Statistical Analysis Plan

*H*igh-flow oxygen for children's *A*irway Surgery: A rando*m*i**s**ed con*t*roll*e*d *t*r*i*al protocol (HAMSTER): A Statistical Analysis Plan for a randomised controlled trial

Authors

Susan Humphreys[1,2,3]

Britta von Ungern-Sternberg[4.5]

Justin Skowno[7,8]

Tara J Williams[1]

Susan Spall[1,2]

Fiona Taverner[12]

Laura Burgoyne[6,12]

David Sommerfield[4.5]

Ben Hallett[9]

Shyan Vijayasekaran[5,13]

Nicola Slee[1]

Hannah Burns[1]

Marcin Sowa[1,3]

Andrew Davidson[9],

Andreas Schibler[14]

Kristen S Gibbons[1]

Author Affiliations:

[1]Paediatric Critical Care Research Group, Child Health Research Centre, The University of Queensland, Queensland, Australia.

[2]Department of Anaesthesia and Pain Management, Queensland Children's Hospital, Queensland, Australia.

[3]School of Medicine, University of Queensland, Australia

[4]Anaesthesia Department, Perth Children's Hospital, Perth, Australia

[5]University of Western Australia, Western Australia, Australia

[6]Children's Anaesthesia, Women's and Children's Hospital, Adelaide, Australia

[7] Department of Anaesthesia, The Children's Hospital at Westmead, Sydney, Australia

[8] Discipline of Child and Adolescent Health, University of Sydney, Australia

[9]Anaesthesia Department, Royal Children's Hospital & Murdoch Children's Research Institute, Melbourne, Australia

[12] University of Adelaide, South Australia, Australia

[13]Department of Otolaryngology, Perth Children's Hospital, Australia

[14]Wesley Research Institute, Auchenflower Queensland, Australia

Ethics approval and consent to participate:

The study protocol has been reviewed and approved by two Australian ethics committees (Children's Health Queensland Human Research Ethics Committee [HREC/18/QRCH/130] and The University of Queensland Human Research Ethics Committee [2018001820]). The study was carried out in compliance with national and state legal and regulatory requirements and according to the International Principles of Good Clinical Practice (ICH-GCP). Written, informed consent was obtained from the legal guardian of all trial participants.

Consent for publication:

Not applicable.

Competing interests:

AS has received travel support from Fisher and Paykel Healthcare. All other authors have no conflicts to disclose.

Author contributions:

The statistical analysis plan first draft was designed by KG, SH and TW. KG was responsible for drafting this manuscript, with comments and feedback from all other authors. All authors attest to having approved the final manuscript.

Funding:

This research is supported by funding from the Thrasher Research Fund (United States of America), the Australian and New Zealand College of Anaesthetists and the Society for Paediatric Anaesthesia in New Zealand and Australia. Fisher and Paykel Healthcare, Masimo

and Radiometer Pacific are providing equipment and consumables for the study but have had no input in the study design.

Abstract:

BACKGROUND: High-flow oxygen for children's Airway Surgery: A randomised controlled trial protocol (HAMSTER) is a multicentre, randomised controlled trial aiming to recruit 530 patients, investigating if nasal high-flow in children aged <16 years of age undergoing elective tubeless upper airway surgery reduces the requirement for a rescue oxygenation attempt for a hypoxaemic event.

OBJECTIVE: To provide a statistical analysis plan (SAP) before completion of data monitoring and locking of the study database. Final analyses for this study will adhere to this SAP which details all pre-planned analyses.

METHODS: This SAP is designed collaboratively by the chief investigators and trial statistician and builds on the previously published study protocol. This SAP provides detail on pre-planned statistical analyses including cohort description and analysis of primary and secondary outcomes. Statistical methods to compare outcomes are planned in detail to ensure methods are verifiable and reproducible.

RESULTS: This SAP provides the trial outline and list of mock tables describing the statistical analyses on cohort baseline description, primary and secondary outcome analyses and adverse event reporting. We detail the pre-specified subgroup and sensitivity analyses and the respective statistical tests.

CONCLUSION: This SAP for the HAMSTER trial establishes detailed pre-planned analyses to analyse the largest trial in the field of paediatric anaesthesia and nasal high-flow therapy. This SAP provides state-of-the art standards for trial analysis validity aiming to minimise bias of analyses.

TRIAL REGISTRATION: ACTRN12618000949280

Key Words:

Paediatric, Children, Anaesthetics, Oxygen Therapy, Statistical Analysis, Randomised Controlled Trial

List of Abbreviations:

ABBREVIATION	TERM
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
COVID	Coronavirus disease
HAMSTER	High-flow oxygen for children's Airway Surgery: A randomised controlled trial
HREC	Human Research Ethics Committee
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IQR	Interquartile range
MLB	Microlaryngoscopy and bronchoscopy
OR	Odds ratio
PICU	Paediatric Intensive Care Unit
RCT	Randomised controlled trial
REDCap	Research Electronic Data Capture
SAP	Statistical analysis plan
SD	Standard deviation
SpO_2	Transcutaneous oxygen saturation
TIVA	Total intravenous anaesthesia

Introduction

Tubeless airway surgery is a common procedure performed in children who present with symptoms suggesting airway abnormalities which require diagnostic and therapeutic interventions (1). The airway in these cases is shared between the surgeon who requires a clear view of the upper airway and the anaesthetist who must maintain airway patency, an adequate depth of anaesthesia, spontaneous ventilation and oxygen delivery to the child. Hypoxaemia has been found to occur in 34% of children during dynamic airway assessment, with 23% of the procedures interrupted for rescue oxygenation (2). Apnoea can occur frequently in infants and small children during anaesthesia and the subsequent onset of oxygen desaturation occurs more quickly than in adults (3).

Oxygen delivery to the airway during anaesthesia occurs via a nasopharyngeal catheter or tube attached to an anaesthesia breathing circuit at 6L/min which describes the low-flow method. Nasal high-flow, delivering a weight-based flow of heated and humidified oxygen, has recently been found to be a successful oxygen delivery method during airway procedures for spontaneous ventilation. It also prolongs the time to oxygen desaturation in apnoeic children (4).

This study aims to determine if high-flow reduces the rate of rescue oxygenation for hypoxaemic events during tubeless airway surgery.

Study design and participants

The HAMSTER trial is a multicentre, RCT in children aged >37 weeks to 16 years undergoing elective tubeless upper airway surgery. A total of 530 patients are anticipated to be recruited from tertiary children's hospitals across five sites in Australia. The primary objective of the

trial is to compare the proportion of rescue oxygenation attempts to manage hypoxaemia during anaesthesia for upper airway surgery between high-flow and low-flow oxygen delivery. The secondary objective of the study is to assess if high-flow reduces the severity of hypoxaemia, the incidence of adverse cardiorespiratory events and unexpected paediatric intensive care admission (PICU) admissions. Eligibility for inclusion is determined prior to randomisation with the following criteria: 1) children aged 0 (>37 weeks gestational age) to 15 years plus 364 days, and 2) presenting for elective tubeless upper airway surgery. Exclusion criteria are: 1) tracheostomy in situ, 2) requirement for laser surgery, 3) known choanal atresia, and 4) high-flow contraindication (5).

The study protocol has been approved by the Children's Health Queensland Human Research Ethics Committee (HREC) (HREC/18/QRCH/130; original submission approved 02/07/2018). Minor modifications to the original study protocol were reviewed and approved by the HREC and are provided in Supplementary Appendix (Section S1). This SAP is based on version 6 of the study protocol.

Sample size

Based on unpublished data from Queensland Children's Hospital in 2016, 34% of children presenting for tubeless upper airway surgery experienced a hypoxaemic event with a desaturation event to less than 90% during the surgical procedure. Twenty-three per cent of these children with a hypoxaemic event required surgical interruption and a rescue oxygenation by positive pressure ventilation. Assuming 90% power to demonstrate a difference between high-flow and low-flow with a reduction of the primary outcome from 23% to 11.5%, and a type 1 error rate of 0.05, we require a total sample size of 530 patients (15% attrition included).

Randomisation

Randomisation is conducted online through the purpose-built REDCap electronic data capture tool hosted at The University of Queensland (6, 7); the randomisation module can only be accessed by the central study coordinator and local research assistant, and only after a patient has been screened, is deemed to have met eligibility criteria and has provided informed consent. A randomisation sequence using variable block randomisation with a 1:1 ratio was generated and loaded into REDCap prior to screening of the first patient. Randomisation is stratified by site and then by age (<1 year, 1-<5 years and 5-<16 years of age).

Intervention

High-flow technique

High-flow will be delivered via the Optiflow device at weight-specific flow rates (Table 1) delivering a FiO_2 of 1.0. Jaw thrust will be applied to ensure a patent airway until airway instrumentation begins. Anaesthesia will be maintained via Total Intra-Venous Anaesthesia (TIVA) adjusted to maintain both adequate depth of anaesthesia and spontaneous ventilation.

Low-flow technique (usual care)

Oxygen insufflation at a flow rate of up to 6 L/min via a nasopharyngeal tube or catheter. Jaw thrust will be applied to ensure a patent airway until airway instrumentation begins, and after airway instrumentation is complete. Anaesthesia technique will be inhalational, intravenous or a combination of both at the discretion of the anaesthetist.

Outcome measures

The definition and detail of calculation of outcome measures can be found in the Supplementary Appendix (Section S2) and the published protocol. Briefly, the outcome measures are (8):

- Primary outcome: successful anaesthesia without any rescue oxygenation attempt for a hypoxemic event ($SpO_2 \geq 90\%$).
- Secondary outcomes:
    - proportion of children requiring rescue intervention for oxygenation and ventilation
    - proportion of children with a hypoxemic event ($SpO_2 <90\%$).
    - Total length of time patient experiences hypoxaemia (seconds) during the entire procedure;
    - Severity of hypoxaemia;
    - Minor adverse events: occurrence of epistaxis, laryngospasm, bronchospasm, coughing at any time during procedure;
    - Major adverse events: occurrence of hypotension requiring treatment, bradycardia requiring treatment, cardiac arrest with or without return of spontaneous circulation at any time during procedure;
    - Requirement for unexpected PICU admission;
    - Requirement for postoperative mechanical ventilation or any other form of non-invasive ventilation including high-flow nasal oxygen;
    - Length of PICU stay; and
    - Length of hospital stay.

While neurodevelopment at six months post intervention was an originally intended secondary outcome, restrictions on funding did not allow this to be pursued.

Data monitoring

Data monitoring is being undertaken throughout the trial, based on a data monitoring plan devised by the study team. The data monitoring plan was developed in accordance with the ICH E6 (R2) Good Clinical Practice Guideline (9) and reflects current best practice for data monitoring practices in investigator-initiated trials. Briefly, the data monitoring plan includes the following components:

- Data verification on all screening data items (i.e. inclusion and exclusion criteria) on a random sample of 20 ineligible patients (or all patients if less than 20 ineligible patients) from each site;
- Data verification on all screening data items (i.e. inclusion and exclusion criteria) for every enrolled patient;
- Data verification on the stratification used for randomisation and consent data items for every enrolled patient and data items related to calculation of the primary outcome and secondary outcomes;
- Data verification on key data items relating to cohort descriptors on a random sample of 10% of enrolled patients from each site; and
- Data verification on reported protocol deviations on a random sample of 10% of enrolled patients from each site.

The original study REDCap database was enhanced to facilitate the activities outlined in the data monitoring plan. Each site is being monitored by a research co-ordinator not involved with the recruitment at that site. This is being undertaken through a combination of on-site monitoring and remote monitoring using the institutional programme to share desktop computer screens as well as via the upload of source documents to the UQ Research Data Manager. Three sites have the required information for demographic data, surgical data, outcomes and patient notes on an electronic health record. Two sites have paper medical health records which requires digital scanning for review or a site visit. During the coronavirus-2019

pandemic (COVID-19), sites are only allowing remote monitoring, however on-site monitoring will likely still occur following easing of COVID-19 restrictions. Each relevant data item is verified individually by comparing the entered value with the value in the source documentation. Where discrepancies are found, the site research co-ordinator and monitor meet to discuss and resolve the discrepancies. If the data item under review is captured from monitoring equipment, the timing and standard details of the relevant annotated events is verified using a purpose-built verification tool. Standard event detail missing from the monitoring equipment capture is also entered through this tool, where additional data exists from other sources. Once data monitoring is finalised, the patient's REDCap data entry record is locked in preparation for analysis.

Statistical analysis

Statistical analysis principles

- The primary analysis will be conducted based on the intention-to-treat principle. Specifically, patients will be analysed based on the treatment group they were allocated to, independent of compliance with the treatment delivered. A per-protocol analysis including all patients who commenced on a study therapy (regardless of whether it was the one to which were randomised) will also be undertaken and reported in supplementary material.
- Statistical tests will be two-sided applying a statistical significance level of 0.05. We will not apply formal correction for multiple testing to any of the subgroup analyses, sensitivity analyses, or to the secondary outcomes. We will ensure conclusions drawn as a result of analyses are interpreted with deference to multiple comparisons.
- If there is missing data for the primary outcome, multiple imputation will be used.

- Continuous variables will be assessed for normality; this will be undertaken using visual inspection of histograms and Q-Q plots.
- Standard descriptive statistics will be used when summarising variables; frequencies (percentages) for discrete variables, mean and standard deviation (SD) for continuous variables, or, if continuous variables are non-normally distributed, median with interquartile range (IQR).
- Subgroup analyses will be executed regardless of any potential treatment effect on the primary or secondary outcomes in the main cohort.
- To ensure transparency and reproducibility, the Stata code that is used to analyse the final study data will be made available on GitHub.
- Changes in the analysis plan by the investigators effective after publication of this SAP will be declared as such.
- The statistical analysis will be undertaken using StataSE version 16 (StataCorp Pty Ltd, College Station, Texas).

Datasets analysed

The planned Consolidated Standards of Reporting Trials (CONSORT) (10) flow diagram will include all patients being screened for the study (Figure 1). All other analyses will be performed on the intention-to-treat cohort, or per-protocol cohort, dependent on the analysis. If consent is not obtained or is withdrawn, data will be excluded from the analyses, unless the withdrawn patient/s permitted the use of data up to the point of withdrawal. The primary dataset for analysis will include baseline variables (demographics, comorbidities, indication for surgery), surgical characteristics, outcomes (primary and secondary), adverse events and protocol deviations. Following completion of the data monitoring process, data will be extracted from

the study REDCap database and imported into StataSE version 16 (StataCorp Pty Ltd, College Station, Texas) for analysis.

Trial profile and overview

Recruitment of patients into the trial will be represented using a flow chart based on the CONSORT guideline (10) (Figure 1). This will describe screened patients, those meeting exclusion criteria, eligible patients, consent process, those randomised into each of the study arms, with the documentation of the primary outcome. We will report on the start and stop date of the trial and provide the recruitment graph by month including division into the contributing sites as a supplementary figure.

Patient baseline and pre-surgical characteristics

Baseline characteristics (including demographic data, comorbidities, respiratory support prior to surgery) at time of randomisation will be reported for each of the two treatment groups (statistical comparison between groups will not be undertaken and analyses of outcome measures will not be adjusted for differences noted in baseline characteristics) (Table 1).

Outcome measures analysis

Primary outcome measure

The primary outcome measure (successful anaesthesia without any rescue oxygenation attempt for a hypoxaemic event) will be analysed using logistic regression adjusting for treatment group and the stratification variable (age group) as fixed effects and site and patient as random effects (allowing for the same patient to be recruited more than once into the study), with unadjusted and adjusted odds ratios (ORs), 95% confidence intervals (CIs) and p-value

reported (Table 2). Assumptions of the models will be tested and reported on. Additionally, a model without adjustment for age group or site will be generated and reported.

Secondary outcome measures

Binary outcome measures (e.g., PICU admission) will be treated in the same manner as the primary outcome, however no p-value will be reported (Table 3). Similar analyses will be undertaken for continuous outcomes; regression with adjustment for treatment group and stratification variable as fixed effects and site and patient as random effects, with reporting of mean difference (unadjusted for stratification variable and adjusted) and 95% CIs. Survival outcomes (length of PICU stay, length of hospital stay) will be visually presented using a Kaplan-Meier plot and a Cox proportional hazard model will be used to assess differences between treatment groups with treatment group and stratification variables as fixed effects and site and patient as random effects (i.e., utilising a shared frailty model). The hazard ratio and 95% CI will be presented as an estimate of treatment effect. Key assumptions of the models (for logistic regression: specification, goodness-of-fit, absence of multicollinearity and absence of influential observations; for survival analysis: proportionality assumption, goodness-of-fit; for linear regression: specification, distribution of residuals, homoscedasticity, absence of multicollinearity, linearity) will be tested and reported on.

Safety outcomes

All adverse outcomes defined in the study protocol will be reported as described in Table 3 and compared between the two study groups using logistic regression as described above for secondary outcomes.

Subgroup analyses

We will undertake the following pre-planned subgroup analyses (Table 2):

1) age group at randomisation (stratification variable); and
2) for children with a rescue attempt, the lowest SpO_2 during the rescue attempt (<80%; ≥80%).

Subgroup analyses will be undertaken using the same analysis methods described for the primary outcome measure, with the addition of the subgroup variable and its related interaction term into the main regression model; the interaction effect (and 95% CI and p-value) will be reported, alongside the descriptive statistics for the outcome under investigation. The first subgroup analysis (age group at randomisation) will be undertaken for the primary outcome only. The second subgroup analysis, relating to lowest SpO_2 during the rescue attempt, will only be undertaken for secondary outcomes.

Treatment of missing data

Missing data will not be imputed for the primary outcome measure if the data is not available.

List of planned figures

Figure 1. CONSORT participant flow diagram

List of planned Supplementary Appendix material

- Funding sources
- Trial steering committee and HAMSTER trial investigators
- Enrolment statistics by month and site
- List of protocol deviations

- List of adverse events
- Results of per-protocol analysis

REFERENCES

1. Mausser G, Friedrich G, Schwarz G. Airway management and anesthesia in neonates, infants and children during endolaryngotracheal surgery. Paediatr Anaesth. 2007;17(10):942-7.
2. Humphreys S, Lee-Archer P, Reyne G, Long D, Williams T, Schibler A. Transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) in children: a randomized controlled trial. Br J Anaesth. 2017;118(2):232-8.
3. Patel R, Lenczyk M, Hannallah RS, McGill WA. Age and the onset of desaturation in apnoeic children. Can J Anaesth. 1994;41(9):771-4.
4. Humphreys S, Rosen D, Housden T, Taylor J, Schibler A. Nasal high-flow oxygen delivery in children with abnormal airways. Paediatr Anaesth. 2017;27(6):616-20.
5. Humphreys S, von Ungern-Sternberg BS, Skowno J, Williams T, Taylor J, Taverner F, et al. High-flow oxygen for children's airway surgery: randomised controlled trial protocol (HAMSTER). BMJ Open. 2019;9(10):e031873.
6. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.
7. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.
8. Franklin D, Shellshear D, Babl FE, Schlapbach LJ, Oakley E, Borland ML, et al. Multicentre, randomised trial to investigate early nasal high-flow therapy in paediatric acute hypoxaemic respiratory failure: a protocol for a randomised controlled trial-a Paediatric Acute respiratory Intervention Study (PARIS 2). BMJ Open. 2019;9(12):e030516.
9. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Harmonised Guideline: Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2). 2016.
10. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332.

Figure 1. Proposed CONSORT participant flow diagram

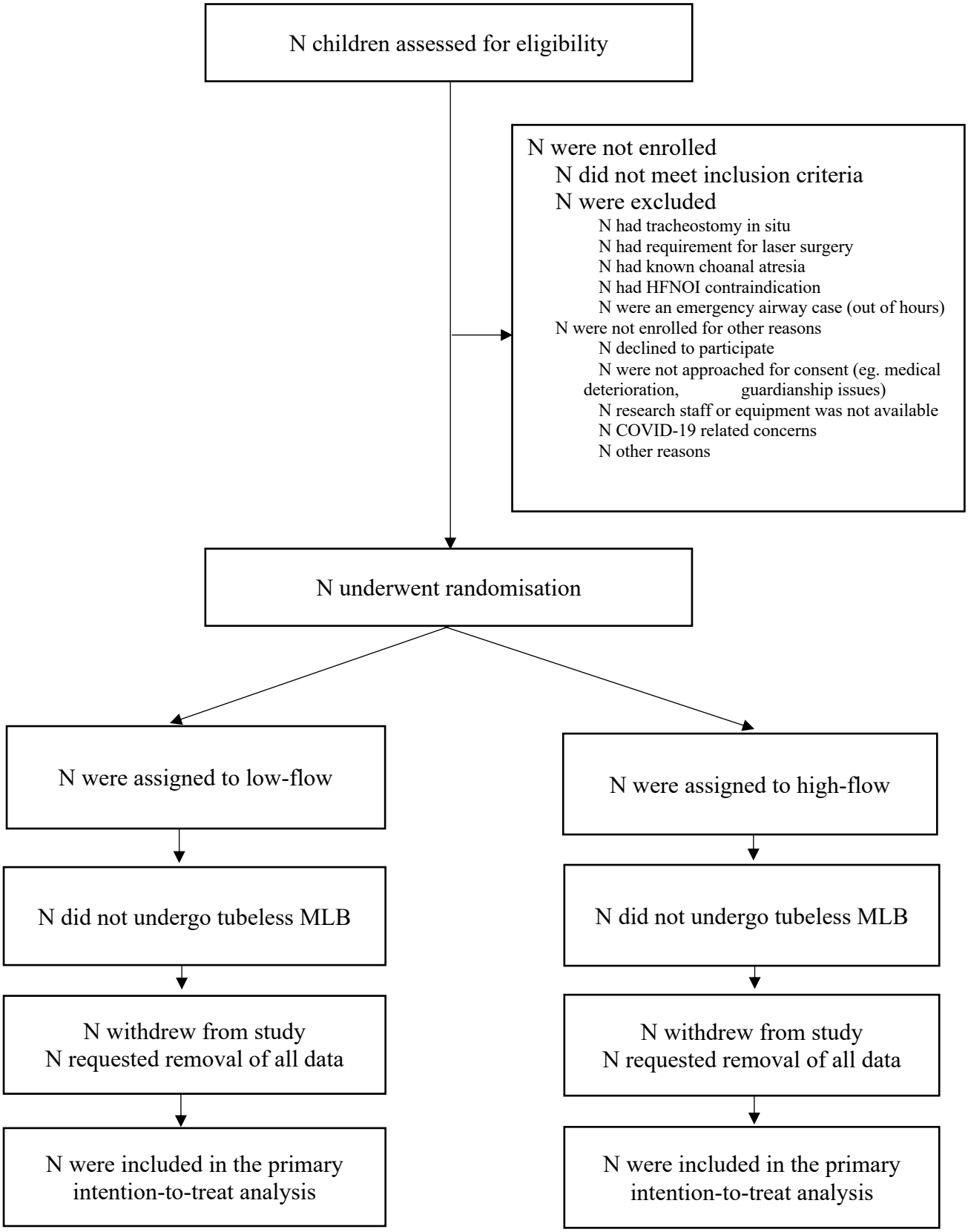

Table 1. Demographic and pre-intervention surgical characteristics of participants enrolled in HAMSTER trial

Characteristic	**Low-flow N=**	**High-flow N=**
Age at randomisation (years) *mean (SD)/median (IQR)*		
Age at randomisation (years)* *n (%)*		
<1 year		
1-<5 years		
5-<16 years		
Weight (kg) *mean (SD)/median (IQR)*		
Female sex *n (%)*		
Ethnicity *n (%)*		
Caucasian		
Aboriginal/Torres Strait Islander		
Asian		
African		
Indian		
Middle Eastern		
Maori		
Pacific Islander		
Other		
Unknown		
Co-morbidities		
None *n (%)*		
OSA *n (%)*		
Known airway anomaly *n (%)*		
Obesity *n (%)*		
Reactive airways disease/asthma *n (%)*		
Vocal cord papillomata *n (%)*		
Congenital heart disease *n (%)*		
Prematurity (<37/40) *n (%)*		
Chronic lung disease *n (%)*		
Home oxygen requirement *n (%)*		
Other *n (%)*		
Gestational age at birth *mean (SD)/median (IQR)*		
Birthweight (g) *mean (SD)/median (IQR)*		
Previous surgery *n (%)*		
Previous mechanical ventilation *n (%)*		
Cardiac pathophysiology *n (%)*		
Univentricular		
Biventricular		
Indication for surgery		
Stridor *n (%)*		
Unexplained desaturation *n (%)*		

Airway trauma *n (%)*		
Papillomata *n (%)*		
Respiratory support pre-operatively *n (%)*		
Respiratory distress *n (%)*		
Known airway anomaly *n (%)*		
OSA/apnoeas *n (%)*		
Other *n (%)*		
Primary respiratory support prior to surgery *n (%)*		
None		
Invasive mechanical ventilation (ETT or tracheostomy)		
Non-invasive ventilation		
High-flow nasal oxygen		
Low-flow oxygen		

*used for stratification

SD standard deviation; IQR interquartile range; OSA obstructive sleep apnoea

Table 2. Primary outcome in the total trial cohort and subgroups as per intention-to-treat analysis

Outcome	**Low-flow N=**	**High-flow N=**	**Estimate of Difference (95% CI)***	**Adjusted Estimate of Difference (95% CI)[#]**	**p-value**
Total trial cohort					
Successful anaesthesia without any rescue oxygenation attempt for a hypoxaemic event *n (%)* [#&*]					
Subgroup: patient age^					
<1 year *n (%)*					
1-<5 years *n (%)*					
5-<16 years *n (%)*					

IQR interquartile range; CI confidence interval

* adjusted for study site and patient; p-value = xx

[#] adjusted for age at randomisation, study site and patient

^ p-value represents interaction term determined by logistic regression

Table 3. Secondary outcomes in the total trial cohort

Outcome	**Low-flow N=**	**High-flow N=**	**Estimate of Difference (95% CI)***	**Adjusted Estimate of Difference (95% CI)#**
Number of procedures with hypoxemic event				
Number of procedures with interruption of the procedure for ventilation				
Total length of time experiencing hypoxaemia *median (IQR)*				
Total area under the curve during hypoxaemic event *median (IQR)*				
Minor adverse events				
Epistaxis *n (%)*				
Laryngospasm *n (%)*				
Bronchospasm *n (%)*				
Major adverse events				
Hypotension requiring treatment *n (%)*				
Bradycardia requiring treatment *n (%)*				
Cardiac arrest *n (%)*				
Death *n (%)*				
Unexpected PICU admission *n (%)*				
Post-operative mechanical ventilation *n (%)*				
Length of PICU stay *n (%)*				
Length of hospital stay *n (%)*				

SD standard deviation; IQR interquartile range; CI confidence interval
^ denominator is number of patients with a PICU admission
* adjusted for study site and patient
# adjusted for age at randomisation, study site and patient

Table 4. Subgroup analysis of secondary outcomes for children with a rescue attempt

Outcome	**Low-flow N=**	**High-flow N=**	**Estimate of Difference (95% CI)***	**Adjusted Estimate of Difference (95% CI)#**
Total length of time experiencing hypoxaemia *median (IQR)*				
SpO_2<80% *median (IQR)*				
SpO_2≥80% *median (IQR)*				
Total area under the curve during hypoxaemic event *median (IQR)*				
SpO_2<80% *median (IQR)*				
SpO_2≥80% *median (IQR)*				
Minor adverse events				
Epistaxis				
SpO_2<80% *n (%)*				
SpO_2≥80% *n (%)*				
Laryngospasm				
SpO_2<80% *n (%)*				
SpO_2≥80% *n (%)*				
Bronchospasm				
SpO_2<80% *n (%)*				
SpO_2≥80% *n (%)*				
Major adverse events				
Hypotension requiring treatment				
SpO_2<80% *n (%)*				
SpO_2≥80% *n (%)*				
Bradycardia requiring treatment				
SpO_2<80% *n (%)*				
SpO_2≥80% *n (%)*				

Outcome	**Low-flow N=**	**High-flow N=**	**Estimate of Difference (95% CI)***	**Adjusted Estimate of Difference (95% CI)#**
Cardiac arrest				
SpO_2<80% *n (%)*				
SpO_2≥80% *n (%)*				
Death				
SpO_2<80% *n (%)*				
SpO_2≥80% *n (%)*				
Unexpected PICU admission *n (%)*				
SpO_2<80% *n (%)*				
SpO_2≥80% *n (%)*				
Post-operative mechanical ventilation *n (%)*				
SpO_2<80% *n (%)*				
SpO_2≥80% *n (%)*				
Length of PICU stay *n (%)*				
SpO_2<80% *median (IQR)*				
SpO_2≥80% *median (IQR)*				
Length of hospital stay *n (%)*				
SpO_2<80% *median (IQR)*				
SpO_2≥80% *median (IQR)*				

SD standard deviation; IQR interquartile range; CI confidence interval
^ denominator is number of patients with a PICU admission
* adjusted for study site and patient
# adjusted for age at randomisation, study site and patient

Supplementary Appendix

S1. List of approved protocol modifications

Version Number and Date	Approval Date	List of Modifications
1; 20/02/2018 (Original)	NA	Original protocol
2; 24/04/2018	07/02/2018	• Minor grammatical changes prior to HREC approval
3; 02/08/2018	23/08/2018	• Extension to a multi-centre study (Women's and Children's Hospital, Adelaide, and Perth Children's Hospital) • Addition of pre-admission email • Addition of study pamphlet as a resource for parents on the day of surgery
4; 15/10/2018	22/10/2018	• Addition of new investigators • Addition of new sites (Royal Children's Hospital, Melbourne, and The Children's Hospital at Westmead, Sydney) • Removal of 2L max for low-flow infants • Addition of phone contact pre-operatively

Version Number and Date	Approval Date	List of Modifications
5; 01/03/2019	21/03/2019	• Changes of terminology HFNO to High-Flow, LFNO to Low-Flow • Addition of ORI monitoring and ICM+ • Sample size from 470 to 530 after statistician review • Addition of new investigators
6; 01/07/2020	05/08/2020	• Addition of substudy including Electrical Impedance Tomography (EIT) monitoring for the cohort of ≥37 gestational weeks and up to 14kg • Removal of investigator
7; 22/12/2021		• Clarification and improved description of secondary outcomes

Section S2. Definition of outcomes

Primary outcome: Successful anaesthesia without any rescue oxygenation attempt for a hypoxaemic event.

Hypoxaemia: Normally, hypoxaemia for anaesthesia is defined as an oxygen saturation of ≤90%. However, dependent on the patient's physiology, age and starting oxygen saturation levels prior to the procedure, the anaesthetist can accept transiently lower oxygen saturation levels if required to allow an uninterrupted surgical procedure. For the purpose of this study, we will not define a specific threshold for acceptable oxygen saturations as these are defined case by case. Similarly, the surgical procedure can contribute to hypoxaemia and acceptance of this is again at the discretion of the anaesthetist and surgeon. The investigators' view is that a hypoxaemic event that requires rescue intervention irrespective of the cause is the true and important outcome measure for this study. Hypoxaemic events due to surgical interventions such as airway ballooning will not contribute to the primary outcome but will be analysed separately. Rescue oxygenation: The surgical procedure is interrupted and the anaesthetist attempts to improve oxygenation of the child using either bag mask ventilation, insertion of an endotracheal tube or laryngeal mask followed by positive pressure ventilation.

Secondary outcomes

- Total length of time patient experiences hypoxaemia (seconds) during the entire microlaryngoscopy (MLB) procedure defined as time from SpO_2<90% until return to ≥90%;

- Severity of hypoxaemia (as per the primary outcome, hypoxaemic events due to surgical interventions such as airway ballooning will not contribute to these outcomes), defined by:
    - the cumulative area under the curve (SpO_2<90%) for all hypoxaemic events that occurred during the procedure;
    - the cumulative area under the curve (SpO_2<90%) divided by cumulative duration for all hypoxaemic events that occurred during the procedure (hypoxaemic load); and
    - geometric centre (x co-ordinate, number of seconds since the start of the hypoxaemic event; y co-ordinate, SpO_2 value) of the worst hypoxaemic event, with the worst hypoxaemic event defined as the hypoxaemic event (SpO_2<90%) with the lowest y co-ordinate of the geometric centre (SpO_2 value);
- Minor adverse events occurring during the MLB:
    - epistaxis;
    - laryngospasm; and
    - bronchospasm.
- Major adverse events:
    - hypotension requiring treatment;
    - bradycardia requiring treatment;
    - cardiac arrest with or without return of spontaneous circulation at any time during procedure;

    - death within 24 hours from start of procedure.
- Requirement for unexpected paediatric intensive care unit (PICU) admission is defined as a PICU admission that was not documented as planned and no PICU bed was booked.
- Requirement for postoperative mechanical ventilation or any other form of non-invasive ventilation including high-flow nasal oxygen.
- Length of PICU stay defined as the time from the start of the MLB to discharge from PICU.
- Length of hospital stay is defined as the time from the start of the MLB to discharge from hospital.