IMPROVE trial statistical analysis plan for morphological analyses

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This document details a statistical analysis plan for a set of analyses to investigate the association between six morphological features of ruptured abdominal aortic aneurysm (rAAA) and 30-day outcomes in patients randomised to the IMPROVE trial. Analyses will generally be observational, i.e. not based on the randomised strategies. A paper will be drafted based on the following proposed analyses.

1) Study population

   The study population for these analyses is defined as all patients randomised in the IMPROVE trial with a confirmed diagnosis of ruptured AAA, who had a pre-operative CT scan and who received an operation (EVAR, Open repair or EVAR converted to Open). Patients in the IMPROVE trial whose final diagnosis was not rAAA (e.g. symptomatic AAA who receive a semi-elective procedure) will therefore be excluded from these analyses. Ruptured iliac aneurysms will also be excluded. Patients will be analysed according to the operation that was commenced.

2) Outcomes

   The primary outcome will be 30-day mortality, with a secondary outcome of any intervention within 30 days of randomisation. Since both these outcomes occur within 30 days of randomisation, both are assumed to be aneurysm-related.

3) Descriptive statistics

   Patient characteristics (e.g. age, sex, Hardman index) and all morphological variables, including derived variables such as within / without Instructions For Use (see Section 4) will be presented for the study population stratified by treatment received and 30-day mortality. Means and standard deviations will be used to summarize continuous variables, unless the variable is highly skewed in which case a median and interquartile range will be presented. Numbers and percentages will be presented for categorical variables. Clinically relevant categories will be presented.

4) Analysis according to Instructions For Use (IFU) guidelines

   We will investigate whether outcomes vary for rAAAs within or without liberal manufacturer's IFU. The definition for IFU derives from Schanzer A et al, Circulation 2011. For a patient to be within liberal IFU, <u>all</u> of the following three anatomical requirements must be met: aortic neck diameter at lowest renal artery < 32mm, aortic neck length ≥10mm, distal aortic neck β-angulation < 60^o.

   For each of the outcomes, a logistic regression model will be fitted, separately by operation received, with IFU, age, gender, Hardman Index, lowest recorded blood pressure and randomised group used as covariates. Adjusting for randomised group should account for some of the patient selection present when cross-overs occur. The adjusted odds ratio of within versus without IFU will be reported together with a p-value (calculated using Wald's test) and 95% confidence interval.

   In a sensitivity analysis we will adjust for type of anaesthesia in the analysis of patients who received EVAR. We will also consider the interaction between IFU and sex to assess whether being outside IFU guidelines has a different effect on 30-day outcomes for women than men. The interaction p-value will be presented along with the individual subgroup odds ratios and confidence intervals.

For a more powerful analysis we will also combine the two treatment groups and present the overall (adjusted) effect of IFU on 30-day outcomes in all rAAA patients irrespective of treatment received

5) Analysis of six key morphological variables

Six key morphological variables have been chosen a-priori for further investigation, these being a) aortic neck length, b) aortic neck diameter at the distal renal artery, c) maximum AAA diameter, d) neck conicality e) proximal aortic neck α-angulation, f) maximum common iliac diameter. These will be examined separately and then in one overarching multivariate analysis, which includes all 6 variables.

Proximal aortic neck angulation is the α-angle defined by Ghatwary et al. Distal aortic neck angulation was defined by Schanzer et. al as the angle calculated between the lowest renal artery, the origin of the aneurysm, and the aortic bifurcation. Most clinicians find the α–angle more useful than the β–angle (even though the β–angle is used to define IFU). The correlation between α and β neck angulation will be assessed and a sensitivity analysis conducted using β- instead of α–angulation if necessary.

Neck conicality was defined by Schanzer et. al as a binary variable with a conical neck being an aortic diameter 15mm below the lowest renal artery that is 10% larger than the aortic diameter at the lowest renal artery. However, this definition was applied even if the neck was less than 15mm in length (i.e. the diameter measured was below the neck). Therefore, in this analysis, we will instead use the ratio of the most distal neck diameter measured (D1) to the diameter at the distal renal artery (D2) relative to the centre line distance between these diameter measurements (L). The relative change per unit length is then calculated as (D1/D2 – 1) / L. This assumes the rate of diameter change stays constant no matter how far apart the measurements are taken. As some patients will have more than one neck diameter taken at different distances from their lowest renal artery this assumption can be investigated further in these patients. Categorical data for the simpler estimate of conicality (D1-D2)/L, which does not consider neck diameter also will be presented.

Each of these variables will be treated as continuous covariates in the regression models. The same analyses will be conducted as specified in the IFU analyses (see above), but with the binary IFU variable replaced by the six key morphological variables. All analyses will be adjusted as previously described and an interaction with sex will be investigated in all six variables. Odds ratios will be presented for each variable based on a 1 standard deviation increase to allow a fairer comparison of the relative importance of each morphological variable.

6) Further Issues

Missing data may be present in both the explanatory covariates (patient characteristics and morphological variables) and the outcomes (e.g. re-interventions in 30-days). Therefore, all missing data will be multiply imputed before analysis. The imputation model will include all morphological variables and relevant patient characteristics as well as outcomes.