Statistical Analysis Plan for the BOTTOMLINE-CS Trial
Finalized on Jan 31, 2024
By Lingzhong Meng, Zhao Zhang, Daniel Sessler, and Ziyue Liu

Trial title: Multisite Tissue Oxygenation Guided Perioperative Care to Reduce Composite Complications in Cardiac Surgical Patients: the BOTTOMLINE-CS trial (**BOTTOMLINE-CS** = **B**etter **O**utcome **T**hrough **T**issue **O**xygenation **M**onitoring **L**inked with **IN**t**E**rvention in **C**ardiac **S**urgery)
ClinicalTrials.gov NCT04896736
Purpose of this document: To establish a full statistical analysis plan prior to data unblinding.

Manuscript title (proposed, subject to revision): Tissue oxygenation-guided care in off-pump coronary bypass grafting

Short Title: BOTTOMLINE-CS trial

Trial site/Sponsor: Tianjin Chest Hospital

Chief Investigators: Drs. Jiange Han, Zhigang Guo, and Lingzhong Meng

Co-Investigator: Dr. Daniel Sessler

Statisticians: Dr. Ziyue Liu (Associate Professor of Biostatistics & Health Data Science, Indiana University School of Medicine, Indianapolis, Indiana, USA)

Steering Committee

- Dr. Jiange Han, Tianjin Chest Hospital, Tianjin University
- Dr. Zhigang Guo, Tianjin Chest Hospital, Tianjin University
- Dr. Daniel Sessler, Cleveland Clinic
- Dr. Lingzhong Meng, Indiana University School of Medicine (Yale University School of Medicine at the time of trial registration)

Data and Safety Monitoring Board (DSMB)

Dong-Xin Wang, M.D., Ph.D. (Potential chair)
Professor and Chair
Department of Anesthesiology and Critical Care Medicine
Peking University First Hospital
8 Xishiku Street
Beijing, 100034
China
Tel: 86 10 83572784
email: wangdongxin@hotmail.com

Alparslan Turan, M.D.
Professor and Vice-chair
Department of Outcomes Research
Cleveland Clinic
9500 Euclid Ave - P77
Cleveland, OH 44195
Tel: 216-445-9857
Mobile: 216-217-2312
email: turana@ccf.org

Karsten Bartels, MD, PhD, MBA
Professor and Vice Chair for Research
Robert Lieberman, MD, PhD Endowed Chair in Anesthesiology
Department of Anesthesiology
University of Nebraska Medical Center
984455 Nebraska Medical Center
Omaha, NE 68198-4455
karbartels@unmc.edu

Introduction

Off-pump CABG is performed to improve cardiac blood flow without the use of a cardiopulmonary bypass machine which may provoke complications including stroke, renal failure, and blood loss. Despite potential benefits, off-pump surgery can cause complications including graft occlusion, myocardial infarction, and neurocognitive deficits. The prevalence of such complications varies widely in the literature, with some studies suggesting it ranges from 5% to 30%, influenced by patient comorbidities and surgical technique. Continuous monitoring of tissue oxygenation may reduce the incidence of such complications by enabling the early detection and correction of tissue hypoperfusion. This approach could lead to more tailored and responsive patient management during and after surgery, potentially improving postoperative outcomes and reducing the overall complication rate associated with off-pump CABG.

Objectives and Endpoints

The following text was from the original protocol registered before the start of the trial.

Primary objective

To establish whether the care guided by cerebral and somatic tissue oxygen saturation monitoring compared to usual care reduces perioperative complications in patients having off-pump coronary artery bypass grafting surgery within 30 days of randomization.

Primary outcome measure

The primary outcome is a collapsed (one or more) composite of the following complications with a Clavien-Dindo grade II or greater arising within 30 days of randomization.

- Brain complications (postoperative delirium, cognition decline, stroke);
- Cardiac complications (non-fatal cardiac arrest, myocardial injury, heart failure, new-onset symptomatic ventricular arrhythmia);
- Respiratory failure;
- Renal complications (AKI stages II and III);
- Infectious complications (surgical site infection involving deep surgical site and/or organ/space, pneumonia, laboratory confirmed bloodstream infection, infection with source uncertain, and sepsis);
- Death.

Secondary objectives

To determine whether the care guided by $SctO_2$ and $SstO_2$ monitoring reduces various complications and duration of hospitalization.

Secondary outcome measures

- Components of the primary composite

- Atrial fibrillation, assessed within postoperative 30 days
- Postoperative delirium assessed from postoperative day 1 to 5
- Postoperative cognitive decline as a continuous variable assessed before surgery and on postoperative days 5 and 30
- Length of hospital stay defined in days from POD 1 to until hospital discharge excluding death

Safety Measures

The following description were based on the original protocol.

Adverse Events (AE)

An AE is any untoward medical occurrence in a subject to whom an intervention has been administered, including occurrences which are not necessarily caused by or related to that intervention. An AE can therefore be any unfavorable and unintended sign, symptom or disease temporarily associated with study activities. However, this study does not involve an investigational medical device, and all trial interventions are already in routine clinical use for patients undergoing a surgical procedure. The safety of the intervention will be monitored by recording acute adverse events at 24 hours and 30 days after randomization as a trial outcome. These events will be monitored at intervals by the DMEC and will be recorded separately as an AE on the CRF.

Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined as an untoward occurrence that:

- results in death
- is life-threatening
- requires hospitalization or prolongation of existing hospitalization significantly beyond normal inpatient stay for the surgery concerned
- results in persistent or significant disability or incapacity

An SAE occurring to a research participant should be reported to the sponsor where in the opinion of the Chief Investigator the event was:

- Related – that is, it resulted from administration of any of the research procedures, and
- Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

This study is an investigation of a perioperative intervention. It is expected that patients undergoing major surgery will suffer complications, with consequences up to and including death. Only complications considered by the Chief Investigator to be *related to the use of study procedures* and not a typical surgical complication should be reported as SAEs.

Study Design

The pragmatic trial design selected for the BOTTOMLINE-CS trial is rooted in its focus on evaluating the effectiveness of multisite tissue oxygen saturation monitoring in a real-world clinical setting. This approach emphasizes the applicability of the trial outcomes to typical clinical scenarios by ensuring that the study conditions closely mimic everyday practice. Unlike explanatory trials, which often employ strict participant selection and controlled conditions to determine efficacy under ideal circumstances, a pragmatic trial embraces broader eligibility criteria and diversity in participant characteristics, mirroring the variability seen in daily medical care. Furthermore, the implementation of interventions and monitoring within the usual care processes enables the assessment of the intervention's practical impact, including its feasibility, adherence, and overall utility in routine clinical workflows. The findings from such a pragmatic study are likely to by generalizable and thus informed clinical decision-making.

Sample Size Determination

The following paragraph was from the original protocol registered before the start of the trial.

"We assume that the incidence of the composite 30-day complication in the regular care group will be 30% versus 24% in the multisite tissue oxygenation-guided perioperative care group, a 20% relative reduction representing a clinically meaningful and important treatment difference. Based on one-sided Z-test group sequential testing with 3 stages (two interim analyses) and boundary values calculated from O'Brien-Fleming Analog alpha (efficacy) and non-binding beta spending (futility) functions, a total of 927 patients will provide 80% power for detecting a 6% absolute reduction from 30% to 24% at a target alpha-level of 0.05. We plan to recruit 980 patients per group considering a potential ~5% of patients who drop out or have missing data."

Interim Analysis

The following is from the original protocol established before the start of the trial.

"For the interim analyses, O'Brien-Fleming Analog alpha and beta spending functions are used (Table 1, Figure 1). Assuming two interim analyses occur after 33% and 67% of total patients are enrolled and their primary outcome are observed, the nominal alpha levels to reject the null hypothesis for efficacy or fail to reject the null hypothesis for futility are calculated as follows.

Table 1. Critical values and alpha levels for two interim analyses and final analysis

Stage	Target Information (%)	N1	N2	Efficacy Boundary (Critical Z-value scale)	Alpha Spent	Futility Boundary	Beta Spent	Power
1	33%	309	309	±3.710	0.0002		0	-

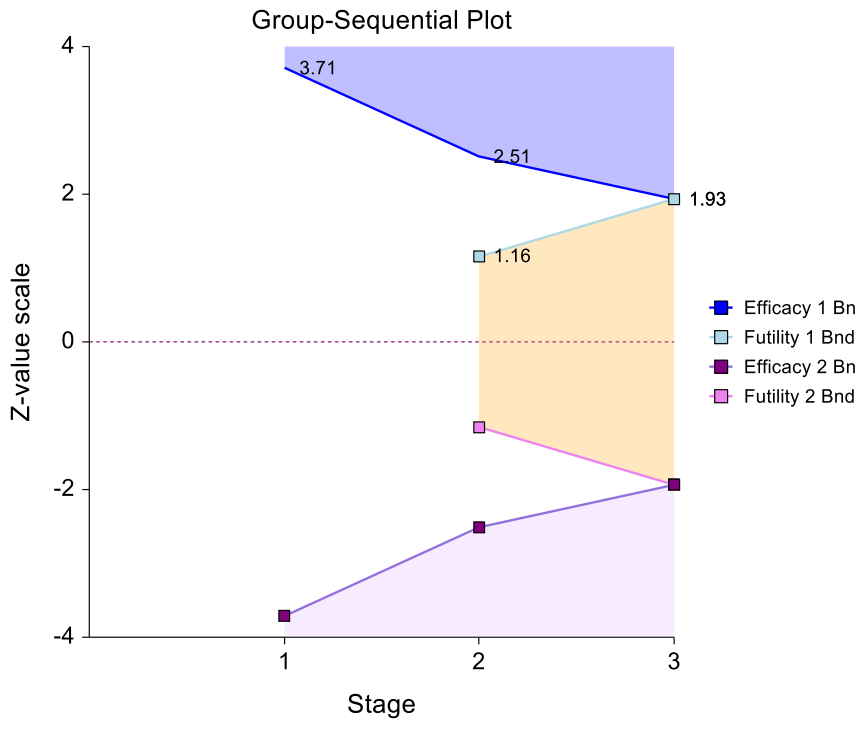
2	67%	618	618	±2.511	0.0119	±1.157	0.0828	-
3 (final)	100%	927	927	±1.932	0.0379	±1.932	0.1172	0.803

Note: O'Brien-Fleming Analog alpha and beta spending function is adopted

The trial could be stopped for efficacy if the efficacy boundary is crossed at first (Z<-3.71, alpha < 0.0002) or second (Z < -2.51, alpha < 0.0119) interim analysis, respectively (Figure 1). We will evaluate the combined outcome incidence at the first intermediate analysis and increase sample size at that point if it proves to be lower than anticipated.

If the futility boundary is not crossed (-1.16 < Z < 1.16) at second interim analysis, and the study will continue if there is no safety concern. If needed, the sample size of the study might be re-estimated by the DSMB statistician using the observed aggregated data (not the treatment effect) using the conditional power analysis at the interim analysis stage. Since the futility boundary is assumed non-binding, even it is crossed, the DSMB will make recommendation on whether or to stop the trial taking in consideration the totality of accumulated evidence, including the patient accrual rate, observed treatment effect, etc. The whole evaluation will be conducted in a blinded manner.

Figure 1. Group sequential plot



”

Two interim analyses were performed as per the protocol. No stopping rules were triggered and the DSMB recommended continuing at each analysis. Therefore, the trial proceeded and

finished.

Analysis Populations

Intention-to-Treat (ITT) population: All randomized patients having at least some outcome data will be included in the analysis in the groups to which they were randomized, regardless of the care they received.

Per-Protocol (PP) population: This analysis includes patients, as long as they have outcome data, who completed the study in accordance with the protocol. The patient in the intervention group is determined to have received the intended intervention if their NIRS measurements during the intervention time window are within 90-110% of the baseline value for 80% of the time. The purpose is to assess the effect of the intervention under optimal conditions.

Documentation of Deviations:

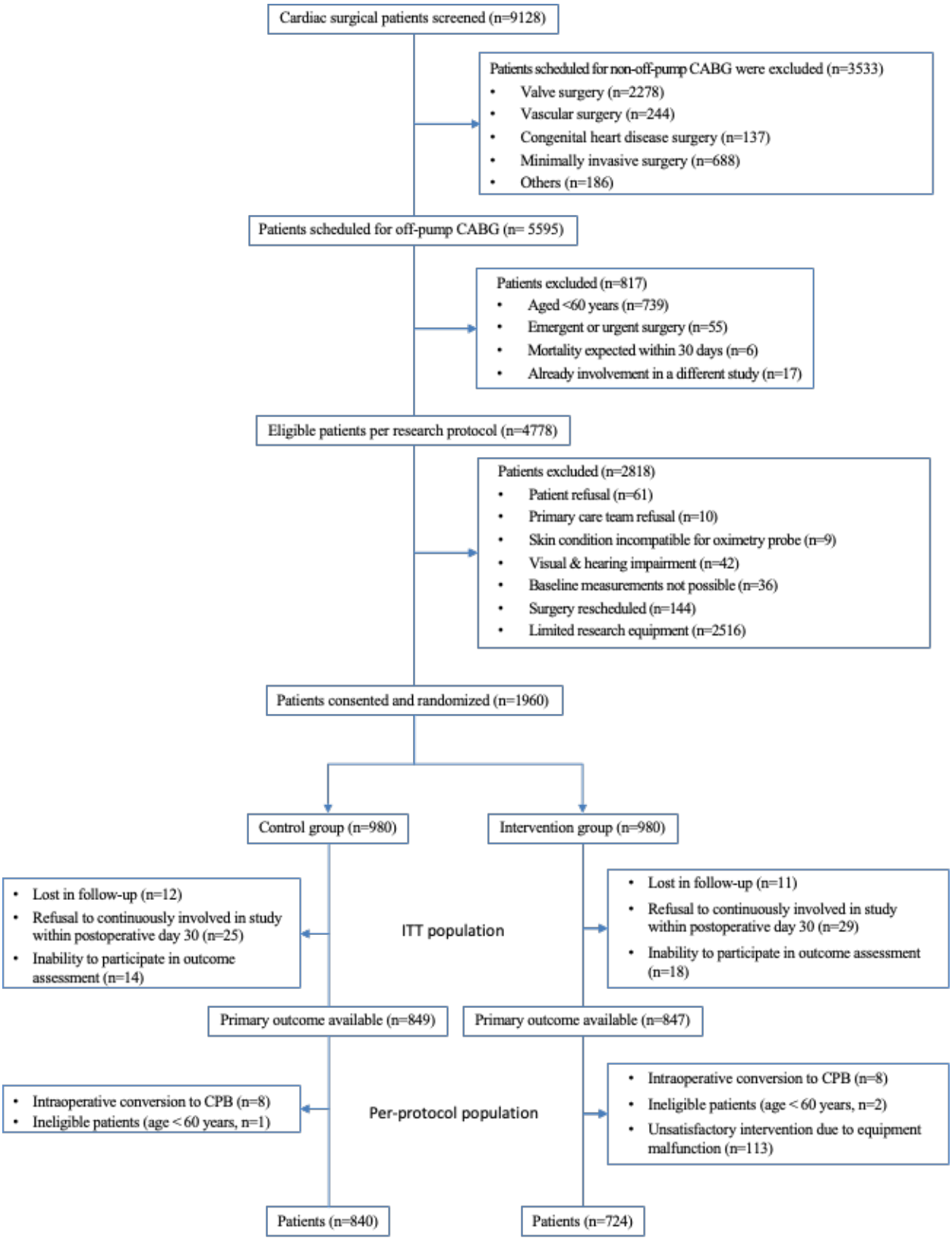
- All protocol deviations will be documented in a protocol deviation log, which will be reviewed regularly by the trial steering committee to ensure consistency in applying the exclusion criteria.

- The rationale for excluding each participant will be documented in detail.

The primary analyses of the primary and secondary outcomes will be based on the ITT population. The per-protocol population will be used in the safety and sensitivity analysis.

Note: Patients who were randomized and treated, but lost to follow up, will be included to the time of dropout. Patients who withdrew their consent to participate the study will not be included in analysis.

The CONSORT diagram as of January 26, 2024 is presented as follows. The last patient was recruited on December 27, 2023. At the time of formulating this statistical analysis plan, the follow-up per research protocol is ongoing. We anticipated to finish patient follow-up in early February 2024.


Cardiac surgical patients screened (n=9128)
Patients scheduled for non-off-pump CABG were excluded (n=3533)
Valve surgery (n=2278)
Vascular surgery (n=244)
Congenital heart disease surgery (n=137)
Minimally invasive surgery (n=688)
Others (n=186)
Patients scheduled for off-pump CABG (n= 5595)
Patients excluded (n=817)
Aged <60 years (n=739)
Emergent or urgent surgery (n=55)
Mortality expected within 30 days (n=6)
Already involvement in a different study (n=17)
Eligible patients per research protocol (n=4778)
Patients excluded (n=2818)
Patient refusal (n=61)
Primary care team refusal (n=10)
Skin condition incompatible for oximetry probe (n=9)
Visual & hearing impairment (n=42)
Baseline measurements not possible (n=36)
Surgery rescheduled (n=144)
Limited research equipment (n=2516)
Patients consented and randomized (n=1960)
Control group (n=980)
Intervention group (n=980)
Lost in follow-up (n=12)
Refusal to continuously involved in study within postoperative day 30 (n=25)
Inability to participate in outcome assessment (n=14)
ITT population
Lost in follow-up (n=11)
Refusal to continuously involved in study within postoperative day 30 (n=29)
Inability to participate in outcome assessment (n=18)
Primary outcome available (n=849)
Primary outcome available (n=847)
Intraoperative conversion to CPB (n=8)
Ineligible patients (age < 60 years, n=1)
Per-protocol population
Intraoperative conversion to CPB (n=8)
Ineligible patients (age < 60 years, n=2)
Unsatisfactory intervention due to equipment malfunction (n=113)
Patients (n=840)
Patients (n=724)

We will evaluate the baseline homogeneity using absolute standardized differences. For both primary and secondary analyses, we will correct for baseline factors with ASDs above the threshold determined by the following equation: 1.96 × sqrt((nt+ nc)/(nt*nc)).1 where t is treatment and c is control.

Analysis of the primary outcome

The primary outcome will be evaluated using logistic regression to estimate the odds of postoperative composite complications. A one-sided Z-value < -1.932 will be considered statistically significant.

A sensitivity analysis evaluating an average relative effects model. (Edward J Mascha, Daniel I Sessler. Statistical grand rounds: design and analysis of studies with binary- event composite endpoints: guidelines for anesthesia research. Anesth Analg. 2011 Jun;112(6):1461-71. doi: 10.1213/ANE.0b013e31821796d3.)

Analysis of the secondary outcomes

For the secondary analysis of continuous and categorical outcomes in the BOTTOMLINE-CS trial, the following details will outline the statistical methods that will be used. All analyses will be adjusted for unbalanced baseline characteristics and reported with 95% confidence intervals.

- Continuous outcomes will be analyzed using linear regression or generalized linear models as appropriate, depending on the distribution of the data and the study design.
- Composite secondary outcomes will be analyzed using the same approach as the primary outcome.
- Categorical outcomes will be analyzed using logistic regression for binary outcomes or chi-squared tests for categorical variables with more than two categories.
- Bonferroni-Holm's method will used for multiplicity adjustment for the p values of those secondary outcomes.

Safety analysis

- This analysis will list all adverse events and serious adverse events that were related to the research procedures.
- The analysis will include rows for each type of adverse event and columns for the intervention group, control group, number of events, percentages, and a comparison column if appropriate.

Sensitivity Analysis

Patients who withdrew from the trial voluntarily will not be included in analysis.

In the sensitivity analyses, we will assess the robustness of the trial findings. These analyses deal with the patients who did not have outcome data and the per-protocol population instead of ITT population. The plan for conducting sensitivity analyses in the BOTTOMLINE-CS trial are outlined as follows:

Missing Data:

- In the analyses of the primary and secondary outcomes as detailed above, we will exclude patients without outcome data. This approach corresponds to missing completely at random (MCAR).

- Under the missing at random (MAR) assumption, we will use Markov Chain Monte Carlo (MCMC) for multiple imputation approach with 20 imputed copies. Standard multiple imputation methods will be adopted.

- Under the missing not at random (MNAR) assumption, we will use the following methods.

    - Best-case and worst-case scenario analysis: For binary outcomes, we will impute all missing outcomes as successes in the intervention group and failures in the control group for the best-case scenario and the opposite for the worst-case scenario.

    - Pattern-mixture models: These models will be used to explore the impact of different missing data patterns on the results.

    - Selection models: We will fit models that make specific assumptions about the mechanism of missingness, such as logistic regression models that include a term for whether data are missing or observed.

Analysis based on the per-protocol population

The above specified analyses for the primary and secondary outcomes will be repeated using the per-protocol population.

Reporting of Sensitivity Analyses:

- Results will be reported focusing any changes in significance or the magnitude of the treatment effect compared to the results of the primary analyses specified above.

- A narrative will be provided to explain the implications of the sensitivity analyses findings in the context of the trial conclusions.

Subgroup Analyses

- The outcomes targeted in the subgroup analyses include all primary and secondary outcomes. Interactions between the intervention and primary outcome will be evaluated for each subgroup. Odds ratio for the primary outcome, as a function of sub-group, will be presented as a forest plot with 95% confidence intervals.
- The subgroup analyses will be based on the following variables:
    - Age (< 65 years vs. ≥ 65 years)
    - Sex (male vs. female)
    - BMI (< 30 kg/m^2 vs. > 30 kg/m^2)
    - Blood component transfusion during the study period (yes vs. no)
    - Duration of surgery (< 3 hours vs. > 3 hours)
    - Temperature during surgery (based on each patient's median value, < 35.5 °C vs. > 35.5 °C)
    - Cerebral tissue oxygen saturation (based on each patient's median value, <70% vs. >/= 70%)
    - Somatic tissue oxygen saturation (based on each patient's median value, <75% vs. >/= 75%)
    - Cardiac output index (based on each patient's median value, <3 $L/min/m^2$ vs. >/= 3 $L/min/m^2$)
    - Systemic vascular resistance (based on each patient's median value, <1000 $dyn{\cdot}s{\cdot}cm^{-5}$ vs. >/= 1000 $dyn{\cdot}s{\cdot}cm^{-5}$)
    - Heart rate (based on each patient's median value, <60 bpm vs. >/= 60 bpm)
    - Mean arterial pressure (based on each patient's median value, <65 mmHg vs. >/= 65 mmHg)
    - End-tidal carbon dioxide (based on each patient's median value, <30 mmHg vs. >/= 30 mmHg)
    - History of stroke (yes vs. no)
    - History of myocardial infarction (yes vs. no)
    - History of hypertension control (based on pre-operative measurement with the threshold of 140/90 mmHg, (yes vs. no)
    - Antihypertensive medication, (yes vs. no)
    - History of diabetes (based on the preoperative diagnosis, yes vs. no)
    - History of chronic renal disease (based on the preoperative diagnosis, yes vs. no)
    - History of chronic obstructive pulmonary disease (based on the preoperative diagnosis, yes vs. no)
    - Current cigarette smoking (yes vs. no)

Ethical Considerations

The ethical considerations were specified in the protocol registered before the start of the trial.

Quality Control and Data Management

The quality control and data management were specified in the protocol registered before the start of the trial.

Software and Programming

R software (version 4.3.2, R Foundation for Statistical Computing, Australia).

Tables and Figures

Creating mock-ups or templates for tables and figures is an essential part of the statistical analysis plan to visualize how the results will be presented. Below are descriptions of the structure and content for the key tables and figures that will typically be included in the results section of a clinical trial report. Please note that actual tables and figures would be created using statistical software and formatted according to the journal or reporting guidelines.

Table 1: Baseline Characteristics of Participants

- This table will present demographic and clinical characteristics of participants at baseline, stratified by treatment groups.
- The table will typically include rows for each characteristic, such as age, sex, BMI, ASA score, comorbidities, and any other relevant baseline measures.
- Columns will be used to display the characteristic's name, the intervention group's data, and the control group's data.
- Standard descriptive statistics will be presented: means and standard deviations for continuous variables; frequencies and percentages for categorical variables. The absolute standardized differences will also be reported.

Table 2: Perioperative Intervention and Relevant Information

- This table will summarize the perioperative interventions, covering both the operative room and intensive care unit periods.
- The table will typically include rows for each intervention or relevant information, such as drugs, fluids, duration of surgery, and mechanical ventilation duration.
- Standard descriptive statistics will be presented: means and standard deviations for

continuous variables; frequencies and percentages for categorical variables. We will report p values depending on the journal style.

Table 3: Primary and Secondary Outcomes Analysis

- This table will summarize the analysis of the primary outcome. Alternatively, and depending on the journal's preference, we can instead present the main results using a forest plot and move the table to supplementary material.
- It will have rows for the outcome measure, the number of events or mean (depending on the nature of the outcome), standard deviation or standard error, and the results of the logistic regression including odds ratios, 95% confidence intervals, and p-values.
- The table will have columns for the intervention group, control group, and the comparison between the two.
- If secondary outcomes are continuous, the table will include mean differences instead of odds ratios.
- Each secondary outcome will be listed with its respective statistical analysis results.
- We plan to move this table to supplementary material as we plan to present the results using a forest plot. The final decision will depend on the journal style.

Table 4: Safety Outcomes

- This table will list all adverse events and serious adverse events reported during the trial. If there are too many AEs to include in the main text, this table will be moved to the supplementary material.
- The table will include rows for each type of adverse event and columns for the intervention group, control group, number of events, percentages, and a comparison column if appropriate.

Figure 1: CONSORT Flow Diagram

- The flow diagram will provide a visual representation of participant flow through the trial, including enrollment, allocation, follow-up, and analysis.
- It will have boxes for each phase and arrows indicating the movement of participants, with numbers for each group at each stage.

Figure 2: Forest plot of the primary and secondary outcomes.

- This figure will present the results of primary and secondary analyses.
- The forest plot will include lines for each subgroup with squares representing the effect estimate (e.g., odds ratio) and horizontal lines representing the 95% confidence intervals.
- A vertical line will represent no effect, and a diamond at the bottom will represent the overall effect size.
- The style of presentation will be similar to the following figure.

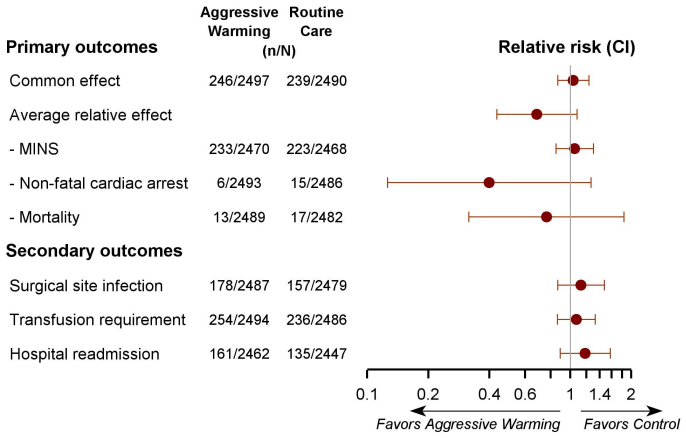


Figure 3: Forest Plot for Subgroup Analysis

- This figure will present the results of pre-specified subgroup analyses.
- The forest plot will include lines for each subgroup with squares representing the effect estimate (e.g., odds ratio) and horizontal lines representing the 95% confidence intervals.
- A vertical line will represent no effect, and a diamond at the bottom will represent the overall effect size.

Appendices

Inclusion of the SAP approval form, mock tables and figures, and any relevant statistical code.