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Title Page:

Trans-nasal Humidified Rapid-Insufflation Ventilatory Exchange in Children Requiring Emergent Intubation (Kids THRIVE): A Protocol for a Randomised Controlled Trial

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Trial Registration:

This trial is registered in the Australian New Zealand Clinical Trial Registry

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Steering Committee:

Each site is represented by at least one member for the steering group:

Shane George, Andreas Schibler, Ben Gelbart, Arjun Chavan, Anusha Ganeshalingham, Stuart Dalziel, Katie Rasmussen, Susan Humphreys

Data and Safety Monitoring Board (DSMB):

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Author contributions:

SG, AS and SH were responsible for identifying the research question and contributing the drafting of the protocol. BG, PS, SD, AG, JF, AC, LJS, TW have contributed to the development of the protocol and study design. SG was responsible for drafting this paper, with comments and feedback from all other authors. All authors attest to having approved the final manuscript. SG and AS take responsibility for the manuscript as a whole.

Declarations:

SG, AS and SD received travel support from Fisher and Paykel Healthcare. All other authors have no conflicts to disclose. Fisher and Paykel have provided equipment and consumables for the study, but have had no input in the study design.

Key Words:

Intubation, Apnoeic Oxygenation, Airway Management, Paediatrics

Abbreviations:

ED – Emergency Department

HFAO – High Flow Apnoeic Oxygenation

ICU – Intensive Care Unit

NHF – Nasal High Flow

THRIVE – Trans-nasal Rapid Insufflation Ventilatory Exchange

Abstract:

Introduction

Emergency intubation of children with abnormal respiratory or cardiac physiology is a high-risk procedure and associated with a high incidence of adverse events including hypoxemia. Successful emergency intubation is dependent on inter-related patient and operator factors. Pre-oxygenation has been used to maximise oxygen reserves in the patient and to prolong the safe apnoeic time during the intubation phase. Trans-nasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) prolongs the safe apnoeic window for a safe intubation during elective intubation [1]. We designed a clinical trial to test the hypothesis that THRIVE reduces the frequency of adverse and hypoxic events during emergency intubation in children and to test the hypothesis that this treatment is cost-effective compared to standard care.

Methods and Analysis

The Kids THRIVE trial is a multicentre randomised controlled trial performed in participating emergency departments and paediatric intensive care units. 960 infants and children aged 0-16 years requiring emergency intubation for all reasons will be enrolled and allocated to THRIVE in a 1:1 allocation with stratification by age (<1 year, 1-7 years, >7 years) and operator (junior and senior). Children allocated to THRIVE will receive weight appropriate trans-nasal flow rates with 100% oxygen whereas children in the control arm will not receive any trans-nasal oxygen insufflation. The primary outcomes are defined as: 1) the proportion of hypoxic events during the intubation phase defined as SpO2 < 90% (patient dependent variable) and; 2) the proportion of first intubation attempt success rate without hypoxaemia (operator dependent variable). Analyses will be conducted on an intention to treat basis.

Ethics and Dissemination. Ethics approval for consent to continue has been obtained (HREC/16/QRCH/81). The trial has been actively recruiting since May 2017. The study findings will be submitted for publication in a peer reviewed journal.

Trial Registration Number ACTRN12617000147381

Strengths and limitations of this study:

- This study is testing the efficacy and safety of a simple intervention during emergency intubation in children.
- The intervention aims to reduce operator and patient related adverse outcomes related to hypoxemia and time pressure.
- The study includes a detailed monitoring of the procedures using video recording of the intubation for high data fidelity in a highly stressful study environment.
- The study includes analysis of length of mechanical ventilation and length of hospital stay.
- The study will be the largest randomised controlled trial performed in paediatric emergency intubation.
- Blinding of the intervention is not possible due to visual differences in the intervention arm.

BACKGROUND:

Emergency intubation of the trachea in critically ill children represents one of the most challenging procedures that a clinician working with acutely ill children performs. The intubation of children with unstable physiology in the emergency department (ED) or intensive care unit (ICU) is associated with a high rate (up to 40%) of life-threatening adverse events [2]. Successful emergency intubation is dependent on inter-related patient and operator factors. While a large body of literature defines optimal practice in intubation and difficult airway management in controlled theatre settings, emergency intubations in critically ill children are characterised by a deteriorating, unstable patient, sometimes with features of a difficult airway, yet are predominantly managed by ED and ICU teams rather than anaesthetists.

The incidence of paediatric emergency intubations is relatively low even in high volume tertiary paediatric emergency departments, resulting in infrequent exposure of medical staff to this vital and time-critical procedure and limited practical experience in comparison to anaesthetists in an operating theatre setting. These challenges are even greater in regional and district hospitals, where paediatric emergency intubations represent relatively rare events. Therefore, techniques to optimise intubation conditions and improve patient related and operator dependent factors are essential to increase the safety of emergency paediatric intubations in all settings [3].

The most critical phase of intubation is the period when clinicians attempt to secure the airway with an endotracheal tube; during this phase the child is apnoeic and residual oxygen capacity of the lung is being depleted. To improve child related factors, pre-oxygenation prior to induction of anaesthesia has been described since 1955 as a mechanism for maximising oxygen reserves and therefore prolonging the safe apnoeic time available for

intubation particularly in emergency and difficult intubations [4]. Infants and children have, in comparison to adults, a much lower tolerance for emergency intubation [5]. As a result, they are more likely to experience alveolar de-recruitment and significant oxygen desaturation. Recent studies have shown that any failed attempt of emergency intubation is associated with a prolonged need for mechanical ventilation in intensive care [6, 7]. Pre-oxygenation does not supply an ongoing gas exchange and therefore there is an urgent need for newer methods to continue improved oxygenation during the apnoeic phase.

We have recently shown that the safe apnoeic time in healthy infants and children undergoing elective intubation can be substantially extended with a new technique, called transnasal humidified rapid insufflation ventilator exchange (THRIVE) [1]. THRIVE provides high-flow humidified oxygen through nasal cannulae and allows continued peri-anaesthetic oxygen delivery during apnoea. The benefit of THRIVE in allowing more time for safe intubation, is thus likely beneficial in those difficult anatomical airways and cardiorespiratory compromise during emergency intubation.

In order to improve emergency intubation conditions in children, our aim is to investigate the efficacy of THRIVE in critically ill children aged between 0 and 16 years of age in a large multi-centre trial. ***We hypothesise that THRIVE reduces the frequency of life-threatening*** **oxygen** ***desaturation and increases frequency of first attempt success without hypoxia in emergent intubation*** of children compared with standard practice. We also aim to demonstrate that this leads to a reduced proportion of adverse events and reduced length of mechanical ventilation or length of stay in intensive care.

Economic evaluation will be critical to determine if cost savings can be made. This project will assess health economic impacts and cost-effectiveness of the intervention, taking into account the heterogeneity of service users, health system, geographical and economic conditions and end implications for resource allocation from the payer's perspective. The modelling will account for the opportunity cost and affordability of the health system payer.

METHODS:

Study Design and Settings

This study is a multicentre, non-blinded, randomised controlled trial evaluating the efficacy of THIRVE used for apnoeic oxygenation during emergency intubation of children aged 0-16 years. The study will be conducted in the EDs and paediatric intensive care units (PICUs) of participating hospitals.

Participants

Infants and children will be identified and recruited by treating clinicians in the ED and PICU of the participating hospitals. All patients being intubated in these locations will be screened for inclusion in the study. Patients meeting all inclusion criteria and no exclusion criteria **(Table 1)** are eligible for randomisation.

Consent and Ethical Considerations

One of the primary challenges in performing research in an emergency setting is the inability to obtain true informed consent. Frequently, parents and guardians are not initially available when their child is brought into the ED. Furthermore, when parents or guardians are present, they are often too distressed by the situation to comprehend study procedures and there is not enough time to obtain informed consent [8-10].

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. Aged less than 16 years at the time of randomisation; AND	1. Planned endotracheal tube changes; OR 2. Intention for a primary nasal intubation; OR
2. Requires emergency intubation and ventilation in the ED or ICU; AND	3. Intubation is required immediately for loss of cardiac output or respiratory arrest; OR
3. Consent can be obtained from a parent or legal guardian (prospectively or delayed)	4. Location of intubation is outside ED or ICU; OR 5. presence of blocked nasal airway due to anatomical abnormalities; OR 6. blocked nasal airway due to acute injury, trauma or disease.

In all participating centres, prospective consent will be obtained from the parent or guardian where possible. When prospective consent is not possible or practical, and local legislation allows, patients will be randomised to the study and written informed consent to remain in the study will be sought from parents and guardians at the earliest possible time after emergency stabilisation of the child (consent-to-continue). Data for children whose parents and guardians do not wish for their child to remain in the study will be handled according to local hospital policies, and the data will not be available for analysis.

This study has ethical approval for delayed consent for participating Australian sites by the Children's Health Queensland Human Research Ethics Committee (HREC/16/QRCH/81). For

sites in New Zealand approval has been received for prospective consent (Health and Disability Ethics Committee 17/NTA/120).

Randomisation

A computer based randomisation will be used to assign patients in a 1:1 ratio using variable block sizes. The allocation will be stratified by age (<1 year, 1-7 years, >7 years), by level of the intended first operator seniority (junior and senior medical officer) and per site (hospital and ED or ICU). Sequentially numbered sealed opaque envelopes containing patient CRFs will be provided to sites and indicate the allocated treatment arm when opened. Randomisation will be undertaken by the enrolling clinician once the operator for the procedure has been determined by selecting the next number study pack.

Intervention

The definition of the different phases of intubation is pertinent for the precision of the data capture and accuracy of the primary outcome (**Figure 1**).

Pre-oxygenation phase

The pre-oxygenation phase is defined as the period in preparation for intubation where oxygen is delivered to the patient to maximise oxygen concentration in the functional residual capacity (FRC) of the lung. For the purposes of this study, pre-oxygenation can be delivered by any method, including nasal high flow, at the discretion of the treating clinician. Pre-oxygenation should be provided with a high fraction of inspired oxygen (FiO_2) for at least 3 minutes where possible. Where pre-oxygenation with high FiO_2 is contra-indicated or considered not appropriate for the patient by the treating clinician (e.g. single ventricle physiology, unbalanced circulations), the FiO_2 applied during the apnoeic phase should be the same as the FiO_2 used during pre-oxygenation. The method used, FiO_2 and duration of preoxygenation will be collected and reported.

Apnoeic oxygenation phase

The apnoeic phase begins at onset of muscle paralysis for rapid sequence induction (RSI) leading to apnoea, or at the time when pre-oxygenation and/or non-invasive ventilation are stopped for the purpose of inserting the endotracheal tube. This is approximately 30 seconds after the administration of suxamethonium or 45-60 seconds after the administration of rocuronium, vecuronium, cisatracurium, or pancuronium. For the purposes of this study, the apnoeic phase will be defined as commencing at the time that the mask (or nasal prongs) used for pre-oxygenation or pre-intubation non-invasive ventilation (e.g. by bag and mask) is removed from the face. This correlates approximately with the time of onset of paralysis or the initiation of the intubation attempt if assisted ventilation is required prior to intubation. The study intervention will be applied at the onset of this period.

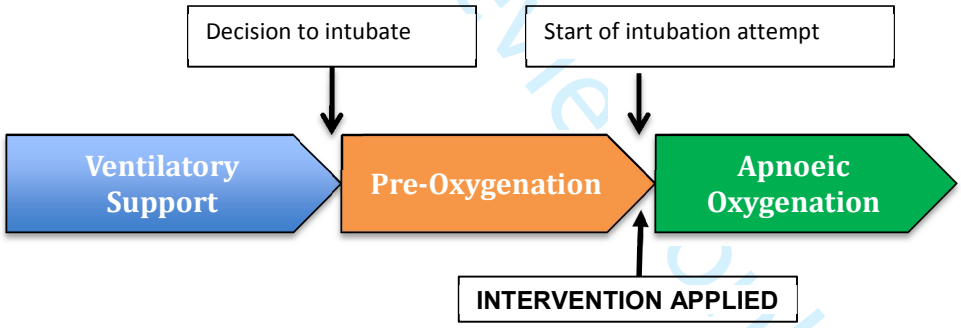

Figure 1. Definition of intubation phases.

Treatment Arms

Patients will be randomised to receive either:

1. Standard care as per site specific procedures / physician discretion
2. THRIVE: Apnoeic oxygenation with nasal high-flow

Standard care. Children randomised to the standard care treatment arm will be intubated as per site specific procedures/guidelines at clinician preference. At the onset of the apnoeic

phase, as defined above, all oxygen sources must be removed from the patient during the intubation attempted.

THRIVE Intervention. Patients in the THRIVE treatment arm will be provided nasal high flow oxygen rates as per the table below (**Table 2**), with an FiO_2 of 1.0 using an Optiflow™ THRIVE system (Fisher and Paykel Healthcare, Auckland, New Zealand). The flow rates selected are consistent with previously published flow rates, and have demonstrated and increase in safe apnoea time in children undergoing elective intubation [1].

Where pre-oxygenation with 100% oxygenation is contra-indicated or considered not appropriate for the patient by the treating clinician (e.g. single ventricle physiology, unbalanced circulations), the FiO_2 applied during the apnoeic phase should be the same as the FiO_2 used during pre-oxygenation. THRIVE is to be applied immediately when the mask for pre-oxygenation is removed from the face and will be maintained throughout the apnoeic period and during intubation attempts. Where NHF is used as a preoxygenation technique it can remain in place for the intervention group, ensuring that the FiO2 is 100%, or the FiO2 is documented on the CRF in cases where high oxygen concentrations are contraindicated. THRIVE nasal prongs may be removed if rescue bag mask ventilation is required due to desaturation. The prongs will be removed on confirmation of successful endotracheal intubation.

Study outcomes

The clinically relevant and patient centred outcome measures for intubation are hypoxia and the number of attempts for a successful intubation, both of which are strongly interlinked [11, 12]. Therefore, the primary outcomes for this study are defined as the 1) proportion of hypoxic events (patient dependent variable) and; 2) the proportion of successful first-attempt intubations (operator dependent variable).

Table 2: THRIVE flow rate regimen

Weight	THRIVE Flow rates
0-12 kg	2L/kg/min
13-15kg	30L/min
16-30 kg	35L/min
31-50 kg	40L/min
>50 kg	50L/min

Primary Outcomes:

1. The proportion of emergency intubations with at least one hypoxic event (patient dependent variable).
2. The proportion of successful intubations (operator dependent variable).

Hypoxia is transcutaneous oxygen saturations (SpO_2) of ≤ 90% or a SpO_2 saturation difference ≥ 10% for patients with cyanotic congenital heart disease with known substantial right-to-left shunts) measured with the bedside monitor and with an accurate quality of the trace within the period from first insertion of laryngoscope until 2 minutes post successful and final ETT placement (Figure 2) [11, 13].

A successful intubation is defined as a successful intubation at first attempt without any hypoxemia (SpO_2 ≤ 90% or saturation difference ≥10% for right left shunt). An *unsuccessful intubation* is either a successful first attempt intubation associated with hypoxia *or* requirement for any multiple (>1) intubation attempts.

Intubation attempt is defined as:

- *An intubation* attempt is defined by a single advanced airway manoeuvre beginning with the insertion of the laryngoscope into the child's mouth and ending when the laryngoscope is removed from the child's mouth [14], or where there is a change in operator during the procedure even if the device is not removed.
- *An intubation attempt with rescue oxygenation* is defined as a period with at least one unsuccessful intubation attempt followed by rescue bag mask ventilation.

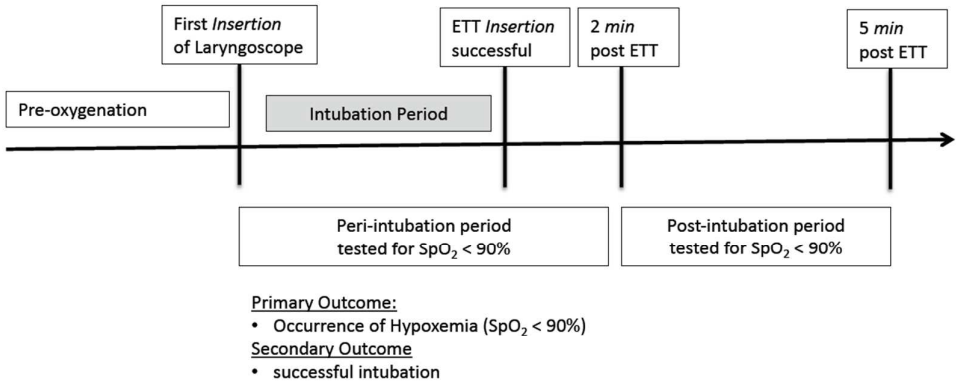

Figure 2. Sequence of events and time lines with the definitions of the study periods.

Additional secondary outcomes

1.) Number of intubation attempts and intubation attempts with rescue oxygenation, 2.) lowest oxygen saturations during each attempt and throughout total intubation period 3.) length of mechanical ventilation, 4.) ventilation free days (VFD, defined as the duration of respiratory support for all episodes with an endotracheal tube *in situ* for the first 28 days post randomisation censored at 28days (VFD will be recorded as 0 in patients that died within 28 days post randomisation), 5.) length of ICU stay in days, 6.) length of hospital stay in days, 7.) proportion of Minor Adverse Events (AE) defined as one of the following in the period starting at the commencement of the intubation attempt until 2 minutes after

intubation: bradycardia, not requiring treatment; hypotension, not requiring treatment; main stem bronchial intubation; oesophageal intubation with immediate recognition; emesis without aspiration; epistaxis; dental or lip trauma, and 8.) proportion of Major Adverse Events (MAE) defined as one of the following in the period starting at the commencement of the intubation attempt until 2 minutes after intubation: cardiac arrest with or without return of spontaneous circulation; oesophageal intubation with delayed recognition (>60 seconds); emesis with aspiration; hypotension requiring treatment; bradycardia requiring treatment; laryngospasm; malignant hyperthermia; pneumothorax or pneumomediastinum [2, 14], and 9.) death defined as death during current hospital admission.

All relevant study data during the study intervention will be recorded directly onto research data form and captured with video recording of the intubation attempt and for 5 minutes post ETT insertion (see below): 1.) Observations prior to first intubation attempt: this includes heart rate, oxygen saturations, blood pressure (this data is routinely recorded), 2.) Operator level of person performing intubation (senior: Consultant or equivalent or junior: registrar), 3.) speciality/discipline of person performing intubation, 4.) intubation technique and devices used (direct, video, stylet, bougie, etc,), 5.) laryngeal view, grade, 6.) lowest oxygen saturation during any attempt, 7.) lowest blood pressure during any attempt, 8.) highest and lowest pulse rate during attempt, 9.) time taken for intubation attempt, 10.) time of successful intubation or abandoned attempt, 11.) observations immediately following successful intubation, 12.) end tidal CO_2 immediately after intubation (if available), 13) Minor and Major Adverse events. Additional data include (but not limited): length of mechanical ventilation, length of ICU stay, length of hospital stay, and death.

One of the research, ED or ICU, nurses will be allocated to undertake the data collection during the procedure; this will usually be the nurse allocated to be the 'scribe' for the

procedure. In addition, a video recording of the intubation will be collected to allow validation of recorded data and collection of missing data.

Video of intubation procedure. To maximise the quality of the data collected during a stressful procedure the entire intubation procedure will be captured by video recording. A video recording device will be provided to all investigating sites. The device will be placed in a location to have a clear view of the intubating clinician and child's face as well as the child's bedside monitor to ensure accurate observations are recorded during the procedure. Video will be analysed for a period of five minutes after successful intubation screening for delayed adverse events. The use of the video has been extensively tested in the feasibility study and has not been perceived by nursing nor medical staff as intrusive.

Data recorded on paper CRFs will be verified against the video recording and corrections made where errors are identified by local research staff. Where there is a discrepancy between manually recorded data and video data, the video collected data will be used for analysis. Local research staff will be responsible for viewing the video and validating/collected the required data for the CRF. Ten percent of the videos will be centrally reviewed for accuracy of data collection. If a discrepancy is identified in the primary outcome, or key secondary outcome, at a site all videos from that site will be reviewed. Video recording of children that are consented to participate in the study constitute research records and as such will be stored on a password protected, encrypted storage device at the local site for five years after the study is closed and then destroyed. Video recordings of children that are not consented due to refusal or death prior to consent will form part of the child's hospital record and will be required to be stored under the usual legal guidelines for paediatric records at that institution.

Sample size

In 2016 we audited 30 children undergoing intubation in LCCH ED, of which 12 (40%) needed a second or third attempt of intubation and 50% experienced an adverse event such as hypoxemia (10%), hypotension (8%) and ETT misplacement (21%) and other (11%). Data obtained from 140 intubations in PICU showed similar results with 30% requiring more than one attempt. This proportion of the hypoxemia primary outcome occurrence and adverse events in our own audit data is comparable to a recent publication reporting emergency intubation in the United States of America [2]. In this setting, the authors described that in 1,256 children undergoing emergency intubation, 16% of children experienced a desaturation to less than 90% during the first attempt of intubation and on average 40% required a second attempt at least. In this paper the authors describe per age group a very similar distribution of failed attempts, with age groups defined <1 year, 1-7years and > 7 years. A conservative estimate of the primary outcome hypoxemia is set at 16%. We assume 90% power to detect a 50% reduction of desaturation events (hypoxia) from 16% to 8% and an alpha of 0.025 (Bonferroni's correction for two primary outcomes). For our other primary outcome, proportion of successful intubations, we estimate an increase from 60% to 80%; with 90% power and an alpha of 0.025, 258 participants are required. Therefore, an overall total sample of 960 children is required including 15% attrition which satisfies the sample size requirements for both outcomes.

Statistical Analysis Plan:

Descriptive statistics will be utilised to report on the baseline characteristics of the total study cohort and each subgroup, as well as by site. The primary and secondary outcome measures investigating binary clinical outcomes will be compared using a chi-squared test, and the difference between treatment groups will be reported as the risk difference, 95% confidence interval and p-value. For continuous outcomes it will first be determined if the data are normally distributed; if so, a t-test will be used for comparison, otherwise, a Mann-

Whitney U test will be used. Analysis will be by intention-to-treat. Statistical significance will be set at the 0.025 level for primary outcomes, and 0.05 for other comparisons. Post-hoc power analyses may be undertaken to determine if results found in sub-group analyses are reliable particularly for age groups (<1 year, 1-7years and > 7 years). A pre-planned secondary analysis of the outcome data will be reported for children with SpO2 < 80% during intubation.

Health economics evaluation

We will undertake ex-post within-trial modelling, to determine the cost-effectiveness of the intervention compared to standard care, using a cost-effectiveness approach. Unit costs will be extracted from standard sources. A standard within-trial cost utility analysis will be undertaken under the horizon of 28 days. This will compare costs and benefits in terms of resource use related to the intervention and other care and length of stay in both PICU and non-intensive care. Estimates of mean costs and confidence intervals will be provided. Models will include sensitivity analysis. Resource use data will be collected for trial participants and the collated unit costs will be assigned to the resource utilization to provide overall costs for both arms of the trial. The analysis will be from the health care provider perspective. The New Zealand country health care costs will be analysed separately and findings from different systems will be compared.

Time Frame:

It is anticipated that a three-year recruitment period is required to achieve the required sample size.

Adverse events and monitoring/reporting:

The Data Safety Monitoring Board (DSMB) consists of an anaesthetist, a paediatric intensivist, and a statistician. None of the DSMB members will be involved in recruitment of study patients at their site. DSMB members will not be supervised by any study investigator, or participate as investigators in any study currently under review by this DSMB. The primary objective of the DSMB is to monitor the safety of the intervention and the validity and integrity of the data from the Kids THRIVE study. Additionally, the DSMB will evaluate the pace of recruitment and will make recommendations to the Kids THRIVE Chief investigator(s) and Steering Board regarding the continuation, modification, or termination of the study.

Adverse event data is collected as part of the study design and form the primary and secondary outcomes of the study. Conditions that are present at screening and do not deteriorate will not be considered adverse events. Patients participating in this trial are critically ill and the reason for requiring the intubation is often respiratory, neurologic, or cardiovascular failure with acute risk of death. Except for death during or within one hour of intubation and oesophageal intubation with late recognition, adverse events as listed in the outcome parameters are expected and according to current clinical practice “accepted” outcomes. Hence these outcomes are not routinely reported as adverse events nor to the DSMB. However, if any of the attending clinicians suspect an adverse event that is related to the study design, such an adverse event will be reported.

Serious adverse events are defined as:

1. Cardiac arrest or death during or within an hour of the intervention.
2. Oesophageal intubation with late recognition

Any SAE will be reported to the HREC within 24-72 hours of occurrence, in accordance with the safety reporting policy of the HREC. Set DSMB review points on the progress and safety of the trial are pre-defined as after the primary outcome is known for 200 children.

Data accuracy and integrity

Intubation and ventilation of a child in the ED and ICU settings represents a highly stressful event, and requires significant human resources to assemble equipment while effectively managing a critically unwell patient. As a result, attention to data collection for a research study is often overlooked, with the immediate needs of the patient always taking priority. This study is dependent on high quality and accurate data at a critical moment of the patient's management, and the potential for missing or inaccurate data collection is high. It is also recognised that significant bias can be introduced to a study of this type when relying on retrospective recall of critical data values. A retrospective review of intubation records compared to video recorded data has highlighted that there is a significant under-reporting of adverse events, especially oxygen desaturation, and an over-reporting of first attempt success rates, in the magnitude of 21% and 12% respectively, when reliant on operator/observer reported data [15].

For this reason, a video recording of the intubation procedure will be captured for data verification purposes and to protect the integrity of the primary end-point. Where a discrepancy between the manually recorded data and video recorded data exists, the video recorded data will be used for analysis as it can be objectively confirmed.

Current status of trial:

The study enrolment has commenced in May 2017 and the sites involved are: Lady Cilento Children's Hospital Brisbane, Townsville Hospital, Gold Coast University Hospital, Royal Children's Hospital Melbourne, Starship Children's Hospital Auckland.

SIGNIFICANCE

This large multicentre randomised trial may help define the role of THRIVE during emergency intubation in infants and children. The intubation of a child in the emergency setting places a tremendous emotional strain on both the child and parents. Dependent on the skill level and experience of the medical doctor performing the procedure, the professional stress level may also be very high as intubation is a high-risk procedure, which needs to be accomplished in a timely manner. The study will provide high fidelity data using video recording of the study interventions and the findings will easily be translated into clinical practice.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	#3	Date and version identifier	
Funding	#4	Sources and types of financial, material, and other support	3
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-3
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	N/A

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	3,19
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7-9
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7-9
Objectives	#7	Specific objectives or hypotheses	13-16
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-13

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/A
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-16
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	N/A
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	11

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15-16,21
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16-17,21
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16-16,21
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18-19
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18-19
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18-19

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	19-20
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	19-20
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	19-20
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	9-11
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9-11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	3
Data access	#29	Statement of who will have access to the final trial dataset,	

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	22
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

BMJ Open

Trans-nasal Humidified Rapid Insufflation Ventilatory Exchange in Children Requiring Emergent Intubation (Kids THRIVE): A Protocol for a Randomised Controlled Trial

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Title Page:

Trans-nasal Humidified Rapid-Insufflation Ventilatory Exchange in Children Requiring Emergent Intubation (Kids THRIVE): A Protocol for a Randomised Controlled Trial

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Trial Registration:

This trial is registered in the Australian New Zealand Clinical Trial Registry

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Author contributions:

SG, AS and SH were responsible for identifying the research question and contributing the drafting of the protocol. BGe, SE, SSG, NS, SRD, AG, KF, AC, LJS, MF, KR and TW have contributed to the development of the protocol and study design. BGa developed the health economic measures and analysis in the study. KG provided expert statistical advice and input. SG was responsible for drafting this paper, with comments and feedback from all other authors. All authors attest to having approved the final manuscript. SG and AS take responsibility for the manuscript as a whole.

Declarations:

SG, AS and SRD received travel support from Fisher and Paykel Healthcare. All other authors have no conflicts to disclose. Fisher and Paykel have provided equipment and consumables for the study, but have had no input in the study design.

Key Words:

Intubation, Apnoeic Oxygenation, Airway Management, Paediatrics, Nasal High-Flow, Transnasal Humidified Rapid Insufflation Ventilatory Exchange.

Abbreviations:

AE – Adverse Event

CRF – Case Report Form

ED – Emergency Department

ETT – Endotracheal Tube

FiO_2 – Fraction of inspired oxygen

FRC – Functional Residual Capacity

HFAO – High Flow Apnoeic Oxygenation

HREC – Human Research Ethics Committee

ICU – Intensive Care Unit

MAE – Major Adverse Events

NHF – Nasal High Flow

PICU – Paediatric Intensive Care Unit

RSI – Rapid Sequence Induction

SAE – Serious Adverse Event

THRIVE – Transnasal Humidified Rapid-Insufflation Ventilatory Exchange

VFD – Ventilator Free Days

Abstract:

Introduction

Emergency intubation of children with abnormal respiratory or cardiac physiology is a high-risk procedure and associated with a high incidence of adverse events including hypoxemia. Successful emergency intubation is dependent on inter-related patient and operator factors. Pre-oxygenation has been used to maximise oxygen reserves in the patient and to prolong the safe apnoeic time during the intubation phase. Trans-nasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) prolongs the safe apnoeic window for a safe intubation during elective intubation. We designed a clinical trial to test the hypothesis that THRIVE reduces the frequency of adverse and hypoxemic events during emergency intubation in children and to test the hypothesis that this treatment is cost-effective compared to standard care.

Methods and Analysis

The Kids THRIVE trial is a multicentre randomised controlled trial performed in participating emergency departments and paediatric intensive care units. 960 infants and children aged 0-16 years requiring emergency intubation for all reasons will be enrolled and allocated to THRIVE in a 1:1 allocation with stratification by site, age (<1 year, 1-7 years, >7 years) and operator (junior and senior). Children allocated to THRIVE will receive weight appropriate trans-nasal flow rates with 100% oxygen whereas children in the control arm will not receive any trans-nasal oxygen insufflation. The primary outcomes are defined as: 1) hypoxemic event during the intubation phase defined as SpO_2 < 90% (patient dependent variable) and; 2) first intubation attempt success without hypoxemia (operator dependent variable). Analyses will be conducted on an intention to treat basis.

Ethics and Dissemination

Ethics approval for consent to continue has been obtained (HREC/16/QRCH/81). The trial has been actively recruiting since May 2017. The study findings will be submitted for publication in a peer reviewed journal.

Trial Registration Number ACTRN12617000147381

Strengths and limitations of this study:

- This is the first study investigating the use of THRIVE in paediatric patients in the emergency and intensive care setting.
- Data collected during a stressful and often unplanned procedure is validated against a video recording to ensure data accuracy and fidelity. Where there is a discrepancy between the two values, video data will be used for analysis.
- Apart from the application of apnoeic oxygenation, all other aspects of the intubation process remain at clinician preference ensuring that bias and confounding is minimised and any observed effect can be more reliably attributed with t0 intervention applied.
- Blinding of the intervention is not possible due to visual differences in the intervention arm.
- Seniority and experience of the intubating clinician may influence the likelihood of intubation success. To limit this potential confounder, there is a stratification into junior and senior operators with a pre-planned sub group analysis.

BACKGROUND:

Emergency intubation of the trachea in critically ill children represents one of the most challenging procedures that a clinician working with acutely ill children performs. The intubation of children with unstable physiology in the emergency department (ED) or intensive care unit (ICU) is associated with a high rate (up to 40%) of life-threatening adverse events [1]. Successful emergency intubation is dependent on inter-related patient and operator factors. While a large body of literature defines optimal practice in intubation and difficult airway management in controlled theatre settings, emergency intubations in critically ill children are characterised by a deteriorating, unstable patient, sometimes with features of a difficult airway, yet are predominantly managed by ED and ICU teams rather than anaesthetists.

The incidence of paediatric emergency intubations is relatively low even in high volume tertiary paediatric EDs, resulting in infrequent exposure of medical staff to this vital and time-critical procedure and limited practical experience in comparison to anaesthetists in an operating theatre setting. These challenges are even greater in regional and district hospitals, where paediatric emergency intubations represent relatively rare events. Therefore, techniques to optimise intubation conditions and improve patient related and operator dependent factors are essential to increase the safety of emergency paediatric intubations in all settings [2].

The most critical phase of intubation is the period when clinicians attempt to secure the airway with an endotracheal tube; during this phase the child is apnoeic and residual oxygen capacity of the lung is being depleted. To improve child related factors, preoxygenation prior to induction of anaesthesia has been described since 1955 as a mechanism for maximising oxygen reserves and therefore prolonging the safe apnoeic time available for intubation

particularly in emergency and difficult intubations [3]. Infants and children have, in comparison to adults, a much lower tolerance for emergency intubation [4]. As a result, they are more likely to experience alveolar de-recruitment and significant oxygen desaturation. Recent studies have shown that any failed attempt of emergency intubation is associated with a prolonged need for mechanical ventilation in intensive care [5, 6]. Preoxygenation does not supply an ongoing gas exchange and therefore there is an urgent need for newer methods to continue improved oxygenation during the apnoeic phase.

We have recently shown that the safe apnoeic time in healthy infants and children undergoing elective intubation can be substantially extended with a new technique, called Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) [7]. THRIVE provides high-flow humidified oxygen through nasal cannulae and allows continued peri-laryngoscopy oxygen delivery during apnoea. The benefit of THRIVE in allowing more time for safe intubation is thus likely beneficial in those difficult anatomical airways and cardiorespiratory compromise during emergency intubation. There are currently no published randomised studies investigating the use of THRIVE or other forms of apnoeic oxygenation in emergency intubation in children. In the adult literature, there have been a number of systematic reviews and meta-analyses on the topic of apnoeic oxygenation [8-13]. In these reviews there is significant heterogeneity in the studies included, and a paucity of adequately powered randomised trials. Overall, in adults there is a reduced frequency of oxygen desaturation when apnoeic oxygenation is used during intubation, however this effect has not been demonstrated in patients with respiratory failure.

In order to improve emergency intubation conditions in children, our aim is to investigate the efficacy of THRIVE in critically ill children aged between 0 and 16 years of age in a large multicentre trial. ***We hypothesise that THRIVE reduces the frequency of life-threatening***

oxygen *desaturation and increases frequency of first attempt success without hypoxemia in emergent intubation* of children compared with standard practice. We also aim to demonstrate that this leads to a reduced proportion of adverse events and reduced length of mechanical ventilation or length of stay in intensive care. This project will assess health economic impacts and cost-effectiveness of the intervention, taking into account the heterogeneity of service users, health system, geographical and economic conditions and end implications for resource allocation from the payer's perspective.

METHODS:

Study Design and Setting

This study is a multicentre, non-blinded, randomised controlled trial evaluating the efficacy of THRIVE used for apnoeic oxygenation during emergency intubation of children aged 0-16 years. The study will be conducted in the EDs and paediatric intensive care units (PICUs) of participating hospitals.

Participants

Infants and children will be identified and recruited by treating clinicians in the ED and PICU of the participating hospitals. All patients being intubated in these locations will be screened for inclusion in the study. Patients meeting all inclusion criteria and no exclusion criteria **(Table 1)** are eligible for randomisation.

In all participating centres, prospective consent will be obtained from the parent or guardian where possible. When prospective consent is not possible or practical, and local legislation allows, patients will be randomised to the study and written informed consent to remain in the study will be sought from parents and guardians at the earliest possible time after emergency stabilisation of the child (consent-to-continue). Data for children whose parents

and guardians do not wish for their child to remain in the study will be handled according to local hospital policies, and the data will not be available for analysis.

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. Aged less than 16 years at the time of randomisation; AND 2. Requires emergency intubation and ventilation in the ED or PICU; AND 3. Consent can be obtained from a parent or legal guardian (prospectively or delayed)	1. Planned endotracheal tube changes; OR 2. Intention for a primary nasal intubation; OR 3. Intubation is required immediately for loss of cardiac output or respiratory arrest; OR 4. Location of intubation is outside ED or ICU; OR 5. Presence of blocked nasal airway due to anatomical abnormalities; OR 6. Blocked nasal airway due to acute injury, trauma or disease.

Randomisation

A computer based randomisation will be used to assign patients in a 1:1 ratio using variable block sizes. The allocation will be stratified by age (<1 year, 1-7 years, >7 years), by level of the intended first operator seniority (junior and senior medical officer) and per site (hospital and ED or ICU). Sequentially numbered sealed opaque envelopes containing patient Case Report Forms (CRFs) will be provided to sites and indicate the allocated treatment arm when opened. Randomisation will be undertaken by the enrolling clinician once the operator for the procedure has been determined by selecting the next number study pack.

Intervention

The definition of the different phases of intubation is pertinent for the precision of the data capture and accuracy of the primary outcome (**Figure 1**).

Preoxygenation phase

The preoxygenation phase is defined as the period in preparation for intubation where oxygen is delivered to the patient to maximise oxygen concentration in the functional residual capacity (FRC) of the lung. For the purposes of this study, preoxygenation can be delivered by any method, including nasal high flow, at the discretion of the treating clinician. Preoxygenation should be provided with a high fraction of inspired oxygen (FiO_2) for at least 3 minutes where possible. Where preoxygenation with high FiO_2 is contra-indicated or considered not appropriate for the patient by the treating clinician (e.g. single ventricle physiology, unbalanced circulations), the FiO_2 applied during the apnoeic phase should be the same as the FiO_2 used during preoxygenation. The method used, FiO_2 and duration of preoxygenation will be collected and reported.

Apnoeic oxygenation phase

The apnoeic phase begins at onset of muscle paralysis for rapid sequence induction (RSI) leading to apnoea, or at the time when preoxygenation and/or non-invasive ventilation are stopped for the purpose of inserting the endotracheal tube. For the purposes of this study, the apnoeic phase will be defined as commencing at the time that the mask (or nasal prongs) used for preoxygenation or pre-intubation non-invasive ventilation (e.g. by bag and mask) is removed from the face. This correlates approximately with the time of onset of paralysis or the initiation of the intubation attempt if assisted ventilation is required prior to intubation. The study intervention will be applied at the onset of this period.

Treatment Arms

Patients will be randomised to receive either:

1. Standard care as per site specific procedures/physician discretion; OR
2. THRIVE: Apnoeic oxygenation with nasal high-flow.

Standard care. Children randomised to the standard care treatment arm will be intubated as per site specific procedures/guidelines at clinician preference. At the onset of the apnoeic phase, as defined above, all oxygen sources must be removed from the patient during the intubation attempted.

THRIVE intervention. Patients in the THRIVE treatment arm will be provided nasal high flow oxygen rates as per **Table 2**, with an FiO_2 of 1.0 using an Optiflow™ THRIVE system (Fisher and Paykel Healthcare, Auckland, New Zealand). The flow rates selected are consistent with previously published flow rates, and have demonstrated an increase in safe apnoea time in children undergoing elective intubation [7].

Where preoxygenation with 100% oxygenation is contra-indicated or considered not appropriate for the patient by the treating clinician (e.g. single ventricle physiology, unbalanced circulations), the FiO_2 applied during the apnoeic phase should be the same as the FiO_2 used during preoxygenation. THRIVE is to be applied immediately when the mask for preoxygenation is removed from the face and will be maintained throughout the apnoeic period and during intubation attempts. Where Nasal High Flow (NHF) is used as a preoxygenation technique it can remain in place for the intervention group, ensuring that the FiO_2 is 100%, or the FiO_2 is documented on the CRF in cases where high oxygen concentrations are contraindicated. THRIVE nasal prongs may be removed if rescue bag mask ventilation is required due to desaturation. The prongs will be removed on confirmation of successful endotracheal intubation.

Study outcomes

The clinically relevant and patient centred outcome measures for intubation are hypoxemia and the number of attempts for a successful intubation, both of which are strongly interlinked [14, 15]. Therefore, the primary outcomes for this study are defined as:

1) hypoxemic event (patient dependent variable) and;

2) successful first-attempt intubation (operator dependent variable).

Table 2: THRIVE flow rate regimen

Weight	THRIVE Flow rates
0-12 kg	2L/kg/min
13-15kg	30L/min
16-30 kg	35L/min
31-50 kg	40L/min
>50 kg	50L/min

Hypoxemia is defined as transcutaneous oxygen saturations (SpO_2) of ≤ 90% or a SpO_2 saturation difference ≥ 10% for patients with cyanotic congenital heart disease with known substantial right-to-left shuntsmeasured with the bedside monitor and with an accurate quality of the trace within the period from first insertion of laryngoscope until 2 minutes post successful and final ETT placement (Figure 2) [14, 16].

A successful first-attempt intubation is defined as a successful intubation at first attempt without any hypoxemia (SpO_2 ≤ 90% or saturation difference ≥10% for right left shunt). An

unsuccessful intubation is either a successful first-attempt intubation associated with hypoxemia *or* requirement for any multiple (>1) intubation attempts.

Intubation attempt is defined as a single advanced airway manoeuvre beginning with the insertion of the laryngoscope into the child's mouth and ending when the laryngoscope is removed from the child's mouth [17], or where there is a change in operator during the procedure even if the device is not removed.

Intubation attempt with rescue oxygenation is defined as a period with at least one unsuccessful intubation attempt followed by rescue positive pressure bag mask ventilation.

Secondary outcomes

1.) Number of intubation attempts and intubation attempts with rescue oxygenation, 2.) lowest oxygen saturations during each attempt and throughout total intubation period 3.) length of mechanical ventilation, 4.) ventilation free days (VFD, defined as the duration of respiratory support for all episodes with an endotracheal tube *in situ* for the first 28 days post randomisation censored at 28days); VFD will be recorded as 0 in patients that died within 28 days post randomisation, 5.) length of ICU stay in days, 6.) length of hospital stay in days, 7.) occurrence of minor adverse events (AE) defined as one of the following in the period starting at the commencement of the intubation attempt until 2 minutes after intubation: bradycardia, not requiring treatment; hypotension, not requiring treatment; main stem bronchial intubation; oesophageal intubation with immediate recognition; emesis without aspiration; epistaxis; dental or lip trauma, 8.) occurrence of major adverse events (MAE) defined as one of the following in the period starting at the commencement of the intubation attempt until 2 minutes after intubation: cardiac arrest with or without return of spontaneous circulation; oesophageal intubation with delayed recognition (>60 seconds); emesis with aspiration; hypotension requiring treatment; bradycardia requiring treatment; laryngospasm;

malignant hyperthermia; pneumothorax or pneumomediastinum [1, 17], and 9.) death defined as death during current hospital admission.

All relevant study data during the study intervention will be recorded directly onto research data form and captured with video recording of the intubation attempt and for 5 minutes post ETT insertion (Figure 2)): 1.) observations prior to first intubation attempt: this includes heart rate, oxygen saturations, blood pressure (this data is routinely recorded), 2.) operator level of person performing intubation (senior: Consultant or equivalent or junior: Registrar), 3.) speciality/discipline of person performing intubation, 4.) intubation technique and devices used (direct, video, stylet, bougie, etc), 5.) laryngeal view, grade, 6.) lowest oxygen saturation during any attempt, 7.) lowest blood pressure during any attempt, 8.) highest and lowest pulse rate during attempt, 9.) time taken for intubation attempt, 10.) time of successful intubation or abandoned attempt, 11.) observations immediately following successful intubation, 12.) end tidal CO_2 immediately after intubation (if available), 13) minor and major adverse events. Additional data include (but not limited): length of mechanical ventilation, length of ICU stay and length of hospital stay.

One of the research, ED or ICU nurses will be allocated to undertake the data collection during the procedure; this will usually be the nurse allocated to be the 'scribe' for the procedure. In addition, a video recording of the intubation will be collected to allow validation of recorded data and collection of missing data.

Video of intubation procedure. To maximise the quality of the data collected during a stressful procedure the entire intubation procedure will be captured by video recording. A video recording device will be provided to all investigating sites. The device will be placed in a location to have a clear view of the intubating clinician and child's face as well as the child's

bedside monitor to ensure accurate observations are recorded during the procedure. Video will be analysed for a period of 5 minutes after successful intubation screening for delayed adverse events. The use of the video has been extensively tested in the feasibility study and has not been perceived by nursing nor medical staff as intrusive.

Data recorded on paper CRFs will be verified against the video recording and corrections made where errors are identified by local research staff. Where there is a discrepancy between manually recorded data and video data, the video collected data will be used for analysis. Local research staff will be responsible for viewing the video and validating/collecting the required data for the CRF. Ten percent of the videos will be centrally reviewed for accuracy of data collection. If a discrepancy is identified in the outcome measures at a site all videos from that site will be reviewed. Video recording of children that are consented to participate in the study constitute research records and as such will be stored on a password protected, encrypted storage device at the local site for five years after the study is closed and then destroyed. Video recordings of children that are not consented due to refusal or death prior to consent will form part of the child's hospital record and will be required to be stored under the usual legal guidelines for paediatric records at that institution.

Sample size

In 2016 we audited 30 children undergoing intubation in Queensland Children's Hospital ED, of which 12 (40%) needed a second or third attempt of intubation and 50% experienced an adverse event such as hypoxemia (10%), hypotension (8%), ETT misplacement (21%) and other (11%). Data obtained from 140 intubations in PICU showed similar results with 30% requiring more than one attempt. This proportion of the hypoxemia primary outcome occurrence and adverse events in our own audit data is comparable to a recent publication reporting emergency intubation in the United States of America [1]. In this setting, the

authors described that in 1,256 children undergoing emergency intubation, 16% of children experienced a desaturation to less than 90% during the first attempt of intubation and on average 40% required a second attempt at least. In this paper the authors describe per age group a very similar distribution of failed attempts, with age groups defined <1 year, 1-7years and >7 years. A conservative estimate of the primary outcome of hypoxemia is set at 16%. We assume 90% power to detect a 50% reduction of desaturation events (hypoxia) from 16% to 8% and an alpha of 0.025 (Bonferroni's correction for two primary outcomes), resulting in 816 participants required. For our other primary outcome, successful first-attempt intubation, we estimate an increase from 60% to 80%; with 90% power and an alpha of 0.025, 258 participants are required. Therefore, an overall total sample of 960 children is required including 15% attrition which satisfies the sample size requirements for both outcomes.

Statistical analysis plan

Descriptive statistics will be utilised to report on the baseline characteristics of the total study cohort and each subgroup, as well as by site. The primary and secondary outcome measures investigating binary clinical outcomes will be compared using a chi-squared test, and the difference between treatment groups will be reported as the risk difference, 95% confidence interval and p-value. For continuous outcomes it will first be determined if the data are normally distributed; if so, a t-test will be used for comparison, otherwise, a Mann-Whitney U test will be used. Analysis will be by intention-to-treat. Statistical significance will be set at the 0.025 level for primary outcomes, and 0.05 for other comparisons. Post-hoc power analyses may be undertaken to determine if results found in sub-group analyses are reliable particularly for age groups (<1 year, 1-7years and >7 years). A pre-planned secondary analysis of the outcome data will be reported for children with SpO_2 < 80% during intubation.

Health economics evaluation

We will undertake ex-post within-trial modelling, to determine the cost-effectiveness of the intervention compared to standard care, using a cost-effectiveness approach. Unit costs will be extracted from standard sources. A standard within-trial cost utility analysis will be undertaken under the horizon of 28 days. This will compare costs and benefits in terms of resource use related to the intervention and other care and length of stay in both PICU and non-intensive care. Estimates of mean costs and confidence intervals will be provided. Models will include sensitivity analysis. Resource use data will be collected for trial participants and the collated unit costs will be assigned to the resource utilization to provide overall costs for both arms of the trial. The analysis will be from the health care provider perspective. The New Zealand country health care costs will be analysed separately and findings from different systems will be compared.

Ethics and dissemination

One of the primary challenges in performing research in an emergency setting is the inability to obtain true informed consent. Frequently, parents and guardians are not initially available when their child is brought into the ED. Furthermore, when parents or guardians are present, they are often too distressed by the situation to comprehend study procedures and there is not enough time to obtain informed consent [18-20].

In all participating centres, prospective consent will be obtained from the parent or guardian where possible. When prospective consent is not possible or practical, and local legislation allows, patients will be randomised to the study and written informed consent to remain in the study will be sought from parents and guardians at the earliest possible time after emergency stabilisation of the child (consent-to-continue). Data for children whose parents

and guardians do not wish for their child to remain in the study will be handled according to local hospital policies, and the data will not be available for analysis.

The study protocol has been reviewed and approved by ethics committees in Australia (Children's Health Queensland Human Research Ethics Committee, HREC/16/QRCH/81) and New Zealand (Health and Disability Ethics Committee 17/NTA/120). This study has ethical approval for consent-to-continue (deferred consent) for participating Australian sites. For sites in New Zealand approval has been received for prospective consent only due to local regulatory requirements. The method of consent will be presented for all enrolled patients, along with summary data for patients eligible but not enrolled.

Results from the study will be submitted to a peer reviewed journal for publication and for presentation at national and international conferences. Once the outcomes are known, targeted knowledge translation activities will be developed and work to incorporate of the results into airway management guidelines will be undertaken.

Patient and Public Involvement:

During the development of the protocol parents of children being intubated were interviewed regarding the acceptability of research participation during a time critical procedure and the acceptability of video recording during the procedure. Parents were supportive of research in these situations, and also reported no concerns regarding the use of video recording during the procedure. Participants are asked if they would like to receive a copy of the outcomes of the study during the consent process and an email address is collected to facilitate distribution of any relevant publications.

Time Frame:

It is anticipated that a three-year recruitment period is required to achieve the required sample size.

Adverse events and monitoring/reporting:

The Data and Safety Monitoring Board (DSMB) consists of an anaesthetist, a paediatric intensivist, and a statistician. None of the DSMB members will be involved in recruitment of study patients at their site. DSMB members will not be supervised by any study investigator, or participate as investigators in any study currently under review by this DSMB. The primary objective of the DSMB is to monitor the safety of the intervention and the validity and integrity of the data from the Kids THRIVE study. Additionally, the DSMB will evaluate the pace of recruitment and will make recommendations to the Kids THRIVE Chief Investigator(s) and Steering Board regarding the continuation, modification, or termination of the study.

Adverse event data is collected as part of the study design and form the primary and secondary outcomes of the study. Conditions that are present at screening and do not deteriorate will not be considered adverse events. Patients participating in this trial are critically ill and the reason for requiring the intubation is often respiratory, neurologic, or cardiovascular failure with acute risk of death. Except for death during or within one hour of intubation and oesophageal intubation with late recognition, adverse events as listed in the outcome parameters are expected and according to current clinical practice “accepted” outcomes. Hence these outcomes are not routinely reported as adverse events nor to the DSMB. However, if any of the attending clinicians suspect an adverse event that is related to the study design, such an adverse event will be reported.

Serious adverse events are defined as:

1. Cardiac arrest or death during or within an hour of the intervention.

2. Oesophageal intubation with late recognition

Any SAE will be reported to the HREC within 24-72 hours of occurrence, in accordance with the safety reporting policy of the HREC. Set DSMB review points on the progress and safety of the trial are pre-defined as after the primary outcome is known for 200 children.

Data accuracy and integrity

Intubation and ventilation of a child in the ED and ICU settings represents a highly stressful event, and requires significant human resources to assemble equipment while effectively managing a critically unwell patient. As a result, attention to data collection for a research study is often overlooked, with the immediate needs of the patient always taking priority. This study is dependent on high quality and accurate data at a critical moment of the patient's management, and the potential for missing or inaccurate data collection is high. It is also recognised that significant bias can be introduced to a study of this type when relying on retrospective recall of critical data values. A retrospective review of intubation records compared to video recorded data has highlighted that there is a significant under-reporting of adverse events, especially oxygen desaturation, and an over-reporting of first attempt success rates, in the magnitude of 21% and 12% respectively, when reliant on operator/observer reported data [21].

For this reason, a video recording of the intubation procedure will be captured for data verification purposes and to protect the integrity of the primary end-point. Where a discrepancy between the manually recorded data and video recorded data exists, the video recorded data will be used for analysis as it can be objectively confirmed.

Current status of trial:

The study enrolment has commenced in May 2017 and the sites involved are: Queensland Children's Hospital Townsville Hospital, Gold Coast University Hospital, Royal Children's Hospital Melbourne, Womens and Children's Hospital Adelaide, Perth Childrens Hospital and Starship Children's Hospital Auckland. Expansion to additional sites is planned.

SIGNIFICANCE

This large multicentre randomised trial may help define the role of THRIVE during emergency intubation in infants and children. The intubation of a child in the emergency setting places a tremendous emotional strain on both the child and parents. Dependent on the skill level and experience of the clinician performing the procedure, the professional stress level may also be very high as intubation is a high-risk procedure, which needs to be accomplished in a timely manner. The study will provide high fidelity data using video recording of the study interventions and the findings will easily be translated into clinical practice.

Figure Legends:

Figure 1: The phases of intubation are clearly defined in the protocol to ensure the intervention is applied at a standardised phase of the intubation procedure. The study allows for any method and duration of preoxygenation as per clinician standard practice, with details of preoxygenation technique and duration recorded. At the start of the intubation attempt (removal of the mask used for preoxygenation or insertion of laryngoscope blade) the intervention is applied. In the control group all sources of apnoeic oxygen are removed at the start of intubation.

Figure 2: In this study, the intubation period is defined as the start of intubation from removal of the mask used for preoxygenation and/or insertion of the laryngoscope blade and ends with successful intubation or abandonment of the attempt. Data collection continues for 5 minutes after intubation. The period from the start in intubation until 2 minutes after

intubation is defined as the peri-intubation period and the period from 2-5 minutes defined as the post intubation period.

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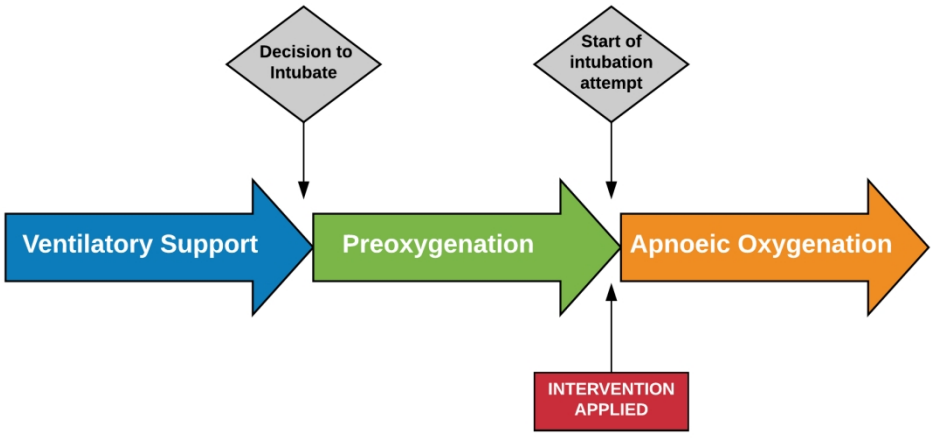

Figure 1: Definition of intubation phases

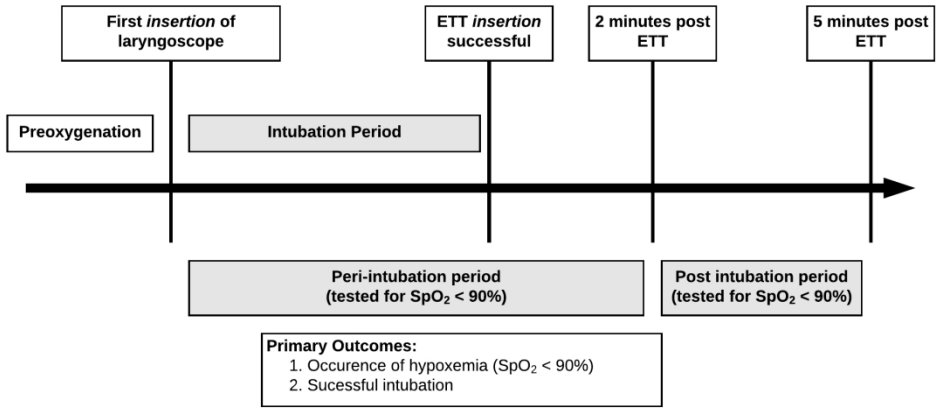

Figure 2: Sequence of event and time lines with definitions of study periods

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	#3	Date and version identifier	
Funding	#4	Sources and types of financial, material, and other support	3
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-3
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	N/A

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	3,19
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7-9
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7-9
Objectives	#7	Specific objectives or hypotheses	13-16
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-13

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/A
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-16
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	N/A
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	11

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15-16,21
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16-17,21
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16-16,21
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18-19
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18-19
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18-19

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	19-20
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	19-20
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	19-20
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	9-11
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9-11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	3
Data access	#29	Statement of who will have access to the final trial dataset,	

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	22
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A