ENDORSE-HF – ISRCTN registry

Statistical analysis plan

Sample size

A 1:1 ratio was established for the two trial groups. The required sample size was determined based on primary endpoints, considering three outcome types: (a) numerical continuous variables (e.g., changes in weight, echo B-lines, IVC diameter, NT-proBNP); (b) numerical scores (e.g., EVEREST scores); (c) proportions of safety-related outcomes (e.g., hyponatremia or hypokalemia).

The R package "*webPower*" v. 0.9.0, applying J. Cohen's theory, was utilized for the calculations involving proportions and numerical continuous variables. A medium effect size was assumed with d=0.6 and h=0.6 for differences in numerical outcomes and observed proportions, respectively; two-sided tests were employed with alpha=0.05 and power=0.8. The resultant sample size indicated a need for 45 subjects in each group. A 10% dropout adjustment was applied, leading to initial randomization of 50 patients in each group.

For numerical scores, the R package "*MKpower*" v. 0.7 (using Monte Carlo simulation for empirical power calculations) confirmed that for a 1-point difference with a 1.5-point standard deviation in two samples of 50 subjects each, the resultant power was > 0.9.

Randomization was performed with the R 4.2.2 package "*blockrand*" version 1.5.

Data analysis

Descriptive statistics included observed frequency counts with corresponding percentages for categorical variables, and mean ± standard deviation for numerical variables, irrespective of their distribution. Normality was assessed using the Kolmogorov-Smirnov test. When the distribution of values exhibited significant asymmetry, the median with inter-quartile range (i.e., Q1 and Q3) were additionally provided as descriptive statistics.

The chi-square statistical test (either asymptotic or using Fisher's exact test) was applied to assess statistical significance in the observed proportions' differences among categorical variables. Non-parametric tests, specifically the Mann-Whitney U test, were employed for comparing numerical value distributions in independent groups.

Non-parametric Wilcoxon signed rank test was applied for paired samples of values.

The statistical analysis was conducted at a confidence level of 95% and a significance level of 5%. All reported probability values were two-tailed.

Statistical analyses were performed using IBM SPSS v. 20 and R v. 4.3.1 packages.