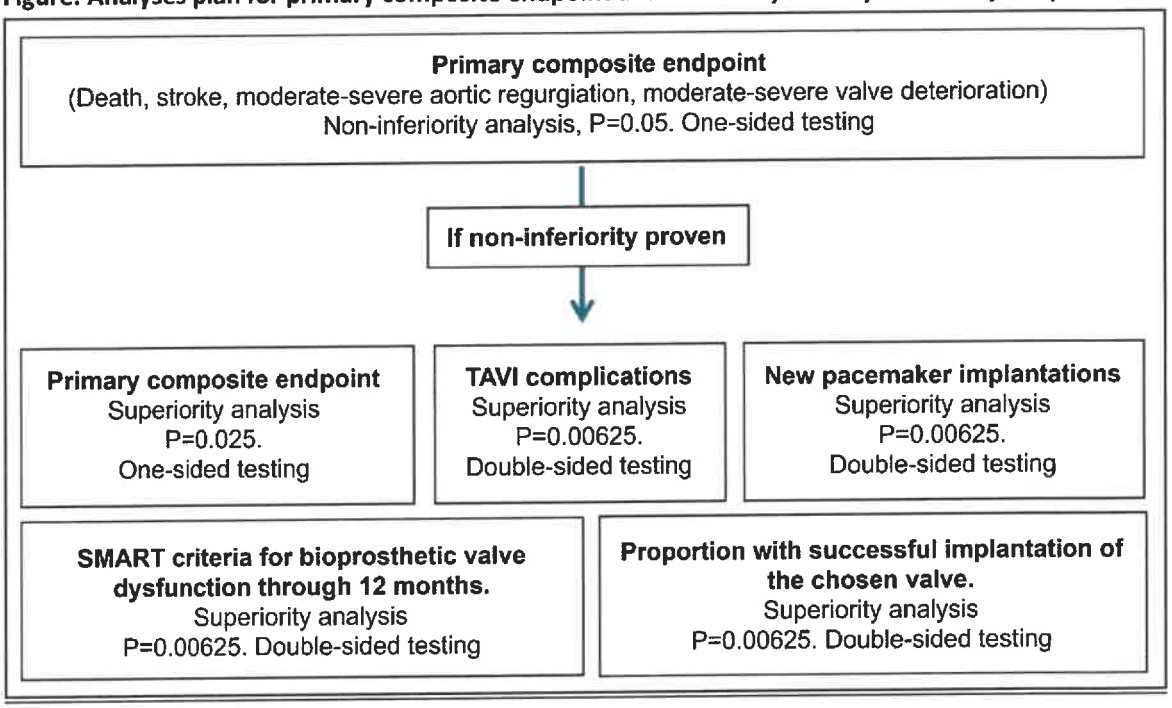
Stroke: to be adjudicated by an endpoint committee according to VARC-3 criteria [10].

Moderate/severe aortic regurgitation: to be evaluated by the echo core laboratory using VARC-3 criteria [10]. For aortic regurgitation the latest available echocardiogram will be used to determine degree of aortic regurgitation (1-year, 30-days, or post-procedure for the 1-year evaluation). If moderate aortic regurgitation at 1 month is reduced to mild at 1 year, then it will not contribute to the primary composite endpoint at 1 year, since only moderate-severe aortic regurgitation will count.

Moderate/severe hemodynamic valve deterioration: This component will be determined by the core laboratory according to VARC-3 criteria [10], and defined as an increase in mean transvalvular gradient ≥10 mmHg resulting in mean gradient ≥20 mmHg, with a concomitant decrease ≥0.3 cm^2 or ≥25% in EOA and/or ≥0.1 or ≥20% decrease in Doppler velocity index compared with an echocardiographic assessment performed 1–3 months post-procedure. THV deterioration can be documented only if both 30-day and 1-year echocardiograms are available. If not, the patient will be classified as having "no documented THV deterioration" and evaluated as having no THV deterioration in the analyses.

The primary composite endpoint will be ascertained at one year and a non-inferiority test will be performed. Separate analyses of each component of the primary outcome, *i.e.*, mortality, stroke, moderate/severe aortic regurgitation, and moderate/severe THV deterioration, will be presented, in accordance with the FDA (Multiple Endpoints in Clinical Trials | FDA) and EMA (Points to consider on multiplicity issues in clinical trials (europa.eu)) guidelines. This will allow better understanding of their contributions to the primary endpoint. If non-inferiority is proven for the primary composite endpoint, a split alfa will be used to test for superiority (alfa=0.025) and to test secondary safety and efficacy endpoints (total alfa=0.025) (Figure). The composite endpoint will be re-analyzed after 3, 5, and 10 years, but as superiority analyses (2-sided alfa=0.05).

Figure. Analyses plan for primary composite endpoint and secondary efficacy and safety endpoints.



Secondary safety and efficacy endpoints:

Bonferroni correction will be used due to multiple testing, *i.e.,* alfa=0.025/4. Results will be interpretable only if the primary endpoint proves non-inferiority; otherwise the findings will be just hypothesis-generating, in line with the exploratory endpoints.

1. **TAVI-related complications:** Conversion to open surgery during implantation, unplanned use of cardiopulmonary support (CPS), coronary artery obstruction, ventricular septal perforation, mitral valve apparatus damage or dysfunction, cardiac tamponade / pericardial effusion resulting in pericardiocentesis, valve embolization, valve migration, need for TAVI-in-TAVI deployment using VARC-3 criteria [10], or annulus rupture, aortic rupture/perforation, aortic dissection, and shunts other than VSD.
2. **Proportion with successful implantation of the chosen valve.** Successful implantation of the chosen valve is defined as no need for more than 1 TAVI valve, no change to another valve during the procedure because it was impossible to implant the planned valve, and no conversion to surgery or procedure-related death.
3. **SMART criteria for bioprosthetic valve dysfunction within 12 months, composed of the following components:** (1) hemodynamic structural valve dysfunction, defined as aortic valve mean gradient ≥ 20 mmHg at any time up to the 12-month visit echocardiogram; (2) nonstructural valve dysfunction, defined as severe prosthesis-patient mismatch or ≥ moderate total aortic regurgitation at any time up to the 12-month visit echocardiogram; (3) clinical valve thrombosis; (4) endocarditis; or (5) aortic valve reintervention.
4. **Pacemaker-implantation:** New pace-maker implantation within 1 year following TAVI.

Exploratory endpoints for main trial (hypothesis-generating only):

Procedural and early in-hospital complications:

1. **Major vascular access site and access-related complications resulting in endovascular or open surgery** using VARC-3 criteria during admission or within 30-days [10].
2. **Major bleeding resulting in drop in hgb-level ≥1.86 mmol/l and/or erythrocyte transfusion ≥ 2 units:** during admission, or 30-day, 1-year, 3-year, 5-year, or 10-year follow-up, modified from BARC type 3-5 criteria [11, 12]. This complication will be adjudicated and presented as VARC-3 type 2,3,4 bleeding.

Bioprosthetic valve dysfunction

1. **Endocarditis,** during 30 days, 1 year, 3 years, 5 years, or 10 years.
2. **Reoperation** (TAVR, SAVR, BAV paravalvular leakage closure), within 30 days, 1 year, 3 years, 5 years, or 10 years, according to VARC-3 criteria [10].
3. **Moderate/severe prosthesis-patient mismatch: EOA/body surface area** ≤0.85 cm2/m2 if BMI<30 kg/cm2 or <=0.70 cm2/m2 if BMI>=30 kg/cm2 at 30 days according to VARC-3 criteria.

Readmissions, clinical and paraclinical findings:

1. **Pacemaker implantation:** new pacemaker implantation either prophylactically before TAVI (<1 month before) or within 30 days, 3 years, 5 years, or 10 years following TAVI.
2. **Readmission for congestive heart failure:** within 30 days, 1 year, 3 years, 5 years, or 10 years. Definition: Adjudication by endpoint committee.
3. **AMI (Acute Myocardial Infarction)**: within 30 days, 1 year, 3 years, 5 years, or 10 years according to VARC-3 criteria [10]. Definition: Adjudication by endpoint committee.
4. **Revascularization by PCI (Percutaneous Coronary Intervention)** (not scheduled before TAVI) or **CABG (Coronary Artery Bypass Grafting)** (not scheduled before TAVI): within 30 days, 1 year, 3 years, 5 years, or 10 years according to VARC-3 criteria [10].
5. **Newly diagnosed atrial fibrillation/flutter**: within 30 days, 1 year, 3 years, 5 years, and 10 years according to VARC-3 criteria [10].
6. **Increase in renal creatinine level more than to ≥200%** (AKIN stage 2-3, VARC-3 criteria) or resulting in dialysis (AKIN stage 4) according to VARC-3 criteria: during admission and within 30 days [10].

B) Hemodynamic substudy, N=440

All outcomes will be evaluated by the hemodynamic core lab.

Co-primary outcome

1. EOA during a dobutamine stress test following TAVI.

Secondary outcomes

2. Cardiac output by thermodilution during a dobutamine stress test following TAVI.

C) MSCT-substudy, N expected to be 850 patients:

All outcomes will be evaluated by the MSCT core lab and echo core lab.

Co-primary outcome:

1. Leaflet thickening (hypoathenuated leaflet thickening = HALT) or reduced leaflet motion or thrombus assessed by MSCT at 1 month and 12 months

Secondary outcomes:

1. Commisural misalignment: mild, moderate, severe
2. LM misalignment: mild, moderate, severe
3. RCA misalignment: mild, moderate, severe
4. Depth of implantation (mm below annulus)

Subgroup analyses:

1. Severity of aortic regurgitation stratified according to level of annular calcium on MSCT (low/medium/high)
2. Mean gradient (aorta) stratified according to level of annular calcium on MSCT (low/medium/high)

D) CMR-substudy, N=166.

All outcomes will be evaluated by the CMR core lab.

Co-primary outcome

1. Aortic regurgitation fraction (ARF) and aortic regurgitation volume at ST-junction at follow-up (planned at 30 days).

Secondary outcomes

2. Effective orifice area
3. Mean and peak gradients
4. ARF and ARI in left ventricle outflow tract.

Subgroup analyses for main study:

The following subgroup analyses will be performed for the primary combined endpoint and for selected secondary endpoints:

Age (<75, ≥75 years)
Sex (Female, Male)
Known IHD (Yes/no)
Previous PCI (Yes/no)
LM-takeoff, distance from annulus (<10, ≥10 mm)
Annulus area (<430, 430-545, ≥545 mm^2)
LVEF (<50, >=50)
Anatomy (Tricuspid, bicuspid, ViV)

Missing data:

The number of subjects included in each analysis will be reported. If more than 5% of data is missing, and Cox regression analysis with adjustment for confounders is performed, multiple imputation will be used to replace missing data. In primary outcome and secondary outcome analyses, complete case analyses will be perfomed as described above.

Statistical software: STATA, R, and SAS are expected to be used for data analyses.
Monitoring: See separate plan for monitoring.