

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

A multicentre, randomised trial of stabilisation with nasal high flow during neonatal endotracheal intubation (the SHINE trial): a study protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-039230
Article Type:	Protocol
Date Submitted by the Author:	08-Apr-2020
Complete List of Authors:	Hodgson, Kate; The Royal Women's Hospital, Newborn Research Centre; The University of Melbourne, Department of Obstetrics and Gynaecology Owen, Louise; The Royal Women's Hospital, Newborn Research Centre; The University of Melbourne, Department of Obstetrics and Gynaecology Kamlin, Camille; The Royal Women's Hospital, Newborn Research Centre; The University of Melbourne, Department of Obstetrics and Gynaecology Roberts, Calum; Monash Children's Hospital, Monash Newborn; Monash University, Department of Paediatrics Donath, Susan; Murdoch Childrens Research Institute, Clinical Epidemiology and Biostatistics Unit Davis, Peter; The Royal Women's Hospital, Newborn Research Manley, Brett; The Royal Women's Hospital, Newborn Research Centre
Keywords:	Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE, INTENSIVE & CRITICAL CARE, NEONATOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title Page

Title:

A multicentre, randomised trial of stabilisation with nasal high flow during neonatal endotracheal intubation (the SHINE trial): a study protocol.

Authors:

Hodgson KA^{1,2}, Owen LS^{1,2,3}, Kamlin CO^{1,2,3}, Roberts CT^{4,5}, Donath S^{3,6}, Davis PG^{1,2,3}, Manley BJ^{1,2,3}.

Affiliations:

- 1 Newborn Research Centre, Royal Women's Hospital, Melbourne, Australia
- 2 Department of Obstetrics and Gynaecology, University of Melbourne, Parkville, Victoria, Australia
- 3 Murdoch Children's Research Institute, Parkville, Victoria, Australia
- 4 Monash Newborn, Monash Children's Hospital, Melbourne, Australia
- 5 Department of Paediatrics, Monash University, Melbourne, Australia
- 6 Department of Paediatrics, University of Melbourne, Parkville, Victoria, Australia

Contact details:

Kate.Hodgson@thewomens.org.au

Louise.Owen@thewomens.org.au

Omar.Kamlin@thewomens.org.au

Calum.Roberts@monash.edu

Susan.Donath@mcri.edu.au

Pgd@unimelb.edu.au

Brett.Manley@thewomens.org.au

Trial registration:

Australia and New Zealand Clinical Trial Registry: ACTRN12618001498280.

Keywords:

1
2
3 Infant, Preterm, Endotracheal Intubation, Nasal High Flow Therapy, Apnoeic
4 Oxygenation
5
6
7

8 **Abstract**

9 **Introduction**

10 Neonatal endotracheal intubation is an essential but potentially destabilising
11 procedure. With an increased focus on avoiding mechanical ventilation, particularly
12 in preterm infants, there are fewer opportunities for clinicians to gain proficiency in
13 this important emergency skill. Rates of successful intubation at the first attempt are
14 relatively low, and adverse event rates are high, when compared with intubations in
15 paediatric and adult populations. Interventions to improve operator success and
16 patient stability during neonatal endotracheal intubations are needed. Using nasal
17 high flow therapy extends the safe apnoea time of adults undergoing upper airway
18 surgery and during endotracheal intubation. This technique is untested in neonates.
19
20
21
22
23
24
25
26

27 **Methods and analysis**

28
29 The SHINE (Stabilisation with nasal High flow during Intubation of Neonates) trial is
30 a multicentre, randomised controlled trial comparing the use of nasal high flow during
31 neonatal intubation with standard care (no nasal high flow). Intubations are
32 randomised individually, and stratified by site, use of premedications, and
33 postmenstrual age (<28 weeks' gestation; ≥28 weeks' gestation). The primary
34 outcome is the incidence of successful intubation on the first attempt without
35 physiological instability of the infant. Physiological instability is defined as an
36 absolute decrease in peripheral oxygen saturation >20% from pre-intubation
37 baseline, and/or bradycardia (<100 beats per minute).
38
39
40
41
42
43
44

45 **Ethics and dissemination**

46 The SHINE trial received ethical approval from the Human Research Ethics
47 Committees of The Royal Women's Hospital, Melbourne, Australia and Monash
48 Health, Melbourne, Australia. The trial is currently recruiting in these two sites. The
49 findings of this study will be disseminated via peer-reviewed journals and presented
50 at national and international conferences. The trial was prospectively registered with
51 the Australian and New Zealand Clinical Trials Registry (ACTRN12618001498280).
52
53
54
55
56
57

58 **Strengths and limitations of the study**

- Strength: The first randomised controlled trial of nasal high flow to improve procedure success and physiologic stability during neonatal intubation
- Strength: A low risk, easily generalisable intervention to assist with a difficult, life saving procedure
- Strength: Interventions are video recorded to enable accurate and objective data collection
- Limitation: Likelihood of intubation success may be affected by operator experience and the use of videolaryngoscopy; these factors will be addressed in a sensitivity analysis
- Limitation: Due to the nature of the intervention, blinding is not possible

Introduction

Opportunities for clinicians to acquire proficiency in neonatal endotracheal intubation have decreased over time [1, 2]. The increased use of 'non-invasive' respiratory support (without an endotracheal tube), less-invasive surfactant administration techniques, and the move away from routine endotracheal suctioning of babies born through meconium-stained amniotic fluid have contributed to this trend. In extremely preterm infants, the use of nasal continuous positive airway pressure (CPAP) for primary respiratory support results in fewer days of mechanical ventilation, less surfactant administration and a lower risk of bronchopulmonary dysplasia, compared with intubation and mechanical ventilation [3, 4]. Nasal high flow therapy (nHF) is a newer mode of non-invasive respiratory support that delivers heated, humidified gas via two small nasal prongs. In preterm infants, nHF has been evaluated for the management of early respiratory distress and post extubation support, leading to widespread use in neonatal intensive care units [5, 6]. Nasal HF is commonly used in preterm and term newborn infants [5, 6], as well as in children [7] and adults [8]. Current clinical applications of nasal HF in neonates include primary support of respiratory distress syndrome, and post-extubation support in preterm infants [9].

Whilst non-invasive modes of respiratory support are utilised whenever possible for neonates, endotracheal intubation is still sometimes required, particularly for the most immature infants [10]. With decreasing clinical experience in this procedure, neonatal intubation success rates at the first attempt are low but increase with

1
2
3 increasing operator experience. In a large international registry study of adverse
4 events associated with endotracheal intubation, Foglia *et al.* demonstrated that
5 overall first attempt intubation success was 49% for intubations in the neonatal
6 intensive care unit (NICU) [11]. O'Donnell *et al.* reviewed 60 intubation attempts and
7 reported success rates of 24% for residents (junior trainees), 78% for fellows (senior
8 trainees) and 86% for consultants [12]. Furthermore, the duration of neonatal
9 intubation attempts is often longer than the international guidelines recommend [13]
10 and varies with the experience of the operator [12]. Neonates are often clinically
11 unstable during endotracheal intubation, due to a lower functional residual capacity
12 and greater metabolic demand than older children and adults [14]. In one study,
13 severe hypoxaemia (defined as peripheral oxygen saturation [SpO₂] <60%) was
14 reported in 44% of neonatal intubations, and bradycardia (heart rate <60 beats per
15 minute [bpm] for at least 5 seconds) in 24% [15].

16
17
18
19
20
21
22
23
24
25
26
27 Transnasal Humidified Rapid Insufflation Ventilatory Exchange (THRIVE) is the use
28 of nHF during apnoea for laryngoscopy and endotracheal intubation. Nasal HF
29 provides heated, humidified air and oxygen via small nasal cannulae during a period
30 of apnoea. There is evidence that nHF use during apnoea may improve both
31 oxygenation and carbon dioxide clearance, compared with 'low flow' oxygen or jaw
32 support only [16, 17]. Proposed mechanisms include removal of carbon dioxide
33 through enhanced dead space washout and supraglottic flow changes due to
34 cardiogenic oscillations [18, 19]. THRIVE has been shown to prolong the safe
35 apnoeic time (time prior to desaturation) in adults [17] and in healthy infants and
36 children undergoing general anaesthesia and elective intubation [20]. In a
37 randomised controlled trial of THRIVE for apnoeic oxygenation during general
38 anaesthesia of 48 children aged <10 years, THRIVE significantly prolonged the
39 apnoea time (time prior to SpO₂ <92%) in all age groups [20]. All but one patient in
40 the control group desaturated to <92% within the anticipated time frame, which was
41 predefined as twice the length of previously published age-related values [21]. In
42 contrast, the THRIVE group had no desaturations and a mean SpO₂ of 99.6% (range
43 97-100%).

1
2
3 There are currently no published studies of the use of THRIVE during neonatal
4 intubation, nor in emergency settings in older patients with respiratory distress. The
5 aim of the SHINE (Stabilisation with nasal High flow during Intubation of Neonates)
6 randomised controlled trial is to investigate whether nHF during neonatal
7 endotracheal intubation after (1) birth in the delivery room and (2) in the neonatal
8 intensive care unit improves the likelihood of successful intubation on the first
9 attempt without physiological instability of the infant.
10
11
12
13
14
15
16

17 **Methods and analysis**

18 **Study design**

19 A multicentre, unblinded, randomised controlled trial investigating the efficacy of nHF
20 to improve success and stability during neonatal endotracheal intubation. Intubations
21 performed in the delivery room or NICU will be randomised, with a 1:1 ratio. Infants
22 will either receive nHF during the endotracheal intubation attempt, or standard care
23 (no nHF). Intervention will be applied for the first intubation attempt of the episode
24 only.
25
26
27
28
29
30
31

32 **Sample size**

33 The sample size of 246 infants is based on a study of videolaryngoscope use for
34 teaching neonatal intubation [22], which examined 206 intubations by junior medical
35 staff. This study reported a 29% successful intubation rate at the first attempt without
36 desaturation >20% or bradycardia <100 bpm. With a power of 90% to detect an
37 increase in the incidence of successful intubation without physiological instability
38 from 30% to 50%, 123 infants in each group (246 total) are required.
39
40
41
42
43
44
45

46 **Patient population**

47 Any neonate undergoing endotracheal intubation in the delivery room or NICU is
48 eligible for inclusion. In participating centres, all infants who undergo endotracheal
49 intubation will be screened for study eligibility. Infants already studied can have
50 subsequent intubation episodes randomised again if 1) the premedication
51 randomisation stratum differs between intubations, or 2) there is at least one week
52 between the studied intubations for intubations using premedications.
53
54
55
56
57
58
59
60

Inclusion criteria

Infants undergoing endotracheal intubation in the delivery room or NICU are eligible for inclusion.

Exclusion criteria

Exclusion criteria are:

- planned nasal intubation
- a requirement for immediate endotracheal intubation as determined by the treating clinician (insufficient time for researcher to randomise and set up study equipment)
- heart rate <120 bpm prior to randomisation (as at higher risk of bradycardia as defined in the trial)
- contraindications to nHF use, e.g. congenital nasal anomaly, congenital diaphragmatic hernia or abdominal wall defect
- cyanotic congenital heart disease.

Randomisation

Each intubation episode is randomised to one of the two groups using random permuted blocks with varying block sizes. Pre-randomisation stratification is by centre, post-menstrual age (<28 weeks; ≥28 weeks) and use of premedication for intubation. To enable rapid randomisation following the decision to intubate by the clinical team, the randomisation is performed at the cotside using a smartphone or computer with online access to the REDCap [23] randomisation tool.

Clinical management

Nasal HF group (intervention)

The intervention is performed by a trial investigator, for the first intubation attempt only. Immediately prior to intubation, infants will be receiving either CPAP via nasal prongs, nasal mask or a facemask, or positive pressure ventilation via a facemask. The Precision Flow ® device (Exeter, New Hampshire) and weight-appropriate binasal cannulae will be used to provide nHF. The cannulae will be sized to occupy approximately 50% of the nares and enable leak. At the time of the face mask, nasal mask or nasal prongs being removed for laryngoscopy, the investigator will apply the

1
2
3 nHF prongs, with gas flow set to and fixed at 8 Litres per minute (L/min) for the
4 duration of the study intervention. The fraction of inspired oxygen (FiO_2) prior to the
5 intubation attempt, including the use of any pre-oxygenation (an increase in FiO_2
6 prior to the intubation attempt), will be at the discretion of the clinical team. The trial
7 investigator will set the nHF FiO_2 to the same amount the infant was receiving prior to
8 laryngoscopy, and if the infant desaturates to $<90\%$ during the intubation attempt,
9 the investigator will increase the nHF FiO_2 to 1.0 (100% supplemental oxygen) until
10 the end of the intubation attempt. The nHF prongs will be secured only by tightening
11 the cannula tubing behind the infant's head; no adhesive tapes will be applied to the
12 face. Nasal HF will continue during laryngoscopy, and the nHF prongs will be
13 removed by the investigator when the first intubation attempt is either ceased, or
14 successfully completed (see definition below). The commencement, duration and
15 termination of an intubation attempt will be at the discretion of the most senior
16 clinician caring for the infant.

27 28 29 **Standard care group (control)**

30
31 Patients in the control arm will receive standard care. The intubation attempt
32 (laryngoscopy) will proceed without the application of nHF or the use of
33 supplemental oxygen. In the event that an infant in the NICU is already receiving
34 respiratory support from nHF prior to intubation being planned, this may continue up
35 until the time of induction medications being administered (if applicable). The
36 commencement, duration and termination of an intubation attempt will be at the
37 discretion of the most senior clinician caring for the infant.

43 44 **Outcomes**

45 46 **Primary outcome**

47
48 The primary outcome is the incidence of successful intubation at the first attempt
49 without physiological instability.

52 53 **Definitions:**

- 54
55 • Intubation attempt: the insertion of the laryngoscope blade beyond the infant's
56 lips
57
58
59
60

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
- 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 SpO₂ >20% from baseline (immediately prior to the intubation attempt), and/or bradycardia (heart rate <100 bpm), during the first intubation attempt

Secondary outcomes

1. Incidence of successful intubation on the first intubation attempt
2. Incidence of desaturation (absolute decrease in SpO₂ >20% from baseline) or bradycardia (heart rate <100 bpm) during the first intubation attempt
3. Time to desaturation (absolute decrease in SpO₂ >20% from baseline) during the first intubation attempt in seconds
4. Time to bradycardia (heart rate <100 bpm) during the first intubation attempt in seconds
5. Duration of desaturation (absolute decrease in SpO₂ >20% from baseline) during first intubation attempt in seconds
6. Duration of bradycardia (heart rate <100 bpm) during first intubation attempt in seconds
7. Number of intubation attempts
8. Duration of all intubation attempts (successful and unsuccessful), in seconds
9. Incidence of cardiac compressions and/or adrenaline administration within one hour after the first intubation attempt
10. Incidence of pneumothorax within 72 hours after randomisation, diagnosed either by transillumination of the chest and/or by chest X-ray
11. Incidence of pneumothorax requiring drainage (via needle thoracocentesis or insertion of an intercostal catheter) within 72 hours after randomisation
12. Death within 72 hours after randomisation

Data analysis plan

1
2
3 The incidence of the primary outcome will be compared using risk difference and
4 two-sided 95% confidence interval (CI). Secondary outcomes will be compared using
5 risk difference (with 95% CI) (outcomes 1, 2, and 9 to 12), and difference of means
6 or medians with 95% CI (outcomes 3 to 8). Planned subgroup analyses by each of
7 the pre-randomisation strata will be performed for the primary outcome and selected
8 secondary outcomes. Analyses will be by intention-to-treat, with an additional *per-*
9 *protocol* analysis for the primary outcome. The primary analysis will be adjusted for
10 stratification factors. Regression models with the stratification factors used in
11 randomisation included as covariates will be used for all analyses. A sensitivity
12 analysis will be conducted to account for repeated randomisation events within
13 individual subjects. If an imbalance in demographics known to affect intubation
14 success (e.g. postmenstrual age, weight, videolaryngoscope use, operator
15 experience) is detected, a further sensitivity analysis adjusting for the relevant
16 demographics will be conducted. Data will be exported from an electronic database
17 to an electronic statistical package for analysis.
18
19
20
21
22
23
24
25
26
27
28
29

30 **Ethics and Dissemination**

31
32 Prospective consent will be sought from a parent for inclusion of their infant in the
33 study, whenever possible. Prospective consent will be obtained for all eligible
34 intubation episodes through the course of the infant's stay in NICU, in the event that
35 multiple intubations are required for the same patient. In the event of emergent
36 intubation in the delivery room or within the first 24 hours after admission to NICU, it
37 may not be practical to obtain prospective informed consent. In these situations, the
38 study has approval to use a retrospective consent process at both study sites. The
39 infant will be included in the study, then consent to continue (retrospective consent)
40 will be sought from a parent or guardian as soon as possible after the procedure.
41 This consent process was pursued due to the known safety and efficacy of nHF use
42 in neonates, and the lack of any anticipated risk compared with standard clinical
43 practice. Furthermore, it is not always practical to obtain prospective written consent
44 from parents or guardians of infants undergoing intubation in the delivery room or the
45 NICU, as they may require intubation quickly and unpredictably.
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Video recording

The intubation will be video-recorded in order to optimise the quality of data collection. A GoPro® (GoPro Inc, San Mateo, California) video camera will be placed in a location that provides a clear overhead view of the intubation procedure, the infant's face, and the Masimo® pulse oximeter displaying real time SpO₂ and heart rate data, with averaging time of 2 seconds and set at maximum sensitivity. Data will be recorded by the study investigator on a Case Report Form and verified against the video recording and corrections made where errors are identified. The observed primary outcome will also be recorded in real time by the study investigator present, to be used in the case of video failure. The observed primary outcome will be verified by an independent assessor reviewing the video footage. Any discrepancies or disagreements will be resolved by a third assessor from the trial steering committee. Additional consent to use the video for the purposes of the study and for educational or research purposes will be obtained from the parent or guardian. Consent will also be obtained from the staff member performing the intubation for the video to be used.

Patient and public involvement

The study was discussed with parents of infants who had undergone endotracheal intubation in the neonatal unit during a pilot phase, prior to commencement of the trial, in order to assist with study design and to determine the acceptability of the intervention and trial procedures.

Adverse events

Adverse events (AEs) will be captured from the time of randomisation until the time the infant is successfully intubated. AEs are recorded as part of the study design, and AEs are components of the primary and secondary outcomes of the study. The investigator will be responsible for recording all AEs, regardless of their relationship to the intervention. Conditions that are present at screening and do not deteriorate will not be considered AEs.

The following AEs will be collected and recorded on the CRF:

1. Desaturation: Absolute decrease in oxygen saturation >20% from baseline
2. Bradycardia: Heart rate falling below 100 beats per minute

3. Oesophageal intubation: Misplacement of endotracheal tube
4. Difficult intubation: defined as intubation requiring two or more intubation attempts

Serious adverse events

Serious adverse events (SAEs) will be captured from the time of randomisation until 72 hours after randomisation. All SAEs will be reported to the Ethics Committee within 24 hours of occurring.

SAEs are defined as:

1. Death within 72 hours after the randomised intubation attempt
2. Cardiopulmonary resuscitation and/or adrenaline administration within one hour of the randomised intubation attempt
3. Newly-diagnosed pneumothorax requiring drainage within 72 hours of the randomised intubation attempt

Study oversight

A Data Safety Monitoring Board (DSMB) was established prior to the commencement of the trial and consists of two independent neonatologists and an independent statistician. The DSMB will review the safety of the trial at interim analyses after the primary outcome is known for 60, 125 and 180 patients (~25%, ~50% and ~75% recruitment). An additional efficacy analysis of the primary outcome only will be conducted after the primary outcome is known for 125 patients (~50% recruitment). The DSMB may recommend ceasing the trial if there is a highly statistically significant difference ($p < 0.001$) in the incidence of the primary outcome between the groups, or an important difference in the incidence of AEs or SAEs. The DSMB will also consider any new evidence that may make continuing the trial unethical.

Clinical significance

Endotracheal intubation is a life sustaining intervention. However, acquiring this skill is becoming increasingly difficult as the learning opportunities for an individual trainee decline. Many attempts are curtailed because of patient instability leading to loss of confidence amongst neonatal trainees. Improving the success rates of

1
2
3 neonatal endotracheal intubation **and** maintaining cardiorespiratory stability during
4 the attempt is important to minimise morbidity for all, but especially for preterm
5 newborn infants. If effective and safe, nHF use during neonatal intubation can be
6 rapidly translated into clinical practice as it is simple to use and readily generalisable
7 to units with access to this equipment. Results from this study will be disseminated
8 via peer-reviewed journals and presented at national and international scientific
9 conferences.
10
11
12
13
14
15
16
17
18

19 **Authors' Contributions:** KH conceptualised and designed the trial protocol, and
20 drafted and revised the manuscript. LO, COK, CTR, PGD and BJM contributed to
21 study design and revised the protocol manuscript. SD designed the statistical
22 analysis and revised the manuscript. All authors have read and approved the final
23 manuscript and are accountable for its accuracy.
24
25
26
27
28

29 **Funding Statement:** This work was supported by National Health and Medical
30 Research Council program grant #1113902. Nasal high flow equipment and
31 consumables have been supplied by Vapotherm.
32
33

34 **Competing Interests Statement:** No competing interests.
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References

1. Downes KJ, Narendran V, Meinen-Derr J, McClanahan S, Akinbi HT: **The lost art of intubation: assessing opportunities for residents to perform neonatal intubation.** *J Perinatol* 2012, **32**(12):927-932.
2. Leone TA, Rich W, Finer NN: **Neonatal intubation: success of pediatric trainees.** *J Pediatr* 2005, **146**(5):638-641.
3. Schmolzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung PY: **Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis.** *BMJ* 2013, **347**.
4. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB: **Nasal CPAP or intubation at birth for very preterm infants.** *NEJM* 2008, **358**(7):700-708.
5. Manley BJ, Arnolda GRB, Wright IMR, Owen LS, Foster JP, Huang L, Roberts CT, Clark TL, Fan WQ, Fang AYW *et al*: **Nasal High-Flow Therapy for Newborn Infants in Special Care Nurseries.** *N Engl J Med* 2019, **380**(21):2031-2040.
6. Roberts CT, Owen LS, Manley BJ, Froisland DH, Donath SM, Dalziel KM, Pritchard MA, Cartwright DW, Collins CL, Malhotra A *et al*: **Nasal High-Flow Therapy for Primary Respiratory Support in Preterm Infants.** *N Engl J Med* 2016, **375**(12):1142-1151.
7. Franklin D, Babl FE, Schlapbach LJ, Oakley E, Craig S, Neutze J, Furyk J, Fraser JF, Jones M, Whitty JA *et al*: **A Randomized Trial of High-Flow Oxygen Therapy in Infants with Bronchiolitis.** *N Engl J Med* 2018, **378**(12):1121-1131.
8. Papazian L, Corley A, Hess D, Fraser JF, Frat JP, Guitton C, Jaber S, Maggiore SM, Nava S, Rello J *et al*: **Use of high-flow nasal cannula oxygenation in ICU adults: a narrative review.** *Intensive Care Med* 2016, **42**(9):1336-1349.
9. Wilkinson D, Andersen C, O'Donnell CP, De Paoli AG, Manley BJ: **High flow nasal cannula for respiratory support in preterm infants.** *Cochrane Database Syst Rev* 2016, **2**:CD006405.
10. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, Hale EC, Newman NS, Schibler K, Carlo WA *et al*: **Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network.** *Pediatrics* 2010, **126**(3):443-456.
11. Foglia EE, Ades A, Sawyer T, Glass KM, Singh N, Jung P, Quek BH, Johnston LC, Barry J, Zenge J *et al*: **Neonatal Intubation Practice and Outcomes: An International Registry Study.** *Pediatrics* 2019, **143**.
12. O'Donnell CP, Kamlin CO, Davis PG, Morley CJ: **Endotracheal intubation attempts during neonatal resuscitation: success rates, duration, and adverse effects.** *Pediatrics* 2006, **117**(1):e16-21.
13. **Textbook of Neonatal Resuscitation (NRP), 7th Ed; 2016.**
14. Gerhardt T, Reifenberg L, Hehre D, Feller R, Bancalari E: **Functional residual capacity in normal neonates and children up to 5 years of age determined by a N2 washout method.** *Pediatr Res* 1986, **20**(7):668-671.
15. Hatch LD, Grubb PH, Lea AS, Walsh WF, Markham MH, Whitney GM, Slaughter JC, Stark AR, Ely EW: **Endotracheal Intubation in Neonates: A Prospective Study of Adverse Safety Events in 162 Infants.** *J Pediatr* 2016, **168**:62-66 e66.
16. Gustafsson IM, Lodenius A, Tunelli J, Ullman J, Jonsson Fagerlund M: **Apnoeic oxygenation in adults under general anaesthesia using Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) - a physiological study.** *Br J Anaesth* 2017, **118**(4):610-617.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
17. Patel A, Nouraei SA: **Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE): a physiological method of increasing apnoea time in patients with difficult airways.** *Anaesthesia* 2015, **70**(3):323-329.
 18. Hermez LA, Spence CJ, Payton MJ, Nouraei SAR, Patel A, Barnes TH: **A physiological study to determine the mechanism of carbon dioxide clearance during apnoea when using transnasal humidified rapid insufflation ventilatory exchange (THRIVE).** *Anaesthesia* 2019, **74**(4):441-449.
 19. Lyons C, Callaghan M: **Uses and mechanisms of apnoeic oxygenation: a narrative review.** *Anaesthesia* 2019, **74**(4):497-507.
 20. Humphreys S, Lee-Archer P, Reyne G, Long D, Williams T, Schibler A: **Transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) in children: a randomized controlled trial.** *Br J Anaesth* 2017, **118**(2):232-238.
 21. Patel R, Lenczyk M, Hannallah RS, McGill WA: **Age and the onset of desaturation in apnoeic children.** *Can J Anaesth* 1994, **41**(9):771-774.
 22. O'Shea JE, Thio M, Kamlin CO, McGrory L, Wong C, John J, Roberts C, Kuschel C, Davis PG: **Videolaryngoscopy to Teach Neonatal Intubation: A Randomized Trial.** *Pediatrics* 2015, **136**(5):912-919.
 23. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG: **Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support.** *J Biomed Inform* 2009, **42**(2):377-381.

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
Administrative information			
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	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	13

1	Roles and	#5b	Name and contact information for the trial sponsor	1
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	13
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate authority	
12			over any of these activities	
13				
14				
15				
16	Roles and	#5d	Composition, roles, and responsibilities of the coordinating centre,	12
17	responsibilities:		steering committee, endpoint adjudication committee, data	
18	committees		management team, and other individuals or groups overseeing the	
19			trial, if applicable (see Item 21a for data monitoring committee)	
20				
21				
22				
23	Introduction			
24				
25	Background and	#6a	Description of research question and justification for undertaking	4
26	rationale		the trial, including summary of relevant studies (published and	
27			unpublished) examining benefits and harms for each intervention	
28				
29				
30	Background and	#6b	Explanation for choice of comparators	4
31	rationale: choice of			
32	comparators			
33				
34				
35				
36	Objectives	#7	Specific objectives or hypotheses	5
37				
38	Trial design	#8	Description of trial design including type of trial (eg, parallel	6
39			group, crossover, factorial, single group), allocation ratio, and	
40			framework (eg, superiority, equivalence, non-inferiority,	
41			exploratory)	
42				
43				
44				
45	Methods:			
46	Participants,			
47	interventions, and			
48	outcomes			
49				
50				
51	Study setting	#9	Description of study settings (eg, community clinic, academic	6
52			hospital) and list of countries where data will be collected.	
53			Reference to where list of study sites can be obtained	
54				
55				
56				
57	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	6
58			eligibility criteria for study centres and individuals who will	
59				
60				

perform the interventions (eg, surgeons, psychotherapists)

1			
2			
3	Interventions:	#11a	Interventions for each group with sufficient detail to allow
4	description		replication, including how and when they will be administered
5			
6	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for a
7	modifications		given trial participant (eg, drug dose change in response to harms,
8			participant request, or improving / worsening disease)
9			
10			
11	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any
12	adherence		procedures for monitoring adherence (eg, drug tablet return;
13			laboratory tests)
14			
15			
16	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or
17	concomitant care		prohibited during the trial
18			
19			
20			
21	Outcomes	#12	Primary, secondary, and other outcomes, including the specific
22			measurement variable (eg, systolic blood pressure), analysis metric
23			(eg, change from baseline, final value, time to event), method of
24			aggregation (eg, median, proportion), and time point for each
25			outcome. Explanation of the clinical relevance of chosen efficacy
26			and harm outcomes is strongly recommended
27			
28			
29			
30	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins
31			and washouts), assessments, and visits for participants. A
32			schematic diagram is highly recommended (see Figure)
33			
34			
35			
36	Sample size	#14	Estimated number of participants needed to achieve study
37			objectives and how it was determined, including clinical and
38			statistical assumptions supporting any sample size calculations
39			
40			
41	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach
42			target sample size
43			
44			

Methods: Assignment of interventions (for controlled trials)

45			
46			
47			
48			
49			
50	Allocation: sequence	#16a	Method of generating the allocation sequence (eg, computer-
51	generation		generated random numbers), and list of any factors for
52			stratification. To reduce predictability of a random sequence,
53			details of any planned restriction (eg, blocking) should be provided
54			in a separate document that is unavailable to those who enrol
55			participants or assign interventions
56			
57			
58			
59			
60			

1	Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central	7
2	mechanism		telephone; sequentially numbered, opaque, sealed envelopes),	
3			describing any steps to conceal the sequence until interventions are	
4			assigned	
5				
6				
7				
8	Allocation:	#16c	Who will generate the allocation sequence, who will enrol	7
9	implementation		participants, and who will assign participants to interventions	
10				
11				
12	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial	N/A
13			participants, care providers, outcome assessors, data analysts), and	
14			how	
15				
16				
17	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible,	N/A
18	emergency unblinding		and procedure for revealing a participant's allocated intervention	
19			during the trial	
20				
21				
22	Methods: Data			
23	collection,			
24	management, and			
25	analysis			
26				
27				
28				
29	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other	9
30			trial data, including any related processes to promote data quality	
31			(eg, duplicate measurements, training of assessors) and a	
32			description of study instruments (eg, questionnaires, laboratory	
33			tests) along with their reliability and validity, if known. Reference	
34			to where data collection forms can be found, if not in the protocol	
35				
36				
37				
38				
39	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up,	9
40	retention		including list of any outcome data to be collected for participants	
41			who discontinue or deviate from intervention protocols	
42				
43				
44	Data management	#19	Plans for data entry, coding, security, and storage, including any	9
45			related processes to promote data quality (eg, double data entry;	
46			range checks for data values). Reference to where details of data	
47			management procedures can be found, if not in the protocol	
48				
49				
50				
51	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes.	9
52			Reference to where other details of the statistical analysis plan can	
53			be found, if not in the protocol	
54				
55				
56	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted	9
57	analyses		analyses)	
58				
59				
60				

1	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	N/A
2	population and missing		adherence (eg, as randomised analysis), and any statistical methods	
3	data		to handle missing data (eg, multiple imputation)	
4				
5				
6	Methods: Monitoring			
7				
8	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary of its	12
9	formal committee		role and reporting structure; statement of whether it is independent	
10			from the sponsor and competing interests; and reference to where	
11			further details about its charter can be found, if not in the protocol.	
12			Alternatively, an explanation of why a DMC is not needed	
13				
14	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	12
15	interim analysis		including who will have access to these interim results and make	
16			the final decision to terminate the trial	
17				
18				
19				
20				
21				
22	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited	11
23			and spontaneously reported adverse events and other unintended	
24			effects of trial interventions or trial conduct	
25				
26				
27	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and	N/A
28			whether the process will be independent from investigators and the	
29			sponsor	
30				
31				
32				
33	Ethics and			
34	dissemination			
35				
36	Research ethics	#24	Plans for seeking research ethics committee / institutional review	3
37	approval		board (REC / IRB) approval	
38				
39				
40	Protocol amendments	#25	Plans for communicating important protocol modifications (eg,	2
41			changes to eligibility criteria, outcomes, analyses) to relevant	
42			parties (eg, investigators, REC / IRBs, trial participants, trial	
43			registries, journals, regulators)	
44				
45				
46				
47	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial	10
48			participants or authorised surrogates, and how (see Item 32)	
49				
50				
51	Consent or assent:	#26b	Additional consent provisions for collection and use of participant	N/A
52	ancillary studies		data and biological specimens in ancillary studies, if applicable	
53				
54				
55	Confidentiality	#27	How personal information about potential and enrolled participants	9
56			will be collected, shared, and maintained in order to protect	
57			confidentiality before, during, and after the trial	
58				
59				
60				

1	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
2				
3				
4				
5	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	9
6				
7				
8				
9				
10	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
11				
12				
13				
14	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	10
15				
16				
17				
18				
19				
20				
21	Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
22				
23				
24				
25	Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
26				
27				
28	Appendices			
29				
30				
31	Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
32				
33				
34				
35	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
36				
37				
38				
39				

40 The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND
 41 3.0. This checklist was completed on 08. April 2020 using <https://www.goodreports.org/>, a tool made by the
 42 [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
 43
 44
 45
 46
 47
 48
 49
 50
 51
 52
 53
 54
 55
 56
 57
 58
 59
 60

BMJ Open

A multicentre, randomised trial of stabilisation with nasal high flow during neonatal endotracheal intubation (the SHINE trial): a study protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-039230.R1
Article Type:	Protocol
Date Submitted by the Author:	31-Jul-2020
Complete List of Authors:	Hodgson, Kate; The Royal Women's Hospital, Newborn Research Centre; The University of Melbourne, Department of Obstetrics and Gynaecology Owen, Louise; The Royal Women's Hospital, Newborn Research Centre; The University of Melbourne, Department of Obstetrics and Gynaecology Kamlin, Camille; The Royal Women's Hospital, Newborn Research Centre; The University of Melbourne, Department of Obstetrics and Gynaecology Roberts, Calum; Monash Children's Hospital, Monash Newborn; Monash University, Department of Paediatrics Donath, Susan; Murdoch Childrens Research Institute, Clinical Epidemiology and Biostatistics Unit Davis, Peter; The Royal Women's Hospital, Newborn Research Centre Manley, Brett; The Royal Women's Hospital, Newborn Research Centre
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Intensive care
Keywords:	Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE, INTENSIVE & CRITICAL CARE, NEONATOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 1 **Title Page**
4
5 2

6
7 3 **Title:**

8 4 **A multicentre, randomised trial of stabilisation with nasal high flow during**
9 5 **neonatal endotracheal intubation (the SHINE trial): a study protocol.**
10
11 6

12
13 7 **Authors:**

14 8 Hodgson KA^{1,2}, Owen LS^{1,2,3}, Kamlin CO^{1,2,3}, Roberts CT^{4,5}, Donath S^{3,6}, Davis
15 9 PG^{1,2,3}, Manley BJ^{1,2,3}.

16
17 10 **Corresponding author:** Dr Kate Hodgson, Newborn Research Precinct, 7th Floor,
18 11 20 Flemington Rd Parkville VIC 3052 Australia, Kate.Hodgson@thewomens.org.au,
19 12 +61 3 8345 2000
20
21
22
23

24 13 **Affiliations:**

- 25 14 1 Newborn Research Centre, Royal Women's Hospital, Melbourne, Australia
26 15 2 Department of Obstetrics and Gynaecology, University of Melbourne,
27 16 Parkville, Victoria, Australia
28 17 3 Murdoch Children's Research Institute, Parkville, Victoria, Australia
29 18 4 Monash Newborn, Monash Children's Hospital, Melbourne, Australia
30 19 5 Department of Paediatrics, Monash University, Melbourne, Australia
31 20 6 Department of Paediatrics, University of Melbourne, Parkville, Victoria,
32 21 Australia
33
34
35
36
37
38

39 22 **Contact details:**

40 23 Kate.Hodgson@thewomens.org.au

41 24 Louise.Owen@thewomens.org.au

42 25 Omar.Kamlin@thewomens.org.au

43 26 Calum.Roberts@monash.edu

44 27 Susan.Donath@mcri.edu.au

45 28 pgd@unimelb.edu.au

46 29 Brett.Manley@thewomens.org.au
47
48
49
50
51
52
53
54

55 31 **Trial registration:**

56 32 Australia and New Zealand Clinical Trial Registry: ACTRN12618001498280.
57
58
59
60

33 **Keywords:**

1
2
3 1 Infant, Preterm, Endotracheal Intubation, Nasal High Flow Therapy, Apnoeic
4 2 Oxygenation
5
6
7 3

8 4 **Data sharing statement:**

9
10 5 The protocol will be published and publicly available, and the deidentified individual
11 6 patient datasets and statistical code will be available on reasonable request.
12
13 7

14
15 8 **Abstract**

16
17 9 **Introduction**

18
19 10 Neonatal endotracheal intubation is an essential but potentially destabilising
20 11 procedure. With an increased focus on avoiding mechanical ventilation, particularly
21 12 in preterm infants, there are fewer opportunities for clinicians to gain proficiency in
22 13 this important emergency skill. Rates of successful intubation at the first attempt are
23 14 relatively low, and adverse event rates are high, when compared with intubations in
24 15 paediatric and adult populations. Interventions to improve operator success and
25 16 patient stability during neonatal endotracheal intubations are needed. Using nasal
26 17 high flow therapy extends the safe apnoea time of adults undergoing upper airway
27 18 surgery and during endotracheal intubation. This technique is untested in neonates.
28
29

30
31 19 **Methods and analysis**

32 20 The SHINE (Stabilisation with nasal High flow during Intubation of Neonates) trial is
33 21 a multicentre, randomised controlled trial comparing the use of nasal high flow during
34 22 neonatal intubation with standard care (no nasal high flow). Intubations are
35 23 randomised individually, and stratified by site, use of premedications, and
36 24 postmenstrual age (<28 weeks' gestation; ≥28 weeks' gestation). The primary
37 25 outcome is the incidence of successful intubation on the first attempt without
38 26 physiological instability of the infant. Physiological instability is defined as an
39 27 absolute decrease in peripheral oxygen saturation >20% from pre-intubation
40 28 baseline, and/or bradycardia (<100 beats per minute).
41
42

43 29 **Ethics and dissemination**

44 30 The SHINE trial received ethical approval from the Human Research Ethics
45 31 Committees of The Royal Women's Hospital, Melbourne, Australia and Monash
46 32 Health, Melbourne, Australia. The trial is currently recruiting in these two sites. The
47 33 findings of this study will be disseminated via peer-reviewed journals and presented
48
49
50
51
52
53
54
55
56
57
58
59
60

1 at national and international conferences. The trial was prospectively registered with
2 the Australian and New Zealand Clinical Trials Registry (ACTRN12618001498280).

3 4 **Strengths and limitations of the study**

- 5 • Strength: The first randomised controlled trial of nasal high flow to improve
6 procedure success and physiologic stability during neonatal intubation
- 7 • Strength: A low risk, easily generalisable intervention to assist with a difficult,
8 life saving procedure
- 9 • Strength: Interventions are video recorded to enable accurate and objective
10 data collection
- 11 • Limitation: Likelihood of intubation success may be affected by operator
12 experience and the use of videolaryngoscopy; these factors will be addressed in a
13 sensitivity analysis
- 14 • Limitation: Due to the nature of the intervention, blinding is not possible

15 16 **Introduction**

17 Opportunities for clinicians to acquire proficiency in neonatal endotracheal intubation
18 have decreased over time [1, 2]. The increased use of 'non-invasive' respiratory
19 support (without an endotracheal tube), less-invasive surfactant administration
20 techniques, and the move away from routine endotracheal suctioning of babies born
21 through meconium-stained amniotic fluid have contributed to this trend. In extremely
22 preterm infants, the use of nasal continuous positive airway pressure (CPAP) for
23 primary respiratory support results in fewer days of mechanical ventilation, less
24 surfactant administration and a lower risk of bronchopulmonary dysplasia, compared
25 with intubation and mechanical ventilation [3, 4]. Nasal high flow therapy (nHF) is a
26 newer mode of non-invasive respiratory support that delivers heated, humidified gas
27 via two small nasal prongs. In preterm infants, nHF has been evaluated for the
28 management of early respiratory distress and post extubation support, leading to
29 widespread use in neonatal intensive care units [5, 6]. Nasal HF is commonly used in
30 preterm and term newborn infants [5, 6], as well as in children [7] and adults [8].
31 Current clinical applications of nasal HF in neonates include primary support of
32 respiratory distress syndrome, and post-extubation support in preterm infants [9].

1
2
3 1 Whilst non-invasive modes of respiratory support are utilised whenever possible for
4 2 neonates, endotracheal intubation is still sometimes required, particularly for the
5 3 most immature infants [10]. With decreasing clinical experience in this procedure,
6 4 neonatal intubation success rates at the first attempt are low but increase with
7 5 increasing operator experience. In a large international registry study of adverse
8 6 events associated with endotracheal intubation, Foglia *et al.* demonstrated that
9 7 overall first attempt intubation success was 49% for intubations in the neonatal
10 8 intensive care unit (NICU) [11]. O'Donnell *et al.* reviewed 60 intubation attempts and
11 9 reported success rates of 24% for residents (junior trainees), 78% for fellows (senior
12 10 trainees) and 86% for consultants [12]. Furthermore, the duration of neonatal
13 11 intubation attempts is often longer than the international guidelines recommend [13]
14 12 and varies with the experience of the operator [12]. Neonates are often clinically
15 13 unstable during endotracheal intubation, due to a lower functional residual capacity
16 14 and greater metabolic demand than older children and adults [14]. In one study,
17 15 severe hypoxaemia (defined as peripheral oxygen saturation [SpO₂] <60%) was
18 16 reported in 44% of neonatal intubations, and bradycardia (heart rate <60 beats per
19 17 minute [bpm] for at least 5 seconds) in 24% [15].
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34

19 Apnoeic oxygenation refers to oxygenation in the absence of spontaneous
20 respiration or positive pressure ventilation [16]. The physiological principle underlying
21 apnoeic oxygenation is a ventilatory mass flow: in the apnoeic patient, as oxygen
22 moves from the alveoli into the bloodstream, alveolar pressure becomes
23 subatmospheric [17]. This in turn facilitates movement of oxygen (applied via nasal
24 prongs) down a pressure gradient from the atmosphere into the alveoli. Apnoeic
25 oxygenation is used as an adjunct to preoxygenation in anaesthesia, to prolong the
26 period of time prior to desaturation in patients in whom definitive securing of the
27 airway is expected to be difficult (due to anatomy) [17], impossible (due to airway
28 surgery) [18], or the time to desaturation short (due to patient comorbidities) [17].
29

30 Traditionally apnoeic oxygenation was provided via 'low flow' nasal cannulae. More
31 recently, the concept of Transnasal Humidified Rapid Insufflation Ventilatory
32 Exchange (THRIVE) has arisen. THRIVE is the use of nHF (heated, humidified air
33 and oxygen via nasal cannulae) during apnoea. There is evidence that nHF use
34 during apnoea may improve oxygenation and also carbon dioxide clearance,

1 compared with 'low flow' oxygen or jaw support only [17, 18]. Proposed mechanisms
2 include removal of carbon dioxide through enhanced dead space washout and
3 continuous distending pressure, which increases the pressure gradient for oxygen to
4 move down. Furthermore, apnoeic ventilation may be facilitated by cardiogenic
5 oscillations, whereby variations of heart volume during the cardiac cycle promote gas
6 exchange by altering intrathoracic pressure [19, 20]. Turbulent gas flow from nHF,
7 combined with compression and expansion of the alveoli due to blood flow in the
8 pulmonary vasculature, may allow some gas exchange during apnoea [19].

9
10 THRIVE has been shown to prolong the safe apnoeic time (time prior to
11 desaturation) in adults [17] and in healthy infants and children undergoing general
12 anaesthesia and elective intubation [21]. Two randomised controlled trials have
13 examined THRIVE in the paediatric population. Humphreys *et al.* randomised 48
14 children aged <10 years undergoing general anaesthesia to THRIVE (nHF at
15 2L/kg/min for patients up to 15kg), or to control (jaw support only). THRIVE
16 significantly prolonged the apnoea time (time prior to SpO₂ <92%) in all age groups
17 [21]. All but one patient in the control group desaturated to <92% within the
18 anticipated time frame, which was predefined as twice the length of previously
19 published age-related values [22]. In contrast, the THRIVE group had no
20 desaturations and a mean SpO₂ of 99.6% (range 97-100%). Riva *et al.* randomised
21 60 patients aged 1-6 years undergoing general anaesthesia to receive one of three
22 methods of apnoeic oxygenation: low flow oxygen (0.2L/kg/min FiO₂ 1.0), THRIVE
23 100% (nHF at 2L/kg/min FiO₂ 1.0) or THRIVE 30% (nHF at 2L/kg/min FiO₂ 0.3). The
24 primary outcome was apnoea time (time prior to SpO₂ <95%). Additional reasons for
25 termination of the intervention were apnoea time of 10 minutes or hypercarbia
26 (partial pressure of carbon dioxide > 65mmHg). Apnoea time was longer in low flow
27 and THRIVE 100% groups, compared with the THRIVE 30% group. Whilst there was
28 no statistically significant difference between the THRIVE 100% and the low flow
29 groups, the reason for termination of apnoea was time or hypercarbia in all THRIVE
30 100% oxygen patients, not the primary outcome of apnoea time.

31
32 There are currently no published studies of the use of THRIVE during neonatal
33 intubation, nor in emergency settings in older patients with respiratory distress. The

1
2
3 1 aim of the SHINE (Stabilisation with nasal High flow during Intubation of NEonates)
4 2 randomised controlled trial is to investigate whether the use of nHF during neonatal
5 3 endotracheal intubation (1) after birth in the delivery room and (2) in the neonatal
6 4 intensive care unit improves the likelihood of successful intubation on the first
7 5 attempt without physiological instability of the infant.
8
9
10
11
12

13 7 **Methods and analysis**

14 8 **Study design**

15 9 A multicentre, unblinded, randomised controlled trial investigating the efficacy of nHF
16 10 to improve success and stability during neonatal endotracheal intubation. Intubations
17 11 performed in the delivery room or NICU will be randomised, with a 1:1 ratio. Infants
18 12 will either receive nHF during the endotracheal intubation attempt, or standard care
19 13 (no nHF). Intervention will be applied for the first intubation attempt of the episode
20 14 only.
21
22
23
24
25
26
27
28

29 16 **Sample size**

30 17 The sample size of 246 infants is based on a study of videolaryngoscope use for
31 18 teaching neonatal intubation [23], which examined 206 intubations by junior medical
32 19 staff. This study reported a 29% successful intubation rate at the first attempt without
33 20 desaturation >20% or bradycardia <100 bpm. With a power of 90% to detect an
34 21 increase in the incidence of successful intubation without physiological instability
35 22 from 30% to 50%, 123 infants in each group (246 total) are required.
36
37
38
39
40
41
42

43 24 There is some variability in the reporting of success rates for neonatal intubation,
44 25 depending on level of operator experience [12] and use of videolaryngoscopy [23].

45 26 The uncertainty surrounding the baseline rate of the primary outcome may present a
46 27 limitation in this study.
47
48
49
50
51

52 29 **Patient population**

53 30 Any neonate undergoing endotracheal intubation in the delivery room or NICU is
54 31 eligible for inclusion. In participating centres, all infants who undergo endotracheal
55 32 intubation will be screened for study eligibility. Infants already studied can have
56 33 subsequent intubation episodes randomised again if 1) the premedication
57
58
59
60

1
2
3 1 randomisation stratum differs between intubations, or 2) there is at least one week
4
5 2 between the studied intubations for intubations using premedications.
6
7 3

8 **Inclusion criteria**

9
10 5 Infants undergoing endotracheal intubation in the delivery room or NICU are eligible
11
12 6 for inclusion.
13
14 7

15 **Exclusion criteria**

16
17 9 Exclusion criteria are:

- 18
19 10 • planned nasal intubation
- 20
21 11 • a requirement for immediate endotracheal intubation as determined by the
22
23 12 treating clinician (insufficient time for researcher to randomise and set up study
24
25 13 equipment)
- 26
27 14 • heart rate <120 bpm prior to randomisation (as at higher risk of bradycardia as
28
29 15 defined in the trial)
- 30
31 16 • contraindications to nHF use, e.g. congenital nasal anomaly, congenital
32
33 17 diaphragmatic hernia or abdominal wall defect
- 34
35 18 • cyanotic congenital heart disease
- 36
37 19 • infant with suspected or proven COVID-19, or born to a mother with suspected or
38
39 20 proven COVID-19

40 **Randomisation**

41
42 23 Each intubation episode is randomised to one of the two groups using random
43
44 24 permuted blocks with varying block sizes. Pre-randomisation stratification is by
45
46 25 centre, post-menstrual age (<28 weeks; ≥28 weeks) and use of premedication for
47
48 26 intubation. To enable rapid randomisation following the decision to intubate by the
49
50 27 clinical team, the randomisation is performed at the cotside using a smartphone or
51
52 28 computer with online access to the REDCap [24] randomisation tool.
53
54 29

54 **Clinical management**

55 **Nasal HF group (intervention)**

56
57 31 A trial investigator will perform the intervention. Immediately prior to intubation,
58
59 32 infants will be receiving either CPAP via nasal prongs, nasal mask or a facemask, or
60
60 33

1 positive pressure ventilation via a facemask. The Precision Flow ® device (Exeter,
2 New Hampshire) and weight-appropriate binasal cannulae will be used to provide
3 nHF. The cannulae will occupy approximately 50% of the nares and enable leak. The
4 investigator will apply the nHF prongs at the time of the face mask, nasal mask or
5 nasal prongs being removed for laryngoscopy. Gas flow will be set to 8 Litres per
6 minute (L/min) for the duration of the study intervention. The fraction of inspired
7 oxygen (FiO₂) prior to the intubation attempt, including the use of any pre-
8 oxygenation (an increase in FiO₂ prior to the intubation attempt), will be at the
9 discretion of the clinical team. The trial investigator will set the nHF FiO₂ to the same
10 amount the infant was receiving prior to laryngoscopy, and if the infant desaturates
11 to <90% during the intubation attempt, the investigator will increase the nHF FiO₂ to
12 1.0 (100% supplemental oxygen) until the end of the intubation attempt. The nHF
13 prongs will be secured only by tightening the cannula tubing behind the infant's
14 head; no adhesive tapes will be applied to the face. Nasal HF will continue during
15 laryngoscopy, and the investigator will remove the nHF prongs when the first
16 intubation attempt is either ceased, or successfully completed (see definition below).
17 The commencement, duration and termination of an intubation attempt will be at the
18 discretion of the most senior clinician caring for the infant.

19 20 **Standard care group (control)**

21 Patients in the control arm will receive standard care. The intubation attempt
22 (laryngoscopy) will proceed without the application of nHF or the use of
23 supplemental oxygen. In the event that an infant in the NICU is already receiving
24 respiratory support from nHF prior to intubation being planned, this may continue up
25 until the time of induction medications being administered (if applicable). The
26 commencement, duration and termination of an intubation attempt will be at the
27 discretion of the most senior clinician caring for the infant.

28 29 **Outcomes**

30 **Primary outcome**

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

1
2
3 1 Definitions:

- 4
5 2 • Intubation attempt: the insertion of the laryngoscope blade beyond the infant's
6
7 3 lips
8
9 4 • Intubation duration: the time from the insertion of the laryngoscope blade beyond
10
11 5 the infant's lips until the removal of the laryngoscope blade from the infant's
12
13 6 mouth
14
15 7 • Successful intubation: the completion of the intubation attempt with correct
16
17 8 positioning of the endotracheal tube confirmed by detection of expired carbon
18
19 9 dioxide on a colorimetric detector.
20
21 10 • Physiological instability: the incidence (any duration) of an absolute decrease in
22
23 11 SpO₂ >20% from baseline (immediately prior to the intubation attempt), and/or
24
25 12 bradycardia (heart rate <100 bpm), during the first intubation attempt
26
27 13

26 14 **Secondary outcomes**

- 27 15 1. Incidence of successful intubation on the first intubation attempt
28
29 16 2. Incidence of desaturation (absolute decrease in SpO₂ >20% from baseline) *or*
30
31 17 bradycardia (heart rate <100 bpm) during the first intubation attempt
32
33 18 3. Time to desaturation (absolute decrease in SpO₂ >20% from baseline) during the
34
35 19 first intubation attempt in seconds
36
37 20 4. Time to bradycardia (heart rate <100 bpm) during the first intubation attempt in
38
39 21 seconds
40
41 22 5. Duration of desaturation (absolute decrease in SpO₂ >20% from baseline) during
42
43 23 first intubation attempt in seconds
44
45 24 6. Duration of bradycardia (heart rate <100 bpm) during first intubation attempt in
46
47 25 seconds
48
49 26 7. Median SpO₂ during intubation attempt
50
51 27 8. Median heart rate during intubation attempt
52
53 28 9. Duration of SpO₂ ≥97% during intubation attempt, in seconds
54
55 29 10. Number of intubation attempts
56
57 30 11. Duration of all intubation attempts (successful and unsuccessful), in seconds
58
59 31 12. Incidence of cardiac compressions and/or adrenaline administration within one
60
32 hour after the first intubation attempt

1
2
3 1 13. Incidence of pneumothorax within 72 hours after randomisation, diagnosed either
4 by transillumination of the chest and/or by chest X-ray

5 2
6 3 14. Incidence of pneumothorax requiring drainage (via needle thoracocentesis or
7 insertion of an intercostal catheter) within 72 hours after randomisation

8 4
9 5 15. Death within 72 hours after randomisation

10 6 11 7 **Data analysis plan**

12 8 The incidence of the primary outcome will be compared using risk difference and
13 two-sided 95% confidence interval (CI). Secondary outcomes will be compared using
14 risk difference (with 95% CI) (outcomes 1, 2, and 9 to 12), and difference of means
15 or medians with 95% CI (outcomes 3 to 8). Planned subgroup analyses by each of
16 the pre-randomisation strata will be performed for the primary outcome and selected
17 secondary outcomes. Analyses will be by intention-to-treat, with an additional *per-*
18 *protocol* analysis for the primary outcome. The primary analysis will be adjusted for
19 stratification factors. Regression models with the stratification factors used in
20 randomisation included as covariates will be used for all analyses. A sensitivity
21 analysis will be conducted to account for repeated randomisation events within
22 individual subjects. If an imbalance in demographics known to affect intubation
23 success (e.g. postmenstrual age, weight, videolaryngoscope use, operator
24 experience) is detected, a further sensitivity analysis adjusting for the relevant
25 demographics will be conducted. Data will be exported from an electronic database
26 to an electronic statistical package for analysis.

27 23 28 24 **Ethics and Dissemination**

29 25 Prospective consent will be sought from a parent for inclusion of their infant in the
30 study, whenever possible. Prospective consent will be obtained for all eligible
31 intubation episodes through the course of the infant's stay in NICU, in the event that
32 multiple intubations are required for the same patient. In the event of emergent
33 intubation in the delivery room or within the first 24 hours after admission to NICU, it
34 may not be practical to obtain prospective informed consent. In these situations, 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 a 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

1
2
3 1 in neonates, and the lack of any anticipated risk compared with standard clinical
4 2 practice. Furthermore, obtaining prospective written consent from parents or
5 3 guardians of infants undergoing intubation in the delivery room or the NICU is not
6 4 always practical, as they may require intubation quickly and unpredictably. The
7 5 SHINE trial received ethical approval from the Human Research Ethics Committees
8 6 of The Royal Women's Hospital, Melbourne, Australia and Monash Health,
9 7 Melbourne, Australia.
10 8

9 **Video recording**

10 The intubation will be video-recorded in order to optimise the quality of data
11 11 collection. A GoPro® (GoPro Inc, San Mateo, California) video camera will be
12 12 placed in a location that provides a clear overhead view of the intubation procedure,
13 13 the infant's face, and the Masimo® pulse oximeter displaying real time SpO₂ and
14 14 heart rate data, with averaging time of 2 seconds and set at maximum sensitivity.
15 15 The study investigator will record data on a Case Report Form and verify this against
16 16 the video recording. Corrections will be made where errors are identified. The study
17 17 investigator will also record the observed primary outcome in real time by, in case of
18 18 video failure. An independent assessor will also review the video footage to verify the
19 19 primary outcome. Any discrepancies or disagreements will be resolved by a third
20 20 assessor from the trial steering committee. Additional consent will be obtained from
21 21 the parent or guardian to use the video for the purposes of the study and for
22 22 educational or research purposes. Consent will also be obtained from the staff
23 23 member performing the intubation for the video to be used.
24 24

25 **Patient and public involvement**

26 26 The study was discussed with parents of infants who had undergone endotracheal
27 27 intubation in the neonatal unit during a pilot phase, prior to commencement of the
28 28 trial, in order to assist with study design and to determine the acceptability of the
29 29 intervention and trial procedures.
30 30

31 **Adverse events**

32 32 Adverse events (AEs) will be captured from the time of randomisation until the time
33 33 the infant is successfully intubated. AEs are recorded as part of the study design,
34 34 and AEs are components of the primary and secondary outcomes of the study. The

1 investigator will be responsible for recording all AEs, regardless of their relationship
2 to the intervention. Conditions that are present at screening and do not deteriorate
3 will not be considered AEs.

4
5 The following AEs will be collected and recorded on the CRF:

- 6 1. Desaturation: Absolute decrease in oxygen saturation >20% from baseline
- 7 2. Bradycardia: Heart rate falling below 100 beats per minute
- 8 3. Oesophageal intubation: Misplacement of endotracheal tube
- 9 4. Difficult intubation: defined as intubation requiring two or more intubation
10 attempts

11 12 **Serious adverse events**

13 Serious adverse events (SAEs) will be captured from the time of randomisation until
14 72 hours after randomisation. All SAEs will be reported to the Ethics Committee
15 within 24 hours of occurring.

16
17 SAEs are defined as:

- 18 1. Death within 72 hours after the randomised intubation attempt
- 19 2. Cardiopulmonary resuscitation and/or adrenaline administration within one hour
20 of the randomised intubation attempt
- 21 3. Newly-diagnosed pneumothorax requiring drainage within 72 hours of the
22 randomised intubation attempt

23 24 **Study oversight**

25 A Data Safety Monitoring Board (DSMB) was established prior to the
26 commencement of the trial and consists of two independent neonatologists and an
27 independent statistician. The DSMB will review the safety of the trial at interim
28 analyses after the primary outcome is known for 60, 125 and 180 patients (~25%,
29 ~50% and ~75% recruitment). An additional efficacy analysis of the primary outcome
30 only will be conducted after the primary outcome is known for 125 patients
31 (~50% recruitment). The DSMB may recommend ceasing the trial if there is a highly
32 statistically significant difference ($p < 0.001$) in the incidence of the primary outcome
33 between the groups, or an important difference in the incidence of AEs or SAEs. The

1 DSMB will also consider any new evidence that may make continuing the trial
2 unethical.

3 4 **Clinical significance**

5 Endotracheal intubation is a life sustaining intervention. However, acquiring this skill
6 is becoming increasingly difficult as the learning opportunities for an individual
7 trainee decline. Many attempts are curtailed because of patient instability leading to
8 loss of confidence amongst neonatal trainees. Improving the success rates of
9 neonatal endotracheal intubation **and** maintaining cardiorespiratory stability during
10 the attempt is important to minimise morbidity for all, but especially for preterm
11 newborn infants. If effective and safe, nHF use during neonatal intubation can be
12 rapidly translated into clinical practice as it is simple to use and readily generalisable
13 to units with access to this equipment. Results from this study will be disseminated
14 via peer-reviewed journals and presented at national and international scientific
15 conferences.

16
17 **Authors' Contributions:** KH conceptualised and designed the trial protocol, and
18 drafted and revised the manuscript. LO, COK, CTR, PGD and BJM contributed to
19 study design and revised the protocol manuscript. SD designed the statistical
20 analysis and revised the manuscript. All authors have read and approved the final
21 manuscript and are accountable for its accuracy.

22
23 **Funding Statement:** This work was supported by National Health and Medical
24 Research Council program grant #1113902. Nasal high flow equipment and
25 consumables have been supplied by Vapotherm.

26
27 **Competing Interests Statement:** No competing interests.

References

1. Downes KJ, Narendran V, Meinen-Derr J, McClanahan S, Akinbi HT: **The lost art of intubation: assessing opportunities for residents to perform neonatal intubation.** *J Perinatol* 2012, **32**(12):927-932.
2. Leone TA, Rich W, Finer NN: **Neonatal intubation: success of pediatric trainees.** *The Journal of pediatrics* 2005, **146**(5):638-641.
3. Schmolzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung PY: **Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis.** *BMJ* 2013, **347**.
4. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB: **Nasal CPAP or intubation at birth for very preterm infants.** *NEJM* 2008, **358**(7):700-708.
5. Manley BJ, Arnolda GRB, Wright IMR, Owen LS, Foster JP, Huang L, Roberts CT, Clark TL, Fan WQ, Fang AYW *et al*: **Nasal High-Flow Therapy for Newborn Infants in Special Care Nurseries.** *N Engl J Med* 2019, **380**(21):2031-2040.
6. Roberts CT, Owen LS, Manley BJ, Froisland DH, Donath SM, Dalziel KM, Pritchard MA, Cartwright DW, Collins CL, Malhotra A *et al*: **Nasal High-Flow Therapy for Primary Respiratory Support in Preterm Infants.** *N Engl J Med* 2016, **375**(12):1142-1151.
7. Franklin D, Babl FE, Schlapbach LJ, Oakley E, Craig S, Neutze J, Furyk J, Fraser JF, Jones M, Whitty JA *et al*: **A Randomized Trial of High-Flow Oxygen Therapy in Infants with Bronchiolitis.** *N Engl J Med* 2018, **378**(12):1121-1131.
8. Papazian L, Corley A, Hess D, Fraser JF, Frat JP, Guitton C, Jaber S, Maggiore SM, Nava S, Rello J *et al*: **Use of high-flow nasal cannula oxygenation in ICU adults: a narrative review.** *Intensive Care Med* 2016, **42**(9):1336-1349.
9. Wilkinson D, Andersen C, O'Donnell CP, De Paoli AG, Manley BJ: **High flow nasal cannula for respiratory support in preterm infants.** *Cochrane Database Syst Rev* 2016, **2**:CD006405.
10. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, Hale EC, Newman NS, Schibler K, Carlo WA *et al*: **Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network.** *Pediatrics* 2010, **126**(3):443-456.
11. Foglia EE, Ades A, Sawyer T, Glass KM, Singh N, Jung P, Quek BH, Johnston LC, Barry J, Zenge J *et al*: **Neonatal Intubation Practice and Outcomes: An International Registry Study.** *Pediatrics* 2019, **143**.
12. O'Donnell CP, Kamlin CO, Davis PG, Morley CJ: **Endotracheal intubation attempts during neonatal resuscitation: success rates, duration, and adverse effects.** *Pediatrics* 2006, **117**(1):e16-21.
13. **Textbook of Neonatal Resuscitation (NRP), 7th Ed; 2016.**
14. Gerhardt T, Reifenberg L, Hehre D, Feller R, Bancalari E: **Functional residual capacity in normal neonates and children up to 5 years of age determined by a N2 washout method.** *Pediatr Res* 1986, **20**(7):668-671.
15. Hatch LD, Grubb PH, Lea AS, Walsh WF, Markham MH, Whitney GM, Slaughter JC, Stark AR, Ely EW: **Endotracheal Intubation in Neonates: A Prospective Study of Adverse Safety Events in 162 Infants.** *J Pediatr* 2016, **168**:62-66 e66.
16. Lyons C, Callaghan M: **Apnoeic oxygenation in paediatric anaesthesia: a narrative review.** *Anaesthesia* 2020.
17. Patel A, Nouraei SA: **Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE): a physiological method of increasing apnoea time in patients with difficult airways.** *Anaesthesia* 2015, **70**(3):323-329.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
18. Gustafsson IM, Lodenius A, Tunelli J, Ullman J, Jonsson Fagerlund M: **Apnoeic oxygenation in adults under general anaesthesia using Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) - a physiological study.** *Br J Anaesth* 2017, **118**(4):610-617.
 19. Hermez LA, Spence CJ, Payton MJ, Nouraei SAR, Patel A, Barnes TH: **A physiological study to determine the mechanism of carbon dioxide clearance during apnoea when using transnasal humidified rapid insufflation ventilatory exchange (THRIVE).** *Anaesthesia* 2019, **74**(4):441-449.
 20. Lyons C, Callaghan M: **Uses and mechanisms of apnoeic oxygenation: a narrative review.** *Anaesthesia* 2019, **74**(4):497-507.
 21. Humphreys S, Lee-Archer P, Reyne G, Long D, Williams T, Schibler A: **Transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) in children: a randomized controlled trial.** *Br J Anaesth* 2017, **118**(2):232-238.
 22. Patel R, Lenczyk M, Hannallah RS, McGill WA: **Age and the onset of desaturation in apnoeic children.** *Can J Anaesth* 1994, **41**(9):771-774.
 23. O'Shea JE, Thio M, Kamlin CO, McGrory L, Wong C, John J, Roberts C, Kuschel C, Davis PG: **Videolaryngoscopy to Teach Neonatal Intubation: A Randomized Trial.** *Pediatrics* 2015, **136**(5):912-919.
 24. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG: **Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support.** *J Biomed Inform* 2009, **42**(2):377-381.

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
Administrative information			
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	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	13

1	Roles and	#5b	Name and contact information for the trial sponsor	1
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	13
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate authority	
12			over any of these activities	
13				
14				
15				
16	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	12
17	responsibilities:		centre, steering committee, endpoint adjudication committee,	
18	committees		data management team, and other individuals or groups	
19			overseeing the trial, if applicable (see Item 21a for data	
20			monitoring committee)	
21				
22				
23				
24	Introduction			
25				
26				
27	Background and	#6a	Description of research question and justification for	4
28	rationale		undertaking the trial, including summary of relevant studies	
29			(published and unpublished) examining benefits and harms for	
30			each intervention	
31				
32				
33				
34	Background and	#6b	Explanation for choice of comparators	4
35	rationale: choice of			
36	comparators			
37				
38				
39	Objectives	#7	Specific objectives or hypotheses	5
40				
41	Trial design	#8	Description of trial design including type of trial (eg, parallel	6
42			group, crossover, factorial, single group), allocation ratio, and	
43			framework (eg, superiority, equivalence, non-inferiority,	
44			exploratory)	
45				
46				
47				
48	Methods:			
49	Participants,			
50	interventions, and			
51	outcomes			
52				
53				
54				
55	Study setting	#9	Description of study settings (eg, community clinic, academic	6
56			hospital) and list of countries where data will be collected.	
57			Reference to where list of study sites can be obtained	
58				
59				
60				

1	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)	6
2				
3				
4				
5				
6	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
7	description			
8				
9				
10	Interventions:	#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)	7
11	modifications			
12				
13				
14				
15	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
16	adherence			
17				
18				
19				
20				
21	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
22	concomitant care			
23				
24				
25	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	8
26				
27				
28				
29				
30				
31				
32				
33				
34	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)	7
35				
36				
37				
38				
39				
40	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	6
41				
42				
43				
44				
45	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
46				
47				
48				
49	Methods: Assignment			
50	of interventions (for			
51	controlled trials)			
52				
53				
54	Allocation: sequence	#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	7
55	generation			
56				
57				
58				
59				
60				

provided in a separate document that is unavailable to those who enrol participants or assign interventions

1			
2			
3			
4	Allocation	#16b	Mechanism of implementing the allocation sequence (eg, central
5	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
6			describing any steps to conceal the sequence until interventions
7	mechanism		are assigned
8			
9			
10			
11	Allocation:	#16c	Who will generate the allocation sequence, who will enrol
12	implementation		participants, and who will assign participants to interventions
13			
14			
15	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial
16			participants, care providers, outcome assessors, data analysts),
17			and how
18			
19			
20	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible,
21	emergency unblinding		and procedure for revealing a participant's allocated
22			intervention during the trial
23			
24			
25	Methods: Data		
26	collection,		
27	management, and		
28	analysis		
29			
30			
31			
32	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and
33			other trial data, including any related processes to promote data
34			quality (eg, duplicate measurements, training of assessors) and a
35			description of study instruments (eg, questionnaires, laboratory
36			tests) along with their reliability and validity, if known.
37			Reference to where data collection forms can be found, if not in
38			the protocol
39			
40			
41			
42			
43	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up,
44	retention		including list of any outcome data to be collected for
45			participants who discontinue or deviate from intervention
46			protocols
47			
48			
49			
50	Data management	#19	Plans for data entry, coding, security, and storage, including any
51			related processes to promote data quality (eg, double data entry;
52			range checks for data values). Reference to where details of data
53			management procedures can be found, if not in the protocol
54			
55			
56			
57			
58			
59			
60			

1	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	9
2				
3				
4				
5				
6	Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
7				
8				
9				
10	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)	N/A
11				
12				
13				
14				
15	Methods: Monitoring			
16				
17				
18	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	12
19				
20				
21				
22				
23				
24				
25				
26				
27	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	12
28				
29				
30				
31				
32				
33	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	11
34				
35				
36				
37				
38	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
39				
40				
41				
42				
43	Ethics and dissemination			
44				
45				
46				
47	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	3
48				
49				
50				
51	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)	2
52				
53				
54				
55				
56				
57				
58				
59				
60				

1	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
2				
3				
4	Consent or assent:	#26b	Additional consent provisions for collection and use of	N/A
5	ancillary studies		participant data and biological specimens in ancillary studies, if applicable	
6				
7				
8				
9				
10	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	9
11				
12				
13				
14				
15	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
16				
17				
18				
19	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	9
20				
21				
22				
23				
24	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
25				
26				
27				
28	Dissemination policy:	#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	10
29	trial results			
30				
31				
32				
33				
34				
35				
36	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
37	authorship			
38				
39				
40	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2
41	reproducible research			
42				
43				
44	Appendices			
45				
46	Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Uploaded
47				
48				
49				
50	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
51				
52				
53				
54				
55				

The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist was completed on 08. April 2020 using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)