The SHINE Trial (A Multicentre, Randomised Trial of Stabilisation with Nasal High Flow During Neonatal Endotracheal Intubation): Statistical Analysis Plan

Kate Hodgson (kate.hodgson@thewomens.org.au)
Royal Women's Hospital https://orcid.org/0000-0002-2908-1049
Brett Manley
Royal Women's Hospital
Omar Kamlin
Royal Women's Hospital
Louise Owen
Royal Women's Hospital
Calum Roberts
Monash Health
Kate Francis
MCRI: Murdoch Childrens Research Institute
Peter Davis
Royal Women's Hospital
Susan Donath
MCRI: Murdoch Childrens Research Institute

Update

Keywords: Endotracheal intubation, neonates, preterm infants, apnoea

Posted Date: April 27th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-388244/v1

Abstract

Endotracheal intubation is an essential but potentially destabilising procedure for neonates. With an increased focus on avoiding mechanical ventilation, particularly in preterm infants, there are fewer opportunities for clinicians to gain proficiency in this important emergency skill. Rates of successful intubation at the first attempt are relatively low, and adverse event rates including desaturation and bradycardia are high, when compared with intubations in paediatric and adult populations. Interventions to improve operator success and patient stability during neonatal endotracheal intubations are needed. Using nasal high flow therapy during apnoea extends the safe apnoea time of adults undergoing upper airway surgery and during endotracheal intubation [1]. This technique is untested in neonates.

Introduction

Background and rationale for trial

Endotracheal intubation is an essential but potentially destabilising procedure for neonates. With an increased focus on avoiding mechanical ventilation, particularly in preterm infants, there are fewer opportunities for clinicians to gain proficiency in this important emergency skill. Rates of successful intubation at the first attempt are relatively low, and adverse event rates including desaturation and bradycardia are high, when compared with intubations in paediatric and adult populations. Interventions to improve operator success and patient stability during neonatal endotracheal intubations are needed. Using nasal high flow therapy during apnoea extends the safe apnoea time of adults undergoing upper airway surgery and during endotracheal intubation [1]. This technique is untested in neonates.

The SHINE (Stabilisation with nasal High flow during Intubation of NEonates) trial is a multicentre, randomised controlled trial comparing the use of nasal high flow (nHF) during neonatal intubation with standard care (no nHF). Intubations are randomised individually, and stratified by site, use of premedications, and postmenstrual age of the infant (≤28 weeks' gestation; >28 weeks' gestation). The primary outcome is the incidence of successful intubation on the first attempt without physiological instability of the infant. Physiological instability is defined as an absolute decrease in peripheral oxygen saturation >20% from pre-intubation baseline, and/or bradycardia (<100 beats per minute).

Research question

In neonates undergoing emergent or elective (with premedication) endotracheal intubation, does the use of nHF during laryngoscopy increase the likelihood of successful intubation on the first attempt without physiological instability, compared with no nHF?

Objectives

The primary objective of the SHINE trial is to investigate the efficacy of nHF in improving first attempt intubation success without physiological instability in neonates.

Study Methods

Trial design

The SHINE trial is a multicentre, unblinded, randomised controlled trial investigating the efficacy of nHF to improve success and stability during neonatal endotracheal intubation. Intubations performed in the delivery room (DR) or neonatal intensive care unit (NICU) will be randomised, with a 1:1 ratio.

Infants will receive either:

1. **Nasal HF** during the endotracheal intubation attempt, or
2. **Standard care** (no nHF during the endotracheal intubation attempt)

Full explanation of the trial design is included in the trial protocol [2].

Study protocol development and conduct

The SHINE trial was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN126128001498280) on 6th September 2018. The trial was approved by the Human Research Ethics Committee of The Royal Women's Hospital (Melbourne, Australia) on 8th November 2018, and by the Human Research Ethics Committee of Monash Health (Melbourne, Australia) on 1st March 2019.

The consent process involves written, prospective consent wherever possible from parents for inclusion of their infant in the study. However, in the event of an emergency intubation in the DR or within the first 24 hours after admission to NICU, the study has approval to use a retrospective consent process at both study sites. The infant will be included in the study, then consent to continue (retrospective consent) will be sought from the parent or guardian as soon as possible after the procedure. This consent process was pursued due to the known safety and efficacy of nHF use in neonates, and the lack of any anticipated risk compared with standard clinical practice.

An independent data and safety monitoring board (DSMB) is monitoring the study progress. The trial will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines [3].

Outcomes

The primary outcome is the incidence of **successful intubation at the first attempt without physiological instability.**

Definitions and secondary outcomes are further outlined in Section 6 and in the trial protocol [2].

Randomisation

Each intubation episode is randomly allocated in a 1:1 ratio to either nHF or control, stratified by:

1. **centre**,
2. **gestationalage** (≤28 weeks; >28 weeks), and
3. use of **premedication** for intubation.

The randomisation sequence uses random permuted blocks with varying block sizes. To enable rapid randomisation following the decision to intubate by the clinical team, the randomisation is performed at the cot-side using a smartphone or computer with online access to the Research Electronic Data Capture (REDCap) [4] randomisation tool. Randomisation is web-based, using a password-protected, secure sockets layer (SSL)-encrypted website. The randomisation sequence was developed by an independent statistician at the Murdoch Children's Research Institute, Melbourne, Australia. The group allocations are unblinded, due to the nature of the intervention. Intubation episodes, rather than infants, are randomised. An infant who has previously had an intubation episode randomised within the study can have subsequent intubation episodes randomised if (1) the premedication randomisation stratum differs between the studied intubations, or (2) there is at least 1 week between the studied intubations for intubations where premedications are used.

Sample size

The sample size of **246 intubation episodes** is based on a previous study [5], which examined 206 neonatal intubations by junior medical staff. This study found a 29% successful intubation rate at the first attempt without peripheral oxygen desaturation >20% or bradycardia <100 beats per minute. With a power of 90% to detect an increase in the incidence of successful intubation without physiological instability from 30% to 50%, and two-sided alpha 0.05, at least 123 intubation episodes in each group (246 total) are required.

Framework

The SHINE trial is investigating the superiority of nHF, compared with standard care (no nHF) for the primary outcome. Secondary outcomes will also be compared using a superiority framework.

Statistical interim analysis and stopping guidance

An external DSMB has been convened and is chaired by **Dr Chris McKinlay** (Liggins Institute, University of Auckland, New Zealand). The DSMB consists of two consultant neonatologists (Dr Chris McKinlay and **Dr Peter Dargaville**) and an independent statistician (**Dr Myra McGuinness**). The terms of reference of the DSMB were outlined in the SHINE trial DSMB charter (version 4, 25th June 2019) and ratified by the Trial Steering Committee and all members of the DSMB during the first DSMB meeting.

Safety analyses, including of pre-defined significant adverse events (SAEs), were planned and performed after recruitment of:

- **60 patients** (~25% total)
- **125 patients** (~50% total) and
- **180 patients** (~75% total).

The defined SAEs were:

- Incidence of **pneumothorax** within 72 hours after randomisation, diagnosed either by transillumination of the chest and/or by chest X-ray
- Incidence of **cardiac compressions and/or adrenaline** administration within 1 hour after the first intubation attempt
- **Death** within 72 hours after randomisation

After **125 patients** were recruited (~50% total), an interim efficacy analysis was undertaken, comparing the two treatment groups (blinded) for the primary endpoint and its components:

- Successful intubation on the first attempt without desaturation >20% from baseline, or bradycardia <100bpm
- Successful intubation on the first attempt
- Desaturation >20% from baseline
- Bradycardia <100bpm

The information was presented by pseudo-labelled treatment arm (e.g. 'A' and 'B'); the key to identify the treatment arms was able to be supplied by the independent statistician if requested by the DSMB.

As per the DSMB charter, the DSMB could recommend stopping the trial on the basis of *safety* using clinical judgment informed by statistical comparison of adverse event rates. Accumulating signals of harm did not necessarily require statistically significant differences to warrant an alert and recommendation from the DSMB. The DSMB were also able to consider recommending stopping the trial if there was a very strong statistically significant difference ($p<0.001$) in the primary outcome between groups at the interim efficacy analysis. There was no planned adjustment of the significance level due to interim analysis.

At each time-point, the DSMB recommended continuation of the trial, with an unchanged protocol.

Timing of final analysis

Final analysis will be conducted after data entry is completed and the database cleaned and closed.

Data collection and management

Demographic data are collected on paper Case Report Forms, or by directly inputting data into the REDCap [4] database, by investigators at the recruiting hospitals. Each intubation episode is video recorded using a GoPro camera (GoPro, San Mateo, California), placed in a location that provides a clear overhead view of the intubation procedure, the infant's face and the Masimo (Irvine, CA, USA) pulse oximeter. Each video recording is reviewed by an investigator to determine primary and secondary outcomes. The primary outcome is also recorded on the Case Report Form in real time, in case of video failure. Outcomes are then entered into an secure, password-protected, online electronic database (REDCap [4]) by an investigator at each hospital.

After data entry, records were reviewed for missing data. Requests for addition of missing data or clarification were resolved by an investigator at each site.

All data will be checked and cleaned by the trial statistician, A/Prof Susan Donath, prior to analysis.

Timing of outcome assessments

The primary outcome is successful intubation on the first attempt, without physiological instability. The first intubation attempt is defined as the insertion and removal of laryngoscope beyond the baby's lips.

The secondary outcomes are measured during the intubation episode (all intubation attempts for that infant) and up to 72 hours after the intubation episode (for the pre-defined SAEs of pneumothorax, cardiac compressions and/or adrenaline administration, death).

Statistical Principles

Overall principles

Data analysis will include all outcome data for all randomised intubation episodes. Analysis will start once all primary and secondary outcome are available, missing data has been sought, the database has been cleaned and locked, and the SAP has been submitted for publication.

Adjustment for multiplicity

All secondary outcomes will be reported as point estimates with unadjusted 95% confidence intervals only. There will be no adjustment for multiplicity.

Confidence intervals to be reported

For all outcomes, 95% confidence intervals will be presented.

Analysis population

The randomised population will comprise at least 246 intubation episodes, with infants randomized to either nHF or control. The analysis population will be created by removing the infants who met post-randomisation exclusion criteria from the randomised population, as outlined below.

On October 29th 2020, the Trial Steering Committee sought advice from the independent DSMB regarding post-randomisation exclusion criteria, with three deidentified randomisation episodes presented for discussion. These DSMB were blinded to trial data regarding the treatment arm and outcomes of the infants discussed.

Based on advice from the DSMB, the Trial Steering Committee reached consensus agreement regarding the following criteria for post-randomisation exclusions on 19th February 2021.

1. Randomised in error (patient was not intubated)
2. Failure to meet inclusion criteria
3. Meeting exclusion criteria at the time of randomisation (e.g. bradycardia, abdominal wall defect)
4. Parental withdrawal of consent
5. Parental consent declined in retrospective consent group

Therefore, the intention-to-treat (ITT) population will include all randomised infants, regardless of exposure to the allocated treatment or adherence to the trial protocol, excluding the infants who meet the post-randomisation exclusion criteria described above.

Per-protocol analysis

We will undertake a per protocol analysis for the primary outcome if there are infants in the control group who received nHF or other apnoeic oxygenation during intubation, or infants in the nHF group who never received the intervention. The following will not be deemed protocol violations: high flow prongs are placed and then dislodge, or mechanical failure of machine.

Trial Population

Screening data

All intubation episodes in both centres will be assessed for eligibility for inclusion in the trial. The CONSORT flow diagram in figure 1 will be used to detail enrolment, randomisation, treatment allocation, follow up and analysis.

Eligibility criteria

Any patient undergoing endotracheal intubation in the DR or NICU is eligible for inclusion. Specific inclusion and exclusion criteria are outlined in the protocol [2].

CONSORT diagram

Please see figure 1.

Withdrawal/follow up

Infants where prospective consent is withdrawn, or retrospective consent is not gained, will be treated as post-randomisation exclusions (figure 1).

Baseline patient characteristics

The following baseline characteristics will be summarised (see Table 1):

- Mothers:
    - Mode of delivery: vaginal delivery, caesarean section under spinal anaesthesia, caesarean section under general anaesthesia: number (%)
- Infants:
    - Gestational age (weeks): mean (standard deviation, SD)
    - Birth weight (grams): mean (SD)
    - Age at randomisation (hours): mean (SD)
    - Corrected gestational age at randomisation (weeks): mean (SD)
    - Weight at randomisation (grams): mean (SD)
    - Male: number (%)
    - Multiple birth: number (%)
    - Apgar score at 5 minutes: median (interquartile range)

- Respiratory support prior to randomisation (no support, nHF, continuous positive airway pressure, intermittent positive pressure ventilation): number (%)
- Fraction of inspired oxygen prior to randomisation: (mean, SD)

Analysis

Outcome definitions

Primary outcome

The primary outcome is **successful intubation at the first attempt without physiological instability.**

Definitions

- Intubation attempt: the insertion of the laryngoscope blade beyond the infant's lips.
- Intubation duration: the time from the insertion of the laryngoscope blade beyond the infant's lips until the removal of the laryngoscope blade from the infant's mouth.
- Successful intubation: the completion of the intubation attempt with correct positioning of the endotracheal tube confirmed by detection of expired carbon dioxide on a colorimetric detector.
- Physiological instability: the incidence (any duration) of an absolute decrease in peripheral oxygen saturation (SpO_2) >20% from baseline (immediately prior to the intubation attempt), and/or bradycardia (heart rate <100 beats per minute, bpm), during the first intubation attempt.

Secondary outcomes

- Incidence of successful intubation on the first intubation attempt.
- Incidence of desaturation (absolute decrease in SpO_2>20% from baseline) *or* bradycardia (heart rate <100 bpm) during the first intubation attempt.
- Time to desaturation (absolute decrease in SpO_2>20% from baseline) during the first intubation attempt in seconds.
- Time to bradycardia (heart rate <100 bpm) during the first intubation attempt in seconds.
- Duration of desaturation (absolute decrease in SpO_2>20% from baseline) during first intubation attempt in seconds.
- Duration of bradycardia (heart rate <100 bpm) during first intubation attempt in seconds.
- Median SpO_2during intubation attempt.
- Median heart rate during intubation attempt.
- Duration of SpO_2>97% during intubation attempt, in seconds.

- Number of intubation attempts.
- Duration of all intubation attempts (successful and unsuccessful), in seconds.
- Incidence of cardiac compressions and/or adrenaline administration within 1 hour after the first intubation attempt.
- Incidence of pneumothorax within 72 hours after randomisation, diagnosed either by transillumination of the chest and/or by chest X-ray.
- Incidence of pneumothorax requiring drainage (via needle thoracocentesis or insertion of an intercostal catheter) within 72 hours after randomisation.
- Death within 72 hours after randomisation.

Analysis methods

Analyses- primary outcome

The primary analysis will be a modified intention to treat analysis, using the exclusion criteria outlined above. The primary analysis will be adjusted for stratification variables (gestational age group, premedication use and trial centre). Regression models with the stratification factors used in randomisation included as covariates will be used for all analyses. Results of this analysis will be presented as outlined in table 2. The incidence of the primary outcome will be compared using risk difference and two-sided 95% CI.

There will be a subgroup analysis by gestational age and use of premedication for the primary outcome only. We acknowledge that the study is not powered to detect a difference in the subgroups.

A sensitivity analysis will be conducted to account for repeated randomisation events within individual subjects.

If an imbalance in demographics known to affect intubation success (e.g. postmenstrual age, weight, videolaryngoscope use, operator experience) is detected, a further sensitivity analysis adjusting for the relevant demographics will be conducted for the primary outcome and its components.

Analyses: secondary outcomes

Dichotomous secondary outcomes

Dichotomous secondary outcomes will be compared using risk difference with 95% confidence interval using regression models to estimate difference between treatment and control groups.

Dichotomous secondary outcomes include the following:

1. Incidence of successful intubation on the first attempt
2. Incidence of desaturation (absolute decrease in SpO_2 >20% from baseline) during first intubation attempt
3. Incidence of bradycardia (heart rate <100 bpm) during first intubation attempt

All outcomes will be performed on the intention to treat population. Results of these analyses will be presented as outlined in table 3. There will be no subgroup analyses performed for secondary outcomes.

Continuous secondary outcomes

Continuous secondary outcomes will be compared using difference of means with 95% confidence interval to estimate difference between treatment and control groups. For normally distributed outcome variables, difference of means, together with 95% CI and P value will be estimated using linear regression. Where outcome variables are not normally distributed, difference of medians, together with 95% CI and P value will be estimated using quantile regression. Results of these analyses will be presented as outlined in Table 3.

Continuous secondary outcomes include the following:

1. Time to desaturation (absolute decrease in SpO_2 >20% from baseline) during first intubation attempt in seconds
2. Time to bradycardia (heart rate <100 bpm) during first intubation attempt in seconds
3. Duration of desaturation (absolute decrease in SpO_2 >20% from baseline) during first intubation attempt in seconds
4. Duration of bradycardia (heart rate <100 bpm) during first intubation attempt in seconds
5. Median SpO_2 (%) during intubation attempt
6. Median heart rate (bpm) during intubation attempt
7. Duration of SpO_2 >97%
8. Number of intubation attempts
9. Duration of all intubation attempts (successful and unsuccessful), in seconds

There will be no subgroup analyses performed for secondary outcomes.

Subgroup analyses

We will perform pre-specified subgroup analyses for the primary outcome only using logistic regression models. The prespecified subgroup analyses included in the protocol are:

1. Gestational age (≤28 weeks' or >28 weeks')

2. Use of premedication for intubation (yes or no)

In addition, we will perform a pre-specified subgroup analysis for:

3. Operator experience (inexperienced, <20 previous intubations or experienced, ≥ 20 previous intubations)

This subgroup analysis has been specified following the original trial protocol publication, but prior to submission of this statistical analysis plan or performing any data analysis.

Missing data

Every attempt will be undertaken to retrieve missing data. The primary outcome is recorded on a paper CRF by the investigator at the cot-side, to provide a backup to the video recording and time stamped downloadable oximetry recording. We therefore expect there to be very few instances in which the primary outcome cannot be determined and therefore do not anticipate needing to use multiple imputation to deal with missing data. Imputation will not be used for missing physiological data, for example in the event of loss of pulse oximetry signal or failure of video recording.

Multiple imputation or inverse probability case weights may be used to deal with missing data.

Additional analyses

Subsequent analyses that are not specified in the protocol may be performed if requested by journal editors or reviewers. These will be performed consistently with the principles of this analysis plan, as far as possible. Subsequent analyses of a more exploratory nature will not be bound by this strategy, but are expected to follow the broad principles described.

There will be graphical displays of results to present data.

Other additional analyses to be analysed and reported subsequent to the main trial include an additional sub-study will examine Near InfraRed Spectrosocopy (NIRS) in a subset of babies undergoing randomisation in the trial. These data will be analysed separately, and submitted for publication separately.

Harms

Incidence of the following serious adverse events will be compared between groups:

1. Incidence of pneumothorax within 72 hours after randomisation, diagnosed by either transillumination of the chest and/or by chest X-ray

2. Incidence of pneumothorax requiring drainage (via needle thoracocentesis or insertion of an intercostal catheter) within 72 hours after randomisation
3. Incidence of cardiac compressions and/or adrenaline administration within 1 hour after the first intubation attempt
4. Death within 72 hours after randomisation

These outcomes will be reported with 95% CI, without adjustment for multiplicity, given that type I error rates larger than 0.05 may be important. If journal editors or reviewers request it, P values may be reported for the comparisons of adverse events between treatment groups.

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Statistical software

Data will be exported from the study database to STATA (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC) for analysis.

Declarations

Ethics approval and consent to participate

The SHINE trial was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN126128001498280) on 6th September 2018. The trial was approved by the Human Research Ethics Committee of The Royal Women's Hospital (Melbourne, Australia) on 8th November 2018, and by the Human Research Ethics Committee of Monash Health (Melbourne, Australia) on 1st March 2019.

Consent for publication

Not applicable

Availability of data and materials

The datasets during and/or analysed during the current study will be available from the corresponding author on reasonable request.

Competing interests

No competing interests

Funding

This work was supported by National Health and Medical Research Council program grant #1113902. Nasal high flow equipment and consumables have been supplied by Vapotherm.

Authors' contributions

KH conceptualised and drafted the manuscript. OK, LO, BJM, PGD and CTR edited the manuscript. SD, as trial statistician, edited and approved the final manuscript. KF reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1: Baseline characteristics

Characteristic	Nasal HF group (n = XXX)	Control group (n = XXX)
Mothers		
Mode of delivery – no. (%)		
Vaginal delivery	XX (%)	XX (%)
Caesarean section under spinal anaesthesia	XX (%)	XX (%)
Caesarean section under general anaesthesia	XX (%)	XX (%)
Infants		
Gestational age at birth - Weeks	Mean (SD)	Mean (SD)
≤ 28 weeks	XX (%)	XX (%)
> 28 weeks	XX (%)	XX (%)
Birth weight – grams	Mean (SD)	Mean (SD)
Age at randomisation – hours	Mean (SD)	Mean (SD)
Corrected GA at randomisation – weeks	Mean (SD)	Mean (SD)
Weight at randomisation - grams	Mean (SD)	Mean (SD)
Male – no. (%)	XX (%)	XX (%)
Multiple birth – no. (%)	XX (%)	XX (%)
Apgar score at 5 minutes	Mean (SD)	Mean (SD)
Respiratory support prior to randomisation		
Nasal high flow	XX (%)	XX (%)
Continuous positive airway pressure	XX (%)	XX (%)
Intermittent positive pressure ventilation (IPPV) (via face mask, does not include IPPV following premedication)	XX (%)	XX (%)
Fraction of inspired oxygen prior to randomisation	Mean (SD)	Mean (SD)
Intubation characteristic		
Indication for intubation – no. (%)*		
Hypoxia	XX (%)	XX (%)
Hypercarbia	XX (%)	XX (%)
Apnoea	XX (%)	XX (%)

Resuscitation	XX (%)	XX (%)
Other	XX (%)	XX (%)
Use of premedication – no. (%)		
Premedication	XX (%)	XX (%)
No premedication	XX (%)	XX (%)
First intubation attempt operator – no. (%)		
Resident/registrar/neonatal nurse practitioner	XX (%)	XX (%)
Fellow/consultant	XX (%)	XX (%)
Experience of operator (number of previous intubations) – no. (%)		
<20 previous intubations	XX (%)	XX (%)
≥20 previous intubations	XX (%)	XX (%)

* If more than one criteria met, all recorded

Table 2: Primary outcome and components

Outcome	Nasal HF group (n = XXX)	Control group (n = XXX)	Risk difference (95% CI)
Primary outcome (intention-to-treat analysis)			
Successful first attempt intubation without physiological instability	XX (%)	XX (%)	
≤ 28 weeks' GA	XX (%)	XX (%)	
> 28 weeks' GA	XX (%)	XX (%)	
Premedication use	XX (%)	XX (%)	
No premedication use	XX (%)	XX (%)	
Inexperienced operator (<20 previous intubations)	XX (%)	XX (%)	
Experienced operator (≥ 20 previous intubations)	XX (%)	XX (%)	
Primary outcome components			
Successful first attempt intubation			
Desaturation (SpO_2 >20% from baseline) during the first intubation attempt			
Bradycardia (HR <100 bpm) during the first intubation attempt			

Table 3: Secondary outcomes and serious adverse events

Outcome	Nasal HF group (n = XXX)	Control group (n = XXX)	Risk difference (95% CI)
Secondary outcomes			
Time to desaturation- seconds*	Median (IQR)	Median (IQR)	
Duration of desaturation- seconds*	Median (IQR)	Median (IQR)	
Median SpO_2 (IQR)*	Median (IQR)	Median (IQR)	
Time to bradycardia- seconds*	Median (IQR)	Median (IQR)	
Duration of bradycardia- seconds*	Median (IQR)	Median (IQR)	
Median HR (IQR)*	Median (IQR)	Median (IQR)	
Number of intubation attempts	Median (IQR)	Median (IQR)	
Total duration of all intubation attempts (successful and unsuccessful)- seconds**	Median (IQR)	Median (IQR)	
Serious adverse events			
CPR and/or adrenaline administration within 1 hour of intubation attempt	XX (%)	XX (%)	
Pneumothorax diagnosed within 72 hours after randomisation**	XX (%)	XX (%)	
Any	XX (%)	XX (%)	
Requiring drainage with needle thoracocentesis or intercostal catheter	XX (%)	XX (%)	
Death within 72 hours after randomisation	XX (%)	XX (%)	

* During first intubation attempt

** Sum of each separate intubation attempt

IQR: interquartile range

SpO_2: peripheral oxygen saturation

HR: heart rate

Bpm: beats per minute

CPR: cardiopulmonary resuscitation

Figures

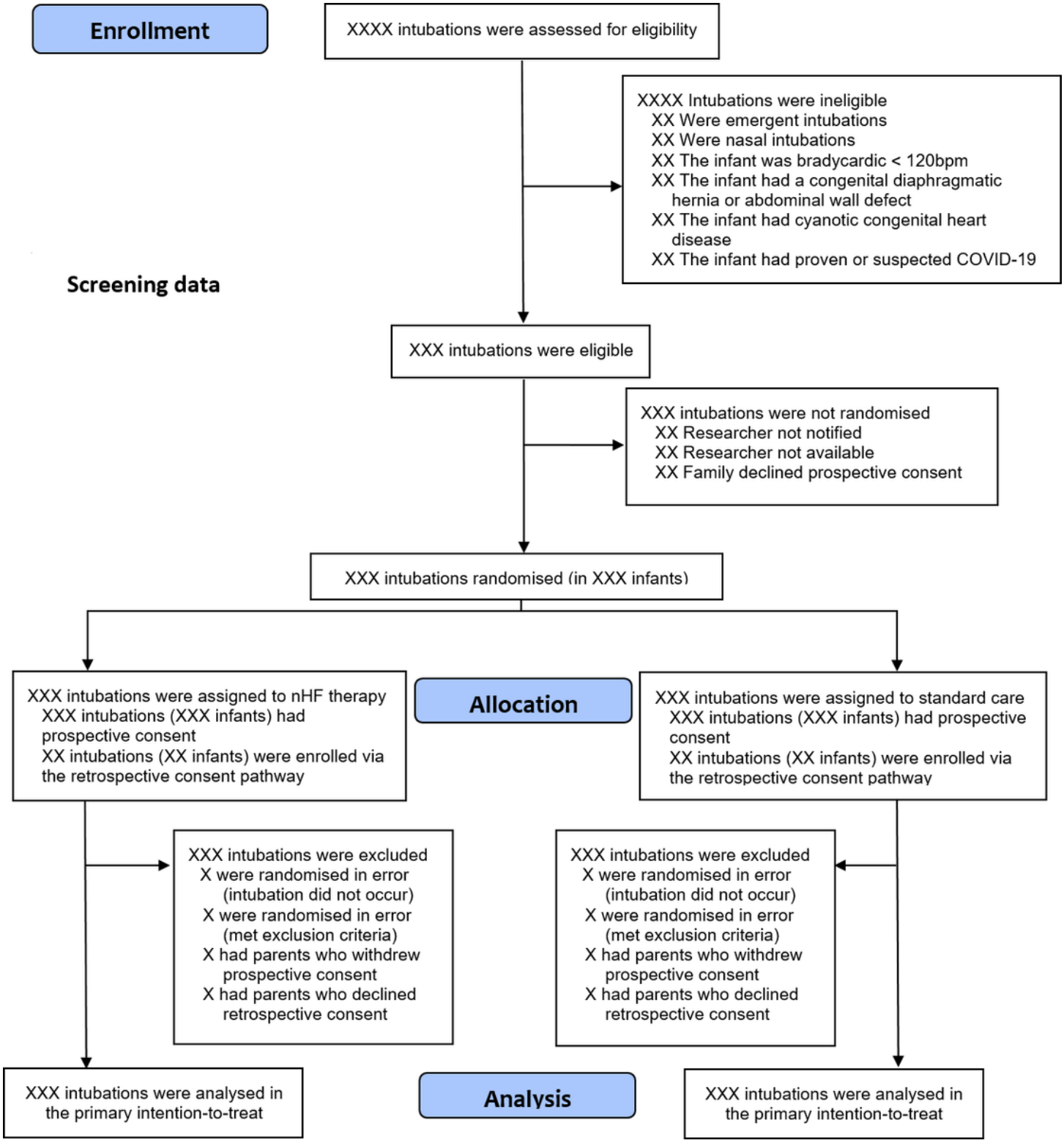

Figure 1

Consolidated Standards of Reporting Trials (CONSORT) 2010 flow diagram

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SAPChecklistSHINE.docx