

BMJ Open Protocol for a randomised controlled trial: reducing reintubation among high-risk cardiac surgery patients with high-flow nasal cannula (I-CAN)

Robert E Freundlich ^{1,2}, Jonathan P Wanderer,¹ Benjamin French,³ Ryan P Moore,³ Antonio Hernandez,¹ Ashish S Shah,⁴ Daniel W Byrne,³ Pratik P Pandharipande¹

To cite: Freundlich RE, Wanderer JP, French B, *et al.* Protocol for a randomised controlled trial: reducing reintubation among high-risk cardiac surgery patients with high-flow nasal cannula (I-CAN). *BMJ Open* 2022;**12**:e066007. doi:10.1136/bmjopen-2022-066007

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-066007>).

Received 23 June 2022
Accepted 08 November 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, Tennessee, USA

²Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, Tennessee, USA

³Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee, USA

⁴Department of Cardiac Surgery, Vanderbilt University Medical Center, Nashville, TN, USA

Correspondence to

Dr Robert E Freundlich;
robert.e.freundlich@vmc.org

ABSTRACT

Introduction Heated, humidified, high-flow nasal cannula oxygen therapy has been used as a therapy for hypoxic respiratory failure in numerous clinical settings. To date, limited data exist to guide appropriate use following cardiac surgery, particularly among patients at risk for experiencing reintubation. We hypothesised that postextubation treatment with high-flow nasal cannula would decrease the all-cause reintubation rate within the 48 hours following initial extubation, compared with usual care.

Methods and analysis Adult patients undergoing cardiac surgery (open surgery on the heart or thoracic aorta) will be automatically enrolled, randomised and allocated to one of two treatment arms in a pragmatic randomised controlled trial at the time of initial extubation. The two treatment arms are administration of heated, humidified, high-flow nasal cannula oxygen postextubation and usual care (treatment at the discretion of the treating provider). The primary outcome will be all-cause reintubation within 48 hours of initial extubation. Secondary outcomes include all-cause 30-day mortality, hospital length of stay, intensive care unit length of stay and ventilator-free days. Interaction analyses will be conducted to assess the differential impact of the intervention within strata of predicted risk of reintubation, calculated according to our previously published and validated prognostic model.

Ethics and dissemination Vanderbilt University Medical Center IRB approval, 15 March 2021 with waiver of written informed consent. Plan for publication of study protocol prior to study completion, as well as publication of results.

Trial registration number clinicaltrials.gov, NCT04782817 submitted 25 February 2021.

Date of protocol 29 August 2022. Version 2.0.

INTRODUCTION

A substantial proportion of cardiac surgery patients experience failed initial extubation after surgery, with an estimated incidence of 3%–10%.¹ Following failed extubation, these patients are more likely to experience prolonged intensive care unit stay,

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Highly pragmatic clinical trial design.
- ⇒ Randomisation, screening, enrolment and data collection entirely embedded within the electronic health record.
- ⇒ Methodology portable and amenable to future multicentre study.
- ⇒ Data elements not amenable to automated electronic data capture will not be captured.

hospitalisation, excess morbidity and subsequent mortality.^{2–6}

Treatment with heated, humidified, high-flow nasal cannula (HFNC) oxygen has been proposed a therapy for hypoxic respiratory failure in numerous clinical settings.⁷ HFNC can deliver up to 100% oxygen at a maximum flow of 60 L/min via nasal cannula, offering important physiological advantages, including improved dead space ventilation, mucociliary clearance and offering some positive end expiratory pressure, compared with standard oxygen therapy.^{1,7,8} HFNC has gained increasing acceptance as a means for postextubation support, particularly after cardiac surgery.^{9–11} While HFNC may decrease the need for escalation of respiratory support, data are mixed about its impact on extubation failure (need for reintubation) and intensive care unit length of stay.⁷ HFNC may also be associated with a decrease in the overall hospital length of stay.¹²

We hypothesise that postextubation treatment with HFNC will decrease the all-cause reintubation rate within the 48 hours following initial extubation after adult cardiac surgery, compared with usual care. Through use of a highly pragmatic randomised trial design, entirely embedded within the electronic health record, we hope to demonstrate

the feasibility of this relatively novel experimental methodology.

METHODS AND ANALYSIS

Clinical trial protocol adherence

This protocol conforms to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.¹³

Study protocol

We have designed a pragmatic randomised trial to evaluate whether HFNC is superior to usual care at reducing the risk of reintubation after adult cardiac surgery, compared with usual care. To enhance pragmatism, we have prioritised broad inclusion and exclusion criteria.¹⁴ Adult (≥ 18 years old) patients undergoing cardiac surgery at Vanderbilt University Medical Center who arrive at the cardiovascular intensive care unit with an endotracheal tube in place and on mechanical ventilation will be eligible for inclusion, from 1 November 2021 until enrolment targets met; we anticipate that this will take approximately 36 months. Exclusion filters have been generated to exclude cases performed in procedural areas and non-operating room areas, including the catheterisation and electrophysiology suite, as well as additional filters to exclude procedures with a total anaesthesia time of less than 3 hours.

Screening, enrolment and randomisation will be performed using tools embedded within our institution's Epic electronic health record (Epic Systems, Verona, Wisconsin). Randomisation is performed using a random number that is generated and associated with the patient's hospital admission medical record, but not visible to clinicians or investigators, at the documentation of 'Anaesthesia Stop' at the conclusion of the surgical procedure, provided patients meet inclusion criteria, using Epic's 'Rule Editor' tool. There is no stratification to randomisation.

Enrolment is performed using Epic's order set function. At the time an order is placed to extubate the patient after surgery, an order set is automatically selected based on the previously generated random number. According to hospital policy, patients may not be extubated without an extubation order. The selected order set will default to either treatment with usual care or treatment with HFNC following extubation. The clinical care team will not be blinded to treatment arm following enrolment, as blinding cannot practically be performed.

Respiratory therapists have been instructed to target 24 hours of HFNC therapy, if clinically appropriate in their judgement and that 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 sole discretion of the treatment team. Similarly, usual care is at the

discretion of the clinical team and may include HFNC, if deemed appropriate by the treating clinicians. Typical treatment modalities in usual care include, but are not limited to, nasal cannula, face mask, HFNC and bilevel positive airway pressure.

Some patients may not receive an extubation order, such as instances of early postoperative mortality with the endotracheal tube still in situ or self-extubation. We will plan to report relevant data on patients who were randomised but not enrolled as a secondary analysis to help ensure that postrandomisation exclusions do not introduce bias. 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 treatment team; there are no protocolised criteria for reintubation.

Patient and public involvement

Patients and the public will not be involved in the design, conduct or reporting plans of our research.

Sample size calculations

Assuming a 3.2% reintubation rate among the control arm¹ and a 1:1 ratio of intervention patients to control patients, with 1436 patients in each group (2872 patients total), 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 (ie, from 3.2% to 1.6%) at a type 1 error rate of 5%.¹⁵ Accounting for at least 10% crossover between groups, we will require 3192 patients enrolled for the full trial (1596 in each arm). The intervention and primary outcome are in hospital; as such, we do not anticipate any drop out.

Analysis plan

Statisticians and investigators will be blinded to group allocation throughout the study and subsequent analysis. Unblinding may occur at the request of the Data Safety Monitoring Board (DSMB). The dataset will be finalised and locked prior to unblinding and final analysis. The primary outcome is all-cause reintubation within 48 hours of initial extubation after surgery. Secondary outcomes include all-cause 30-day mortality, hospital length of stay, intensive care unit length of stay and ventilator-free days. Interaction analyses will be conducted to assess the differential impact of the intervention among strata defined by predicted risk of reintubation, based on our recent prognostic model of risk of reintubation after cardiac surgery.¹⁶ All data analysed, 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 electronic health record. In previous work, we have demonstrated that we are able to obtain these data without any missingness, based on extensive experience querying the electronic health record, as well as limiting our dataset to those data elements that are reliably available.¹ We intend to analyse patients on a modified intention to treat basis. Patients

randomised but not enrolled, for example, those who self-extubate after they have already received a randomisation number or who die prior to extubation will be added to the primary cohort and analysed in a prespecified secondary analysis.

We will summarise continuous variables using median and IQR and categorical variables using proportions and frequencies. We will quantify the difference in reintubation rates between the groups using absolute risk difference with 95% CIs. The effect of the intervention on the primary outcome will be assessed using a χ^2 test. Depending on event rate, a χ^2 or Fisher's exact test will be used to analyse 30-day mortality. Mann-Whitney U tests will be used to compare the remaining 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.

Pragmatic considerations

As this is a pragmatic study, no steps will be taken to facilitate enrolment, retention or adherence to the intervention, aside from routine updates to the respiratory therapist, nursing, physician and advance practice provider teams, on the progress of the study and availability of the principal investigator should there be any questions or concerns. Aside from the initial intervention, HFNC therapy, 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 all be left to the discretion of the treatment team. All documentation and analysis will be limited to data generated by clinicians in routine patient care and available in the electronic health record. No processes will be performed to manipulate data entry or data quality.

Randomisation and enrolment targets will be tracked in real-time using a custom web-based application displaying data from the electronic health record, built using Tableau software (Tableau, Seattle, Washington). This same application will be used to track adherence to the intervention.

As this intervention was adjudicated to constitute 'minimal risk' by the IRB, there are no plans for post-trial care.

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 randomisation,

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.

ETHICS AND DISSEMINATION

Approval was provided by the Vanderbilt University Medical Center Human Subjects Research Protection Program on 15 March 2021. Due to minimal patient risk, perceived clinical equipoise between arms of the intervention, and impracticability of obtaining consent in a timely fashion, a waiver of the requirement for written informed patient consent was obtained under 45 CFR 46.116, similar to other pragmatic clinical trials performed at our institution.¹⁷⁻²⁰ All study data will be stored on secure hospital servers, with code used to generate the data securely stored to ensure rigour and reproducibility. This trial has been registered in clinicaltrials.gov prior to the enrolment of the first participant.

We intend to publish the primary findings of this study, including prespecified secondary analyses. As a second manuscript, we intend to study the differential efficacy of the intervention may have on patients at varying strata of predicted risk of reintubation, using an existing model from the cardiac surgery literature,¹ with a long-term goal of better understanding which specific patients are most likely to benefit. These publications will adhere to the Consolidated Standards of Reporting Trials (CONSORT) framework.²¹ Authorship will be limited to those who meet International Committee of Medical Journal Editors criteria for authorship. We do not intend to employ professional writers. A professional medical editor may be engaged to assist in proofreading and ensuring adherence to journal formatting requirements. The final trial



dataset will be maintained on secure institutional servers. Structured query language used to generate the dataset will be maintained indefinitely. Statistical code will be published as a supplementary appendix in the manuscript publishing the results of the study to help ensure rigour and reproducibility. We do not plan on granting public access to the participant level dataset. While the National Institutes of Health has funded this research, they are not involved in the study design, data collection, data management, analysis or interpretation of the data. They have not participated in the writing of this protocol, nor do they have any role in the decision to submit this protocol, including whether they have ultimate authority over any of these activities.

Twitter Daniel W Byrne @danielwbyrne

Contributors RF: drafted the protocol, conceived of the study, ultimately responsible for the conduct of the described study, ultimately accountable for data collection and data accuracy. RF will have access to the final trial dataset, with no relevant contractual agreements to disclose. He will be responsible for notifying the IRB, clinicaltrials.gov, and relevant parties should protocol amendments be performed. JPW: an experienced clinical informaticist, led the design and implementation of the build for the electronic health record, including the randomisation, screening and enrolment of patients. BF, RM and DWB: biostatisticians with experience in the planning and interpretation of pragmatic randomised trials and automated electronic data capture derived from the electronic health record. They will have access to the final trial dataset, with no relevant contractual agreements to disclose. AH: a cardiac anaesthesiologist and intensivist, medical director of the cardiovascular intensive care unit, responsible for helping to ensure adherence to the protocol during the conduct of the clinical trial, as well as to help ensure equipoise between arms of the study. ASS: a cardiac surgeon and chairman of the department of cardiac surgery is responsible for helping to ensure surgeon adherence to the protocol, as well as to help ensure equipoise between arms of the study. PP: an experienced clinical trialist, primary mentor for the career development grant that is the foundation of the proposed study.

Funding This work was supported by the National Heart Lung and Blood Institute, grant K23HL148640.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Robert E Freundlich <http://orcid.org/0000-0002-0343-9823>

REFERENCES

- Freundlich RE, Li G, Domenico HJ, *et al*. A Predictive Model of Reintubation After Cardiac Surgery Using the Electronic Health Record. *Ann Thorac Surg* 2022;113:2027-2035.
- Freundlich RE, Maile MD, Hajjar MM, *et al*. Years of life lost after complications of coronary artery bypass operations. *Ann Thorac Surg* 2017;103:1893-9.
- Khandelwal N, Dale CR, Benkeser DC, *et al*. Variation in tracheal reintubations among patients undergoing cardiac surgery across Washington state hospitals. *J Cardiothorac Vasc Anesth* 2015;29:551-9.
- Nicolini F, Agostinelli A, Vezzani A, *et al*. The evolution of cardiovascular surgery in elderly patient: a review of current options and outcomes. *Biomed Res Int* 2014;2014:1-10.
- Engoren M, Buderer NF, Zacharias A. Long-Term survival and health status after prolonged mechanical ventilation after cardiac surgery. *Crit Care Med* 2000;28:2742-9.
- Engoren M, Buderer NF, Zacharias A, *et al*. Variables predicting reintubation after cardiac surgical procedures. *Ann Thorac Surg* 1999;67:661-5.
- Ni Y-N, Luo J, Yu H, *et al*. Can high-flow nasal cannula reduce the rate of reintubation in adult patients after extubation? A meta-analysis. *BMC Pulm Med* 2017;17:142.
- Corley A, Caruana LR, Barnett AG, *et al*. Oxygen delivery through high-flow nasal cannulae increase end-expiratory lung volume and reduce respiratory rate in post-cardiac surgical patients. *Br J Anaesth* 2011;107:998-1004.
- Zhu Y, Yin H, Zhang R, *et al*. High-Flow nasal cannula oxygen therapy vs conventional oxygen therapy in cardiac surgical patients: a meta-analysis. *J Crit Care* 2017;38:123-8.
- Stéphan F, Barrucand B, Petit P, *et al*. High-Flow nasal oxygen vs noninvasive positive airway pressure in hypoxemic patients after cardiothoracic surgery: a randomized clinical trial. *JAMA* 2015;313:2331-9.
- Rochweg B, Einav S, Chaudhuri D, *et al*. The role for high flow nasal cannula as a respiratory support strategy in adults: a clinical practice guideline. *Intensive Care Med* 2020;46:2226-37.
- Zochios V, Collier T, Blaudszun G, *et al*. The effect of high-flow nasal oxygen on hospital length of stay in cardiac surgical patients at high risk for respiratory complications: a randomised controlled trial. *Anaesthesia* 2018;73:1478-88.
- Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al*. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
- Lipman PD, Loudon K, Druzak L, *et al*. Framing the conversation: use of PRECIS-2 ratings to advance understanding of pragmatic trial design domains. *Trials* 2017;18:532.
- Fleiss JL, Tytun A, Ury HK. A simple approximation for calculating sample sizes for comparing independent proportions. *Biometrics* 1980;36:343-6.
- Freundlich RE, Li G, Domenico HJ, *et al*. A Predictive Model of Reintubation After Cardiac Surgery Using the Electronic Health Record. *Ann Thorac Surg* 2022;113:2027-35.
- Self WH, Semler MW, Wanderer JP, *et al*. Balanced crystalloids versus saline in Noncritically ill adults. *N Engl J Med* 2018;378:819-28.
- Semler MW, Self WH, Wanderer JP, *et al*. Balanced crystalloids versus saline in critically ill adults. *N Engl J Med* 2018;378:829-39.
- Noto MJ, Domenico HJ, Byrne DW, *et al*. Chlorhexidine bathing and health care-associated infections: a randomized clinical trial. *JAMA* 2015;313:369-78.
- Yiadom MYAB, Domenico H, Byrne D, *et al*. Randomised controlled pragmatic clinical trial evaluating the effectiveness of a discharge follow-up phone call on 30-day Hospital readmissions: balancing pragmatic and explanatory design considerations. *BMJ Open* 2018;8:e019600.
- Schulz KF, Altman DG, Moher D, *et al*. Consort 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010;152:726-32.