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

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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
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Title Page

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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

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Infant, Preterm, Endotracheal Intubation, Nasal High Flow Therapy, Apnoeic Oxygenation

Abstract

Introduction

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

Methods and analysis

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

Ethics and dissemination

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

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

increasing operator experience. In a large international registry study of adverse events associated with endotracheal intubation, Foglia *et al.* demonstrated that overall first attempt intubation success was 49% for intubations in the neonatal intensive care unit (NICU) [11]. O'Donnell *et al.* reviewed 60 intubation attempts and reported success rates of 24% for residents (junior trainees), 78% for fellows (senior trainees) and 86% for consultants [12]. Furthermore, the duration of neonatal intubation attempts is often longer than the international guidelines recommend [13] and varies with the experience of the operator [12]. Neonates are often clinically unstable during endotracheal intubation, due to a lower functional residual capacity and greater metabolic demand than older children and adults [14]. In one study, severe hypoxaemia (defined as peripheral oxygen saturation [SpO_2] <60%) was reported in 44% of neonatal intubations, and bradycardia (heart rate <60 beats per minute [bpm] for at least 5 seconds) in 24% [15].

Transnasal Humidified Rapid Insufflation Ventilatory Exchange (THRIVE) is the use of nHF during apnoea for laryngoscopy and endotracheal intubation. Nasal HF provides heated, humidified air and oxygen via small nasal cannulae during a period of apnoea. There is evidence that nHF use during apnoea may improve both oxygenation and carbon dioxide clearance, compared with 'low flow' oxygen or jaw support only [16, 17]. Proposed mechanisms include removal of carbon dioxide through enhanced dead space washout and supraglottic flow changes due to cardiogenic oscillations [18, 19]. THRIVE has been shown to prolong the safe apnoeic time (time prior to desaturation) in adults [17] and in healthy infants and children undergoing general anaesthesia and elective intubation [20]. In a randomised controlled trial of THRIVE for apnoeic oxygenation during general anaesthesia of 48 children aged <10 years, THRIVE significantly prolonged the apnoea time (time prior to SpO_2 <92%) in all age groups [20]. All but one patient in the control group desaturated to <92% within the anticipated time frame, which was predefined as twice the length of previously published age-related values [21]. In contrast, the THRIVE group had no desaturations and a mean SpO_2 of 99.6% (range 97-100%).

There are currently no published studies of the use of THRIVE during neonatal intubation, nor in emergency settings in older patients with respiratory distress. The aim of the SHINE (Stabilisation with nasal High flow during Intubation of NEonates) randomised controlled trial is to investigate whether nHF during neonatal endotracheal intubation after (1) birth in the delivery room and (2) in the neonatal intensive care unit improves the likelihood of successful intubation on the first attempt without physiological instability of the infant.

Methods and analysis

Study design

A multicentre, unblinded, randomised controlled trial investigating the efficacy of nHF to improve success and stability during neonatal endotracheal intubation. Intubations performed in the delivery room or NICU will be randomised, with a 1:1 ratio. Infants will either receive nHF during the endotracheal intubation attempt, or standard care (no nHF). Intervention will be applied for the first intubation attempt of the episode only.

Sample size

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

Patient population

Any neonate undergoing endotracheal intubation in the delivery room or NICU is eligible for inclusion. In participating centres, all infants who undergo endotracheal intubation will be screened for study eligibility. Infants already studied can have subsequent intubation episodes randomised again if 1) the premedication randomisation stratum differs between intubations, or 2) there is at least one week between the studied intubations for intubations using premedications.

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

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

Standard care group (control)

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

Outcomes

Primary outcome

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

Definitions:

- Intubation attempt: the insertion of the laryngoscope blade beyond the infant's lips

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

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

Ethics and Dissemination

Prospective consent will be sought from a parent for inclusion of their infant in the study, whenever possible. Prospective consent will be obtained for all eligible intubation episodes through the course of the infant's stay in NICU, in the event that multiple intubations are required for the same patient. In the event of emergent intubation in the delivery room or within the first 24 hours after admission to NICU, it 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 in neonates, and the lack of any anticipated risk compared with standard clinical practice. Furthermore, it is not always practical to obtain prospective written consent from parents or guardians of infants undergoing intubation in the delivery room or the NICU, as they may require intubation quickly and unpredictably.

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 SpO_2 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

neonatal endotracheal intubation ***and*** maintaining cardiorespiratory stability during the attempt is important to minimise morbidity for all, but especially for preterm newborn infants. If effective and safe, nHF use during neonatal intubation can be rapidly translated into clinical practice as it is simple to use and readily generalisable to units with access to this equipment. Results from this study will be disseminated via peer-reviewed journals and presented at national and international scientific conferences.

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

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Competing Interests Statement: No competing interests.

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		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

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	6

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
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
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
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
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
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
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9

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
Methods: Monitoring			
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
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
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
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
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	3
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
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
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
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

BMJ Open

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

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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].

Corresponding author: Dr Kate Hodgson, Newborn Research Precinct, 7th Floor, 20 Flemington Rd Parkville VIC 3052 Australia, Kate.Hodgson@thewomens.org.au, +61 3 8345 2000

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:

Infant, Preterm, Endotracheal Intubation, Nasal High Flow Therapy, Apnoeic Oxygenation

Data sharing statement:

The protocol will be published and publicly available, and the deidentified individual patient datasets and statistical code will be available on reasonable request.

Abstract

Introduction

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

Methods and analysis

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

Ethics and dissemination

The SHINE trial received ethical approval from the Human Research Ethics Committees of The Royal Women's Hospital, Melbourne, Australia and Monash Health, Melbourne, Australia. The trial is currently recruiting in these two sites. The findings of this study will be disseminated via peer-reviewed journals and presented

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

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 increasing operator experience. In a large international registry study of adverse events associated with endotracheal intubation, Foglia *et al.* demonstrated that overall first attempt intubation success was 49% for intubations in the neonatal intensive care unit (NICU) [11]. O'Donnell *et al.* reviewed 60 intubation attempts and reported success rates of 24% for residents (junior trainees), 78% for fellows (senior trainees) and 86% for consultants [12]. Furthermore, the duration of neonatal intubation attempts is often longer than the international guidelines recommend [13] and varies with the experience of the operator [12]. Neonates are often clinically unstable during endotracheal intubation, due to a lower functional residual capacity and greater metabolic demand than older children and adults [14]. In one study, severe hypoxaemia (defined as peripheral oxygen saturation [SpO_2] <60%) was reported in 44% of neonatal intubations, and bradycardia (heart rate <60 beats per minute [bpm] for at least 5 seconds) in 24% [15].

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

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

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

THRIVE has been shown to prolong the safe apnoeic time (time prior to desaturation) in adults [17] and in healthy infants and children undergoing general anaesthesia and elective intubation [21]. Two randomised controlled trials have examined THRIVE in the paediatric population. Humphreys *et al.* randomised 48 children aged <10 years undergoing general anaesthesia to THRIVE (nHF at 2L/kg/min for patients up to 15kg), or to control (jaw support only). THRIVE significantly prolonged the apnoea time (time prior to SpO_2 <92%) in all age groups [21]. All but one patient in the control group desaturated to <92% within the anticipated time frame, which was predefined as twice the length of previously published age-related values [22]. In contrast, the THRIVE group had no desaturations and a mean SpO_2 of 99.6% (range 97-100%). Riva *et al.* randomised 60 patients aged 1-6 years undergoing general anaesthesia to receive one of three methods of apnoeic oxygenation: low flow oxygen (0.2L/kg/min FiO_2 1.0), THRIVE 100% (nHF at 2L/kg/min FiO_2 1.0) or THRIVE 30% (nHF at 2L/kg/min FiO_2 0.3). The primary outcome was apnoea time (time prior to SpO_2 <95%). Additional reasons for termination of the intervention were apnoea time of 10 minutes or hypercarbia (partial pressure of carbon dioxide > 65mmHg). Apnoea time was longer in low flow and THRIVE 100% groups, compared with the THRIVE 30% group. Whilst there was no statistically significant difference between the THRIVE 100% and the low flow groups, the reason for termination of apnoea was time or hypercarbia in all THRIVE 100% oxygen patients, not the primary outcome of apnoea time.

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

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

Methods and analysis

Study design

A multicentre, unblinded, randomised controlled trial investigating the efficacy of nHF to improve success and stability during neonatal endotracheal intubation. Intubations performed in the delivery room or NICU will be randomised, with a 1:1 ratio. Infants will either receive nHF during the endotracheal intubation attempt, or standard care (no nHF). Intervention will be applied for the first intubation attempt of the episode only.

Sample size

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

There is some variability in the reporting of success rates for neonatal intubation, depending on level of operator experience [12] and use of videolaryngoscopy [23]. The uncertainty surrounding the baseline rate of the primary outcome may present a limitation in this study.

Patient population

Any neonate undergoing endotracheal intubation in the delivery room or NICU is eligible for inclusion. In participating centres, all infants who undergo endotracheal intubation will be screened for study eligibility. Infants already studied can have subsequent intubation episodes randomised again if 1) the premedication

randomisation stratum differs between intubations, or 2) there is at least one week between the studied intubations for intubations using premedications.

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
- infant with suspected or proven COVID-19, or born to a mother with suspected or proven COVID-19

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 [24] randomisation tool.

Clinical management

Nasal HF group (intervention)

A trial investigator will perform the intervention. 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 occupy approximately 50% of the nares and enable leak. The investigator will apply the nHF prongs at the time of the face mask, nasal mask or nasal prongs being removed for laryngoscopy. Gas flow will be set to 8 Litres per minute (L/min) for the duration of the study intervention. The fraction of inspired oxygen (FiO_2) prior to the intubation attempt, including the use of any pre-oxygenation (an increase in FiO_2 prior to the intubation attempt), will be at the discretion of the clinical team. The trial investigator will set the nHF FiO_2 to the same amount the infant was receiving prior to laryngoscopy, and if the infant desaturates to <90% during the intubation attempt, the investigator will increase the nHF FiO_2 to 1.0 (100% supplemental oxygen) until the end of the intubation attempt. The nHF prongs will be secured only by tightening the cannula tubing behind the infant's head; no adhesive tapes will be applied to the face. Nasal HF will continue during laryngoscopy, and the investigator will remove the nHF prongs when the first intubation attempt is either ceased, or successfully completed (see definition below). The commencement, duration and termination of an intubation attempt will be at the discretion of the most senior clinician caring for the infant.

Standard care group (control)

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

Outcomes

Primary outcome

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

Definitions:

- Intubation attempt: the insertion of the laryngoscope blade beyond the infant's lips
- Intubation duration: the time from the insertion of the laryngoscope blade beyond the infant's lips until the removal of the laryngoscope blade from the infant's mouth
- Successful intubation: the completion of the intubation attempt with correct positioning of the endotracheal tube confirmed by detection of expired carbon dioxide on a colorimetric detector.
- Physiological instability: the incidence (any duration) of an absolute decrease in SpO_2 >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 SpO_2 >20% from baseline) *or* bradycardia (heart rate <100 bpm) during the first intubation attempt
3. Time to desaturation (absolute decrease in SpO_2 >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 SpO_2 >20% from baseline) during first intubation attempt in seconds
6. Duration of bradycardia (heart rate <100 bpm) during first intubation attempt in seconds
7. Median SpO_2 during intubation attempt
8. Median heart rate during intubation attempt
9. Duration of SpO_2 $\geq$97% during intubation attempt, in seconds
10. Number of intubation attempts
11. Duration of all intubation attempts (successful and unsuccessful), in seconds
12. Incidence of cardiac compressions and/or adrenaline administration within one hour after the first intubation attempt

13. Incidence of pneumothorax within 72 hours after randomisation, diagnosed either by transillumination of the chest and/or by chest X-ray
14. Incidence of pneumothorax requiring drainage (via needle thoracocentesis or insertion of an intercostal catheter) within 72 hours after randomisation
15. Death within 72 hours after randomisation

Data analysis plan

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

Ethics and Dissemination

Prospective consent will be sought from a parent for inclusion of their infant in the study, whenever possible. Prospective consent will be obtained for all eligible intubation episodes through the course of the infant's stay in NICU, in the event that multiple intubations are required for the same patient. In the event of emergent intubation in the delivery room or within the first 24 hours after admission to NICU, it 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

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

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 SpO_2 and heart rate data, with averaging time of 2 seconds and set at maximum sensitivity. The study investigator will record data on a Case Report Form and verify this against the video recording. Corrections will be made where errors are identified. The study investigator will also record the observed primary outcome in real time by, in case of video failure. An independent assessor will also review the video footage to verify the primary outcome. Any discrepancies or disagreements will be resolved by a third assessor from the trial steering committee. Additional consent will be obtained from the parent or guardian to use the video for the purposes of the study and for educational or research purposes. 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 neonatal endotracheal intubation ***and*** maintaining cardiorespiratory stability during the attempt is important to minimise morbidity for all, but especially for preterm newborn infants. If effective and safe, nHF use during neonatal intubation can be rapidly translated into clinical practice as it is simple to use and readily generalisable to units with access to this equipment. Results from this study will be disseminated via peer-reviewed journals and presented at national and international scientific conferences.

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

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Competing Interests Statement: No competing interests.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

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

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 SPIRITreporting 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

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6

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
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
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
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
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
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	7

		provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9

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
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
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
Methods: Monitoring			
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
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
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
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
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	3
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

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
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
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Uploaded
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