**Study Protocol and Statistical Analysis Plan**

**Study Protocol**

Background: Minimally invasive cardiac surgery-coronary artery bypass grafting (MICS-CABG) has emerged as a safe alternative to standard cardiac surgery. However, treatment preferences can decrease the generalizability of RCT results to the clinical population (i.e., reduce external validity) and influence adherence to the treatment protocol and study outcomes (i.e., reduce internal validity). However, this has not yet been properly investigated in randomized trials with consideration of treatment preferences.

Study Design: In this study, patients with a preference will be allocated to treatment strategies accordingly, whereas only those patients without a distinct preference will be randomized. The randomized trial is a 248-patient controlled, randomized, investigator-blinded trial. It is designed to compare whether treatment with MICS-CABG is beneficial in comparison to CABG. This study is aimed to establish the superiority hypothesis for the physical component summary (PCS) accompanied by the non-inferiority hypothesis for overall graft patency. Patients with no treatment preference will be randomized in a 1:1 fashion to one of the two treatment arms.

The primary efficacy endpoints are the PCS score at 30 days after surgery and the overall patency rate of the grafts within 14 days after surgery. Secondary outcome measures include the PCS score and patency rate at different time points. Safety endpoints include major adverse cardiac and cerebrovascular events, complications, bleeding, wound infection, death, etc.

Conclusions: This trial will address essential questions of the efficacy and safety of MICS-CABG. The study will also address the impact of patients' preferences on external validity and internal validity.

**Statistical Analysis Plan**

Statistical analyses will be performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, N.Y., USA). First, a descriptive analysis will be conducted. Normally distributed continuous variables will be expressed as the mean and standard deviation, and nonnormally distributed continuous variables will be expressed as the median and interquartile range (IQR). Categorical variables will be expressed as percentages.

The primary efficacy endpoint will be assessed in the per protocol population and the intention-to-treat (ITT) population. Statistical significance is needed for both primary endpoints. Therefore, no formal adjustment of the significance level of the elementary hypothesis tests is necessary. For the primary efficacy endpoint PCS at one month after surgery, the superiority of MICS-CABG to OPCABG could be claimed if the lower limit of the 95% CI (for the difference in progression-free survival [PFS] between groups) is greater than 2. For the other coprimary efficacy endpoint, namely, the overall patency rate at two weeks after surgery, non-inferiority of MICS-CABG to OPCABG could be claimed if the lower limit of the 95% CI (for the difference in patency rate between groups) is greater than −6%.

To explore the impact of patients' preference on external validity, the participation rate and the randomization refusal rate will be analyzed. The differences in baseline characteristics between the random cohort and the preference cohort will be compared to assess if a specific patient group has accepted randomization. To explore the impact of patients' preference on internal validity, the proportion of patients lost to follow-up will be analyzed. To explore the impact of patients' preference on primary outcomes, we will examine treatment-specific differences between the

preference and randomization groups. In addition, we will make comparisons (1) between randomized MICS-CABG and preference MICS-CABG and (2) between randomized sternotomy CABG and preference sternotomy CABG to explore the impact of preference on outcome assessment.

The chi-squared test will be used to examine the differences in binary secondary outcomes (e.g., graft patency rate at different time points and secondary surgery). Kaplan-Meier survival analysis will be employed for timed endpoints such as MACCE. The t test and Mann–Whitney U test will be used to examine the differences in continuous secondary outcomes (e.g., SF-36 at different time points, mechanical ventilation time, hospitalization costs and postoperative hospital stay). The level of significance is set at $\alpha = 0.05$.