STATISTICAL ANALYSIS PLAN

SAFER-TAVI Trial

Secondary Access - Femoral or Radial in Transcatheter Aortic Valve Implantation

ClinicalTrials.gov: NCT06284837
HREC: 99382/Alfred-2023
Sponsor: The Alfred
Sites: The Alfred, Cabrini, Epworth

Companion document to: Protocol V3, dated 18 August 2025
SAP version: 1.0
SAP date: 11 May 2026

1. Purpose and scope

This Statistical Analysis Plan (SAP) supplements SAFER-TAVI Protocol V3.0 (dated 18 August 2025). The trial design, primary and secondary endpoints, sample size justification, randomisation method, endpoint definitions, DSMB arrangements, and safety reporting are specified in the protocol and are not duplicated here. This SAP specifies the analytical methods that will be applied to the locked database for the primary, secondary, subgroup, and sensitivity analyses, and the handling of intercurrent events and missing data. This SAP was finalised prior to database lock, before access to treatment-group outcome data, and before any comparative analysis of the primary endpoint.

2. Reference documents

- SAFER-TAVI Protocol V3, dated 18 August 2025 (HREC/99382/Alfred-2023)
- ClinicalTrials.gov registration: NCT06284837
- Généreux P, et al. Valve Academic Research Consortium 3. J Am Coll Cardiol. 2021;77:2717-2746
- Mehran R, et al. Standardized Bleeding Definitions for Cardiovascular Clinical Trials (BARC). Circulation. 2011;123:2736-2747

3. Patient characteristics

Baseline characteristics will be summarised by allocated arm, including patient demographics, anthropometric measurements, cardiovascular and non-cardiovascular comorbidities, concomitant medications, baseline laboratory parameters, echocardiographic parameters, TAVI risk scores, and clinical features. Continuous variables will be summarised as mean (SD) or median (IQR) as appropriate; categorical variables as n (%). No statistical testing will be performed.

4. Endpoints - analytical clarifications

Study endpoints are defined in Protocol V3 section 2.2. The following clarifications apply for analysis:

4.1 Primary endpoint

Composite of clinically relevant bleeding (BARC ≥2) or any vascular complication (VARC-3, major or minor) within 30 days of the TAVI procedure. A patient is counted as having the primary endpoint if either component occurs. Patients experiencing both components will be counted once in the primary composite analysis. Bleeding and vascular complications will also be analysed and reported separately as individual component endpoints.

4.2 Secondary endpoints

Secondary endpoints listed in the protocol will be grouped for reporting as follows.

Bleeding endpoint component analysis

- Any BARC type ≥2 bleeding (component of the primary composite endpoint)
- By severity (BARC category)
    - BARC 2
    - BARC 3 (overall, and where event numbers permit, separately as 3a / 3b / 3c)
    - BARC 4
    - BARC 5
- By access site
    - Primary access site bleeding (any BARC ≥2; and by BARC category)
    - Secondary access site bleeding (any BARC ≥2; and by BARC category)
    - Non-access-site bleeding (any BARC ≥2; and by BARC category)

Vascular complications endpoint component analysis

- Any vascular complication, defined as VARC-3 major or minor vascular complication (component of the primary composite endpoint)
- By severity
    - Major VARC-3 vascular complication
    - Minor VARC-3 vascular complication
- By access site
    - Primary access site vascular complication (major; minor; any)
    - Secondary access site vascular complication (major; minor; any)

Secondary access site composite endpoint

- BARC type ≥2 bleeding or VARC-3 major or minor vascular complication attributed to the secondary access site within 30 days.

Other secondary endpoints (as listed in Protocol V3 section 2.2):

- All-cause death at 30 days
- Stroke at 30 days (VARC-3 definition; ischaemic, haemorrhagic, and unspecified reported separately)
- Myocardial infarction at 30 days
- Major adverse cardiovascular events (composite of death, stroke, MI) at 30 days
- Length of hospital stay post-procedure (days)
- Total procedure duration (minutes)
- Radiation dose
- Conversion to alternative vascular access site (radial-to-femoral or femoral-to-radial)
- Tertiary access site used to manage a vascular complication
- Failure to perform final angiogram of the primary access site at completion of TAVI

5. Analysis population

Intention-to-treat (ITT, primary analysis population). All randomised patients will be analysed according to their allocated treatment group, irrespective of the secondary access site attempted, used, or successfully completed. Patients with missing 30-day primary endpoint data will be handled according to the missing data plan in Section 11

Modified intention-to-treat (mITT). All randomised patients who undergo the index transfemoral TAVI procedure, analysed according to randomised allocation. This will be used for sensitivity analysis of the primary endpoint as specified in Section 10.

As-treated population. All randomised patients in whom any procedural attempt is made, analysed according to the secondary access site first attempted at TAVI commencement (rather than randomised allocation). Used for the as-treated sensitivity analysis (Section 10).

6. General statistical considerations

- All tests two-sided; $\alpha=0.05$ for the primary endpoint
- No formal multiplicity adjustment across secondary endpoints; reported with 95% confidence intervals and interpreted as supportive or hypothesis-generating
- Continuous variables: mean (SD) if normal distribution; median (IQR) otherwise
- Categorical variables: n(%)
- Confidence intervals: 95%, two-sided
- P-values reported to two decimal places or as $P<0.001$
- Software: Stata 18.0 (StataCorp, College Station, TX)

7. Primary analysis

The primary analysis will compare the proportion of patients experiencing the primary composite endpoint within 30 days between treatment arms in the ITT population. All randomised patients will be analysed according to their original allocation, irrespective of the secondary access site attempted, used, or successfully completed.

Patients who die before 30 days without a recorded primary endpoint event will be classified as not having experienced the primary endpoint; sensitivity analyses will (a) classify these deaths as primary endpoint events, and (b) separately exclude these patients from the analysis (see Section 9). Patients with missing 30-day endpoint data will be handled according to the missing data plan in Section 10.

The primary treatment effect will be summarised as a risk ratio for transradial versus transfemoral secondary access, with 95% confidence interval. The absolute risk difference (transradial minus transfemoral) with 95% confidence interval will also be reported. Pearson's χ^2 test, or Fisher's exact test where any expected cell count is less than 5, will be reported as the corresponding P-value. A risk ratio less than 1.0 will favour transradial secondary access.

8. Secondary analyses

All secondary endpoints will be analysed in the ITT population using methods appropriate to the variable type:

- **Binary endpoints:** Effect sizes will be reported as risk ratios and risk differences with 95% confidence intervals. The P-value for between-group comparison will be derived from Pearson's χ^2 test, or Fisher's exact test where any expected cell count is less than 5.
- **Continuous endpoints:** Continuous variables will be summarised by allocated arm using mean ± SD or median (IQR) as appropriate. Between-group treatment effects will be reported as mean differences with 95% confidence intervals (using the two-sample t-test) for approximately normal variables, or as median differences with bootstrap 95% confidence intervals (with the Mann-Whitney U test for between group comparison) for variables with markedly skewed distributions. Approximate normality will be assessed by visual inspection of histograms and Q-Q plots.
- **Time to event endpoints:** Clinical secondary endpoints (30-day mortality, stroke, myocardial infarction, MACE) are assessed at a fixed 30-day time point and will be analysed primarily as binary endpoints per the methods above. Kaplan-Meier curves over the 30-day follow-up window may be presented as supplementary visualisations to display the timing of events; the log-rank test and Cox proportional hazards regression (with hazard ratios and 95% confidence intervals, and the proportional hazards assumption assessed by scaled Schoenfeld residuals) may be reported as supportive analyses.

No multiplicity adjustment is applied across secondary endpoints. Findings are reported with point estimates and 95% confidence intervals, and are interpreted as supportive or hypothesis-generating rather than confirmatory.

9. Subgroup analyses

Pre-specified subgroup analyses of the primary endpoint will be performed for:

- Sex (male vs female)
- Age (<75 vs ≥75 years)
- BMI (<30 vs ≥30 kg/m²)

- Diabetes (yes or no)
- Peripheral vascular disease (yes or no)
- Baseline anticoagulation (yes vs no)
- Baseline chronic kidney disease (yes or no)

Subgroup-specific risk ratios with 95% confidence intervals will be presented in a forest plot, with absolute risk differences also reported where appropriate. Evidence of heterogeneity of treatment effect will be assessed using treatment-by-subgroup interaction tests. Interaction estimates, 95% confidence intervals, and P-values will be reported where estimable. Subgroup analyses will be considered exploratory, with no adjustment for multiplicity, and will be interpreted cautiously.

10. Sensitivity analyses

- **Missing primary endpoint data:** In the case of missing primary endpoint data, scenario analyses will be performed assuming (a) all patients with missing primary endpoint data did not experience the endpoint (best-case for the null), (b) all patients with missing primary endpoint data experienced the endpoint (worst-case for the null), and (c) extreme bounding by assigning all missing in the transradial arm as events and all missing in the transfemoral arm as non-events, and the reverse.
- **Death before 30 days:** The primary analysis will classify patients who die before 30 days without a prior primary endpoint event as not having experienced the primary endpoint. Sensitivity analyses will classify these deaths as primary endpoint events and, separately, exclude these patients from the analysis.
- **Modified ITT analysis:** The primary endpoint will be analysed in the modified ITT population (randomised patients who undergo transfemoral TAVI, analysed according to randomised allocation)
- **As-treated analysis:** The primary endpoint will be analysed according to the secondary access site first attempted at TAVI commencement.
- **Site-adjusted analysis:** The primary endpoint will be analysed with adjustment for site to assess robustness of the treatment effect estimate to between-site variation.

11. Missing data

Missing primary endpoint data are expected to be low given the 30-day follow-up window and registry-nested data capture via the ACE-TAVI database. Missingness will be reported per arm in the CONSORT flow diagram and the Results.

- **Primary analysis:** complete-case (patients with a recorded 30-day primary endpoint)
- **Sensitivity analysis:** best-case/worst-case analysis as described in section 9.
- **Missing baseline covariates:** will not be imputed. The number of patients with missing data for any baseline variable will be reported in Table 1. For subgroup analyses, patients with missing subgroup-defining variables will be excluded from the relevant subgroup, with the number excluded reported.

12. Reporting

- CONSORT reporting standard, including a flow diagram of randomisation, treatment received, follow-up, and analysis
- Baseline characteristics tabulated by allocated arm, without statistical testing
- Primary, secondary, subgroup & sensitivity analyses presented in line with this SAP