

**Reducing Reintubation Risk in High-Risk Cardiac Surgery
Patients with High-Flow Nasal Cannula**

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Reducing Reintubation Risk in High-Risk Cardiac Surgery Patients with High-Flow Nasal Cannula (iCAN) Study

Statistical Analysis Plan, May 12, 2025

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Trial Registration

ClinicalTrials.gov (NCT04782817); URL: www.clinicaltrials.gov

Study Protocol Manuscript

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Abbreviations and Acronyms

ASA-PS	American Society of Anesthesiologists Physical Status Classification
CVICU	Cardiovascular intensive care unit
DSMB	Data Safety Monitoring Board
EHR	Electronic health record
HFNC	Heated, humidified, high-flow nasal cannula
iCAN	Reducing reintubation risk in high-risk cardiac surgery patients with high-flow nasal cannula
IRB	Institutional Review Board
PI	Principal investigator
VUMC	Vanderbilt University Medical Center

Introduction

The iCAN trial is a pragmatic randomized controlled trial that aims to test the hypothesis that HFNC versus usual care oxygenation strategies applied immediately after initial extubation after cardiac surgery decreases the all-cause 48-hour reintubation rate (extubation failure within 48 hours of initial extubation).

Population

Study Population

The trial will enroll adult patients undergoing cardiac surgery, defined as surgery on the heart or thoracic aorta, excluding percutaneous procedures, at VUMC who fulfill the following inclusion and exclusion criteria:

Inclusion Criteria

- Age ≥ 18 years
- Undergoing cardiac surgery, defined as a documented surgical service of “cardiac surgery” in the EHR, performed in the main operating rooms at Vanderbilt University Medical Center
- Admitted to the cardiovascular intensive care unit postoperatively with an endotracheal tube in place and mechanically ventilated
- Surgery duration (documented time between “Anesthesia start” and “Anesthesia stop” in the EHR) of at least 180 minutes
- Received an order to be extubated by a treating provider
 - Patients who meet all other criteria but do not receive an order to extubate will be randomized but not enrolled

Exclusion Criteria

- None

Study Design

- This study is a prospective, pragmatic, randomized controlled trial. Blinding to treatment assignment will be maintained throughout surgery and the early postoperative period until an order is placed to extubate the patient in the EHR.

Treatment

- Patients will be randomized 1:1 at the time of extubation to either 1] usual care (treatment at the discretion of the treating provider) or 2] HFNC, per the existing intensive care unit protocol. Respiratory therapists will be instructed to target 24 hours of HFNC, if clinically appropriate in the judgement of the patient care team, with an absolute minimum of 1 hour of therapy. Respiratory therapists may use any HFNC device, at their discretion, with initial settings and titration at the discretion of the clinical team. Escalation of care beyond HFNC and transition to alternative means of oxygenation will be at the discretion of the patient care team. Similarly, usual care is at the discretion of the patient care team and may include HFNC. Typical treatment modalities in usual care include, but are not limited to, nasal cannula, face mask, HFNC, and bilevel positive airway pressure. All concomitant care and interventions will be permitted to continue to ensure pragmatism. The decision to

reintubate a patient will be at the sole discretion of the patient care team; there are no protocolized criteria for reintubation.

Randomization

Screening, enrollment, and randomization will be performed using tools embedded within the EHR. Among patients that meet inclusion criteria, randomization will be performed at the documentation of “anesthesia stop” (at the conclusion of the surgical procedure), using a random number that will be generated and associated with the patient’s hospital admission medical record. Randomization will not be visible to clinicians or investigators and will not be stratified.

Enrollment

Enrollment is performed using an order set in the EHR. At the time an order is placed to extubate the patient after surgery, an order set will be automatically placed based on the previously generated random number. According to hospital policy, patients may not be extubated without an extubation order. The order will assign treatment (usual care or HFNC following extubation), based on the randomization allocation.

Blinding

Blinding to the treatment assignment will be maintained throughout surgery and the early postoperative period, until an order is placed to extubate the patient in the EHR. The clinical care team will not be blinded to treatment arm following enrollment, as blinding cannot be practically performed once patients are extubated. Some patients may be randomized but not enrolled if they do not receive an extubation order. Most commonly this is due to self-extubation or patient death prior to planned extubation.

Sample size considerations

Sample size calculations were based on data from a prior study of reintubation after cardiac surgery performed at VUMC (PI: Freundlich, Ann Thorac Surg 2022, PMID 34329600). Assuming a 3.2% reintubation rate among the control arm and a 1:1 ratio of intervention patients to control patients, with at least 1435 patients in each group, a two-sample test of binomial proportions achieves 80% power to detect a relative decrease of 50% in the 48-hour reintubation rate among the HFNC arm (i.e. from 3.2% to 1.6%) at a type 1 error rate of 5%. Accounting for at least 15% crossover between groups, we will require at least 1688 patients in each arm of the study using the N/(1-R) crossover methodology. The intervention and primary outcome are in hospital; as such, we do not anticipate any drop out.

Endpoints

Primary Endpoint

The primary endpoint is all-cause unadjusted reintubation at 48 hours after initial extubation following cardiac surgery (that is, extubation failure within 48 hours). We will not attempt to determine causality of the reintubation as this is frequently multifactorial and would introduce subjective bias into the analysis.

Secondary Endpoints

Prespecified secondary endpoints are listed below

- Reintubation within 72 hours of extubation
- Reintubation at any time after extubation
- All-cause 30-day mortality
- Hospital length of stay
- Intensive care unit length of stay
- Ventilator-free days
- In-hospital mortality
- Adjusted reintubation rate, if needed based on clinically relevant imbalance in baseline characteristics between groups

Analysis Dataset

All data analyzed, including demographic and outcome data, will be limited to data generated by clinicians in routine clinical care and captured via query of existing databases available within the EHR. In previous work, we have demonstrated that we are able to obtain these data without any missingness, based on our extensive experience querying the EHR, as well as by limiting our analysis to those data elements that are readily available (PI: Freundlich, Ann Thorac Surg 2022, PMID 34329600). We have shown that this may be generalizable (PI: Freundlich, J Clin Anesth 2024, PMID 37883900). We will analyze data on a modified intention-to-treat basis that includes all randomized and enrolled participants grouped according to the treatment assigned at randomization as described below.

- Some patients may be randomized but not enrolled if they do not receive an extubation order. Most commonly this is due to self-extubation or patient death prior to planned extubation. We will report demographic and outcome data on patients who were randomized but not enrolled in a separate analysis to help ensure that post-randomization exclusions do not introduce significant bias.
- A proportion of lung transplants are scheduled as being performed by “cardiac surgery” and will be enrolled. Upon the recommendation of the DSMB, these patients will be analyzed in the primary intention-to-treat analysis, but we will perform a prespecified subgroup analysis excluding these patients.

Ethics

Vanderbilt University Medical Center IRB approval, March 15, 2021, with waiver of written informed consent.

Data Safety Plan

A DSMB will act in an advisory capacity to monitor participant safety, data quality and progress. The DSMB will be responsible for reviewing composite data, separated by groups, with a focus on ensuring patient safety. Unmasked data will be provided if safety concerns arise requiring knowledge of the group assignments. At each meeting, the DSMB will consider the rationale for continuation of the study, with respect to progress of randomization, retention, protocol adherence, data management, safety issues and make a recommendation for or against the trial’s

continuation. The DSMB will adjudicate any reported instances of harm and determine appropriate corrective action, if warranted. The DSMB will consist of persons independent from investigators, with no conflict of interest in the trial. The DSMB will consist of experts in cardiovascular critical care, biomedical ethics, and biostatistics, with representation from outside of Vanderbilt University Medical Center. The DSMB will meet once 500 patients have been enrolled in the study for 30 days, as well as when 1500 patients have been enrolled in the study for 30 days. An unscheduled meeting of the DSMB may be called at any time should participant safety questions or other unanticipated problems arise that require the investigators to consult with the DSMB. The primary outcome for the DSMB interim safety analysis will be all-cause mortality, with a stopping boundary of $p < 0.05$. A secondary analysis of all-cause 48-hour reintubation will be performed, with a Haybittle-Peto stopping boundary of $p < 0.001$. The DSMB will prepare a report at the conclusion of each meeting containing the recommendation for continuation of the study. Each meeting must include a recommendation to continue the study made by a formal DSMB majority. A recommendation to terminate the study may be made by the DSMB at any time by majority vote.

Statistical Approach

The primary goal of the statistical analysis will be to evaluate the effect of HFNC on extubation failure after cardiac surgery. Statisticians and investigators will be blinded to group allocation throughout the study and subsequent analysis. Unblinding may occur at the request of the DSMB. The dataset will be finalized and locked prior to unblinding and final analysis.

Descriptive Analysis

To characterize the study sample, baseline demographic and clinical data will be described by intervention group. Categorical variables will be summarized using frequencies and proportions. Quantitative variables will be summarized using medians and quartiles. The following variable types will be described at time of enrollment: age in years, sex, race, ethnicity, ASA-PS classification.

Primary and secondary outcomes will be described by intervention group using similar (standard) descriptive statistics. We will quantify the difference in reintubation rates (primary outcome) between intervention groups using an absolute risk difference with 95% confidence intervals.

The primary outcome will be compared between intervention groups using a chi-squared test. Depending on event rate, either a chi-squared or Fisher's exact test will be used to analyze 30-day mortality. Mann-Whitney U tests will compare continuous and ordinal secondary outcomes. We have not prespecified adjustment for covariates in multivariable models as our primary analysis. We will consider post-hoc adjustment, should there be any clinically relevant imbalance in baseline characteristics between groups. A two-sided p-value of < 0.05 will be used to determine statistical significance for the primary outcome, including accounting for interim analyses performed using the Haybittle-Peto stopping boundaries. While p values (without corrections for multiple comparisons) will also be provided for secondary outcomes, we will not generate inferences regarding statistical significance for secondary outcomes.

Exploratory Analysis

Interaction analyses will be conducted to assess the differential impact of the intervention among strata defined by predicted risk of reintubation, based on our prognostic model of risk of reintubation after cardiac surgery (PI: Freundlich, Ann Thorac Surg 2022, PMID 34329600) and (PI: Freundlich, J Clin Anesth 2024, PMID 37883900). This may be published as a separate manuscript.

Missing Data

We do not anticipate substantial missingness in any primary or secondary endpoint based on our previous work in the CVICU. Participant records with missing endpoints containing no information in the EHR will be excluded from the corresponding analysis of those endpoints.

Type-I Error Control

All statistical hypothesis tests will be made by controlling the type-I error rate at 5%. This means that p-values less than 0.05 will be considered significant and evidence of a treatment effect. DSMB interim analyses will be performed with a conservative Haybittle-Peto stopping boundary of 0.001, which will be included in the total type-I error rate.

Software

All statistical analyses will be performed using R (R Foundation for statistical computing, Vienna, Austria) and any necessary additional packages. We will publish our statistical code as a supplementary appendix in the manuscript to help ensure rigor and reproducibility.

Pragmatic Considerations

No steps will be taken to facilitate enrollment, retention, or adherence to the intervention aside from routine updates to the respiratory therapy, nursing, physician, and advance practice provider teams on the progress of the study and availability of the PI should there be any questions or concerns. Aside from the initial intervention post extubation, no additional interventions or follow-up will be performed outside of usual care. The initial settings, titration, and transition to alternative means of respiratory support will be left to the discretion of the treatment team. All documentation and analysis will be limited to data generated by clinicians in routine care and available in the EHR. No processes will be performed to manipulate data entry or data quality. Data quality will be randomly audited in a subset of at least 10% of the study population. Randomization and enrollment targets will be tracked in near real-time using a custom web-based application displaying data from the EHR, built using Tableau software (Tableau, Seattle, Washington). This same application will be used to monitor crossover rates. As this intervention was adjudicated to constitute minimal risk by the IRB, there are no plans for post-trial care.