

STUDY PROTOCOL

Open Access



# A multicentre neonatal interventional randomised controlled trial of nebulized surfactant for preterm infants with respiratory distress: Neo-INSPIRe trial protocol

Ilse Lategan<sup>1</sup> , David Durand<sup>2</sup> , Michael Harrison<sup>1,3</sup> , Firdose Nakwa<sup>4,5</sup> , Lizelle Van Wyk<sup>6,7</sup> , Sithembiso Velaphi<sup>4,5</sup> , Alan Horn<sup>1,3</sup> , Gugu Kali<sup>6,7</sup> , Roger Soll<sup>8,9</sup> , Danielle Ehret<sup>8,9</sup> , Heather Zar<sup>1,10</sup> and Lloyd Tooke<sup>1,3\*</sup>

## Abstract

**Introduction** Respiratory distress syndrome in preterm infants is an important cause of morbidity and mortality. Less invasive methods of surfactant administration, along with the use of continuous positive airway pressure (CPAP), have improved outcomes of preterm infants. Aerosolized surfactant can be given without the need for airway instrumentation and may be employed in areas where these skills are scarce. Recent trials from high-resourced countries utilising aerosolized surfactant have had a low quality of evidence and varying outcomes.

**Methods and analysis** The Neo-INSPIRe trial is an unblinded, multicentre, randomised trial of a novel aerosolized surfactant drug/device combination. Inclusion criteria include preterm infants of 27–34<sup>+6</sup> weeks' gestational age who weigh 900–1999g and who require CPAP with a fraction of inspired oxygen (FiO<sub>2</sub>) of 0.25–0.35 in the first 2–24 h of age. Infants are randomised 1:1 to control (CPAP alone) or intervention (CPAP with aerosolized surfactant). The primary outcome is the need for intratracheal bolus surfactant instillation within 72 h of age. Secondary outcomes include the incidence of reaching failure criteria (persistent FiO<sub>2</sub> of > 0.40, severe apnoea or severe work of breathing), the need for and duration of ventilation and respiratory support, bronchopulmonary dysplasia and selected co-morbidities of prematurity. Assuming a 40% relative risk reduction to reduce the proportion of infants requiring intratracheal bolus surfactant from 45 to 27%, the study will aim to enrol 232 infants for the study to have a power of 80% to detect a significant difference with a type 1 error of 0.05.

**Ethics and dissemination** Ethical approval has been granted by the relevant human research ethics committees at University of Cape Town (HREC 681/2022), University of the Witwatersrand HREC (221112) and Stellenbosch University (M23/02/004).

**Trial registration** PACTR202307490670785

**Keywords** Surfactant, Aerosolized, Nebulized, Preterm, Neonatal, RDS

\*Correspondence:

Lloyd Tooke

Lloyd.tooke@uct.ac.za

Full list of author information is available at the end of the article



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

## Introduction

### Background and rationale

Respiratory Distress Syndrome (RDS) due to pulmonary surfactant deficiency is an important cause of morbidity and mortality in infants born prematurely [1]. Initial stabilization on continuous positive airway pressure (CPAP) together with early rescue surfactant administration has resulted in reduced rates of bronchopulmonary dysplasia (BPD) and death and has become the standard of care in high income countries [2]. Intratracheal bolus surfactant can be delivered by intubation followed by a period of mechanical ventilation (MV), or via the intubation – surfactant – extubation (INSURE) method which reduces the need for ongoing MV. Newer methods of administering surfactant via thin catheter such as less invasive surfactant administration (LISA) or minimally invasive surfactant therapy (MIST) can be employed for infants breathing spontaneously on CPAP and reduces the need for any positive pressure ventilation.

All methods of intratracheal bolus surfactant administration currently in clinical practice require laryngoscopy and instrumentation of the airway. These procedures require training, supervised practice, and skill. Changes in neonatal practice with the increased utility of non-invasive respiratory support for preterm infants has

resulted in limited opportunities for doctors to become proficient at neonatal intubation [3]. A large international registry study of more than 2600 neonatal intubations found that less than 50% of intubations were successful on the first attempt and that severe oxygen desaturations were common. Furthermore, an increased number of intubation attempts was associated with adverse events such as oesophageal or right main bronchus intubation, bradycardia, and traumatic injury [3]. This problem is further complicated in low resourced settings where access to standardised airway guidelines and key airway equipment is limited [4].

Aerosolized surfactant represents the least invasive method of surfactant delivery. This method facilitates surfactant administration to a spontaneously breathing infant on CPAP whilst limiting the potential complications associated with intratracheal bolus surfactant administration. Four recent trials using a variety of surfactant preparations and nebulising devices have endeavoured to compare early aerosolized surfactant plus CPAP to CPAP alone, with the primary outcome being the need for intratracheal bolus surfactant (Table 1). The results from these trials were varied; Dani et al. found no benefit whilst Jardine et al. reported a non-significant trend toward reduced rates of instilled surfactant [5, 6].

**Table 1** Recent trials on aerosolized surfactant

Study (Author/Year)	Gestational Age	Weight	Age at enrolment	Respiratory support method	Entry FiO <sub>2</sub> requirement or RSS	Findings
<b>Minocchieri [9]</b> Level III neonatal unit in Australia, 2019	29–33+6	1560 g (mean)	< 4 h	Bubble CPAP	FiO <sub>2</sub> 0.22–0.30	Early AS may reduce the need for intubation in the first 72 h of age for infants > 32 weeks
<b>Cummings [7]</b> Level III/IV neonatal units in USA, 2019	23–41	590–4800 g	> 1–< 12 h	Several NIV types	Initially FiO <sub>2</sub> 0.25–0.40, then removed	AS reduced the need for intubation and intratracheal bolus surfactant by 50%, particularly in infants > 31 weeks
<b>Jardine [6]</b> Level III neonatal units in Australia, 2021	26–30+6	1170 g (mean)	15 min—≤ 2 h	nCPAP	Part 1&2: FiO <sub>2</sub> < 0.30 Part 2 re-treat: RSS ≥ 2.0	Non-significant trend toward reduced rates of CPAP failure and need for intratracheal bolus surfactant in AS group
<b>Dani [5]</b> Level III neonatal units in Europe, 2022	28–32	1416 g (mean)	> 1–< 12 h	nCPAP	FiO <sub>2</sub> 0.25–0.40	AS did not reduce the need for intratracheal bolus surfactant administration in the first 72 h of age compared with CPAP alone
<b>Aerogen Pharma Phase IIb</b> Level III neonatal units in USA & Canada, 2020	26–31+6	≤ 2000 g	< 24 h	nCPAP or NIV	RSS 1.4–2.0	Trial underway (clinicaltrials.gov trial no: NCT03969992)

**Abbreviations:** g grams, h hours, min minutes, nCPAP nasal Continuous Positive Airway Pressure, NIV Non-invasive ventilation, FiO<sub>2</sub> Fraction of inspired Oxygen, RSS Respiratory Severity Score (MAP x FiO<sub>2</sub>), AS aerosolized surfactant

Cummings et al. conducted the largest study and reported a reduced need for intratracheal bolus surfactant by up to 50% in the aerosolized group, particularly in infants >31 weeks [7]. Despite the promising findings, there were methodological concerns raised as failure criteria were poorly defined [8]. Minocchieri et al. also showed a reduced need for intubation in the intervention group for infants >32 weeks but there were also methodological flaws [9]. A meta-analysis of 9 studies examining the efficacy of aerosolized surfactant to prevent early intubation revealed that overall, the quality of evidence was low due to bias [1]. All the studies, however, showed that aerosolized surfactant was safe and well tolerated [5–7, 9, 10].

Preterm infants with RDS born in many low- and middle-income countries (LMICs) have limited access to doctors who are trained and skilled in laryngoscopy and instillation of intratracheal bolus surfactant [11]. In these low resourced countries aerosolized surfactant may have particular relevance as it potentially reduces the severity of RDS and improves outcomes of preterm infants without the need for specialized training or technical skills [12].

### Trial design

This is a multicentre, phase 2, non-blinded, randomised controlled trial. Infants will be randomised in a 1:1 manner to either the intervention or control group, according to a balanced block design. This protocol is reported following the Standard Protocol Items: Recommendations for Interventional Trials guidelines (SPIRIT) [13]. See [Supplementary material](#) for SPIRIT checklist.

### Objectives

The primary objective is to determine if aerosolized surfactant given to preterm infants with RDS on nCPAP, compared with nCPAP alone, reduces the need for intratracheal bolus surfactant instillation in the first 72 h of age.

Secondary objectives are:

- To compare the need for repeat intratracheal bolus surfactant dosing between groups
- To compare the need for mechanical ventilation between groups
- To compare the duration of mechanical ventilation, CPAP, high flow nasal cannula (HFNC) and supplementary oxygen between groups
- To compare the rate of adverse events and select comorbidities of prematurity between groups (see Appendix for definitions, included as [Supplementary material](#))

- To compare the incidence of BPD between groups (see Appendix for definitions, included as [Supplementary material](#))
- To compare the incidence of death at any time between groups
- To compare the incidence of death or BPD between groups

## Methods

### Participants, interventions, and outcomes

#### Study setting

The study will enrol infants at three level 3 South African neonatal units that are each affiliated with an academic institution. An observational study was conducted in Cape Town to describe the respiratory support needs and outcomes of preterm infants admitted to these units, and to inform the use case for this interventional trial [14]. All preterm infants with RDS admitted to these units are preferentially managed with nCPAP and inborn infants  $\geq 900$  g have access to intratracheal bolus surfactant administration and invasive ventilation options.

#### Eligibility criteria

Inclusion criteria:

- Inborn
- Birth weight of 900–1999 g
- 27–34 weeks gestational age
- 2–24 h of age at time of randomisation
- Persistent fractional inspired oxygen ( $\text{FiO}_2$ ) of 0.25–0.35 on nCPAP at 5–7 cmH<sub>2</sub>O to maintain peripheral oxygen saturation of 90–95%.  $\text{FiO}_2$  requirement needs to be sustained for at least 15 min.

**Note:** *A best estimate of the gestational age in weeks and days will be recorded for all enrolled infants using the following hierarchy:*

1. Early (<20 weeks gestation) ultrasound
2. Postnatal assessment which will include Ballard score and foot length

Exclusion criteria:

- Administration of inotropes and/or intubation prior to enrolment in the delivery room or Neonatal Intensive Care Unit (NICU)
- 5-min Apgar score  $\leq 5$
- Prior instillation of intratracheal bolus surfactant
- Pneumothorax that requires needle thoracentesis or insertion of an intercostal chest drain
- Life-threatening congenital anomaly

- Known or suspected chromosomal abnormality
- Known or suspected congenital infection
- Enrolment in another interventional study with competing outcomes

## Interventions

### Investigational product

AeroFact™ (Aerogen Pharma) is an investigational drug/device combination product consisting of bovine-origin surfactant SF-RI 1 and a vibrating mesh nebulizer with a nasal interface. SF-RI 1 (Bovactant) is currently marketed under the name Alveofact™ (Lyomark Pharma GmbH). The AeroFact™ drug delivery system delivers fine droplets (2–3 μm) of aerosolized surfactant, synchronized with inspiration, to spontaneously breathing infants on nCPAP.

### Intervention group

See Fig. 1 for intervention group flow chart. Following randomisation to the intervention group, infants will receive one dose of aerosolized SF-RI 1 surfactant of 216 mg/kg per dose if they have a persistent  $\text{FiO}_2$  of 0.25–0.35 on nCPAP at 5–7 cmH<sub>2</sub>O to maintain peripheral oxygen saturation of 90–95%.  $\text{FiO}_2$  requirement needs to be sustained for at least 15 min.

Infants may receive one additional dose of aerosolized SF-RI 1 surfactant of 216 mg/kg per dose (for a total of two doses) if 30 min have elapsed since the end of the first dose and they have an ongoing and persistent  $\text{FiO}_2$  of 0.30–0.40 on nCPAP at 5–7 cmH<sub>2</sub>O to maintain peripheral oxygen saturation of 90–95%.

The Infants in the intervention group will be placed on a Fisher & Paykel (F&P™) Bubble CPAP system for the duration of aerosolization as a dual limb inspiratory and expiratory system is required for use with the AeroFact™ drug delivery circuit. The CPAP systems currently in use at the study sites are single limb CPAP systems. Infants will be left on the F&P™ Bubble CPAP system for 30 min following the end of the first AeroFact™ treatment, after which it will be determined if they meet re-dosing criteria to receive a second AeroFact™ treatment. If the infant meets re-dosing criteria, they will remain on a F&P™ Bubble CPAP system for the duration of the second AeroFact™ treatment. A new drug delivery circuit is required if the infant receives a second dose of aerosolized SF-RI 1, although the respiration sensor may remain in place. If an infant does not meet redosing criteria 30 min following completion of the first dose or following completion of the second dose of SF-RI 1, the drug delivery system and circuit and the respiration sensor will be removed from the infant's bedside and the

infant will be transitioned back to a standard flow driver CPAP device that is commonly used at the study site.

The CPAP strategy is the same during, between and after aerosolization. CPAP at 5–7 cmH<sub>2</sub>O is delivered to maintain peripheral oxygen saturation of 90–95%. CPAP and  $\text{FiO}_2$  will be weaned per study site unit protocol.

### Control group

See Fig. 2 for control group flow chart. Infants randomised to the control group will continue to receive nCPAP alone with the standard flow driver CPAP device that is commonly used at the study site. There is no placebo or sham aerosolization in the control group as this is impractical in a resource-constrained setting and would have additional ethical implications. They will be eligible to receive intratracheal bolus surfactant if they meet failure criteria (see below).

### Failure criteria

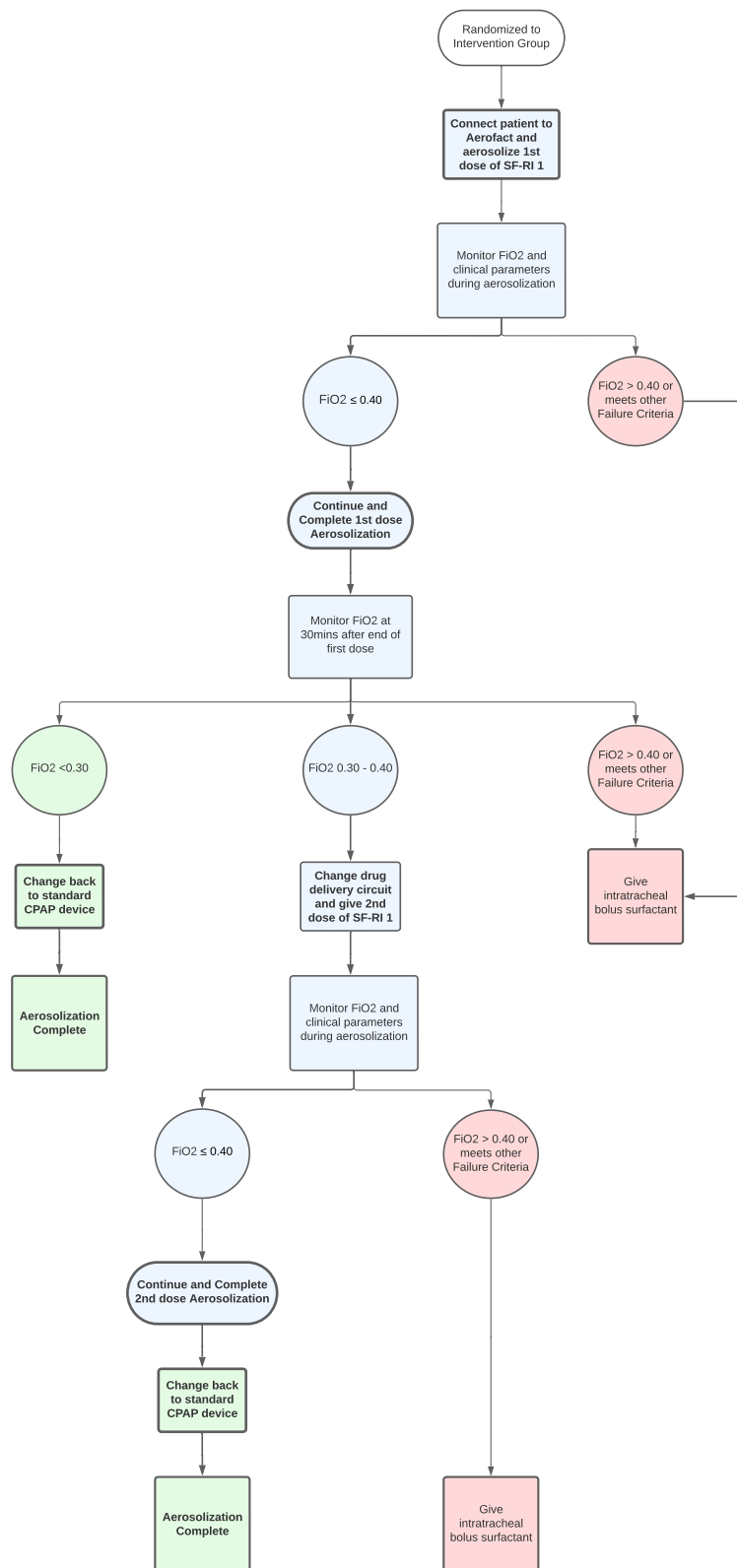
Infants in both the intervention and control groups will be eligible to receive intratracheal bolus surfactant instillation if they meet any of the following failure criteria at any time from randomisation to 72 h of age:

- A persistent  $\text{FiO}_2 > 0.40$  on nCPAP at 5–7 cmH<sub>2</sub>O to maintain peripheral oxygen saturation of 90–95%.  $\text{FiO}_2$  requirement needs to be sustained for at least 15 min, and/or
- Severe apnoeas defined as two or more apnoeas per hour requiring bag-mask ventilation, or at the treating clinician's discretion, and/or
- Severe increased work of breathing (at the treating clinician's discretion) not responding to nCPAP optimization, repositioning of infant or suctioning of secretions.

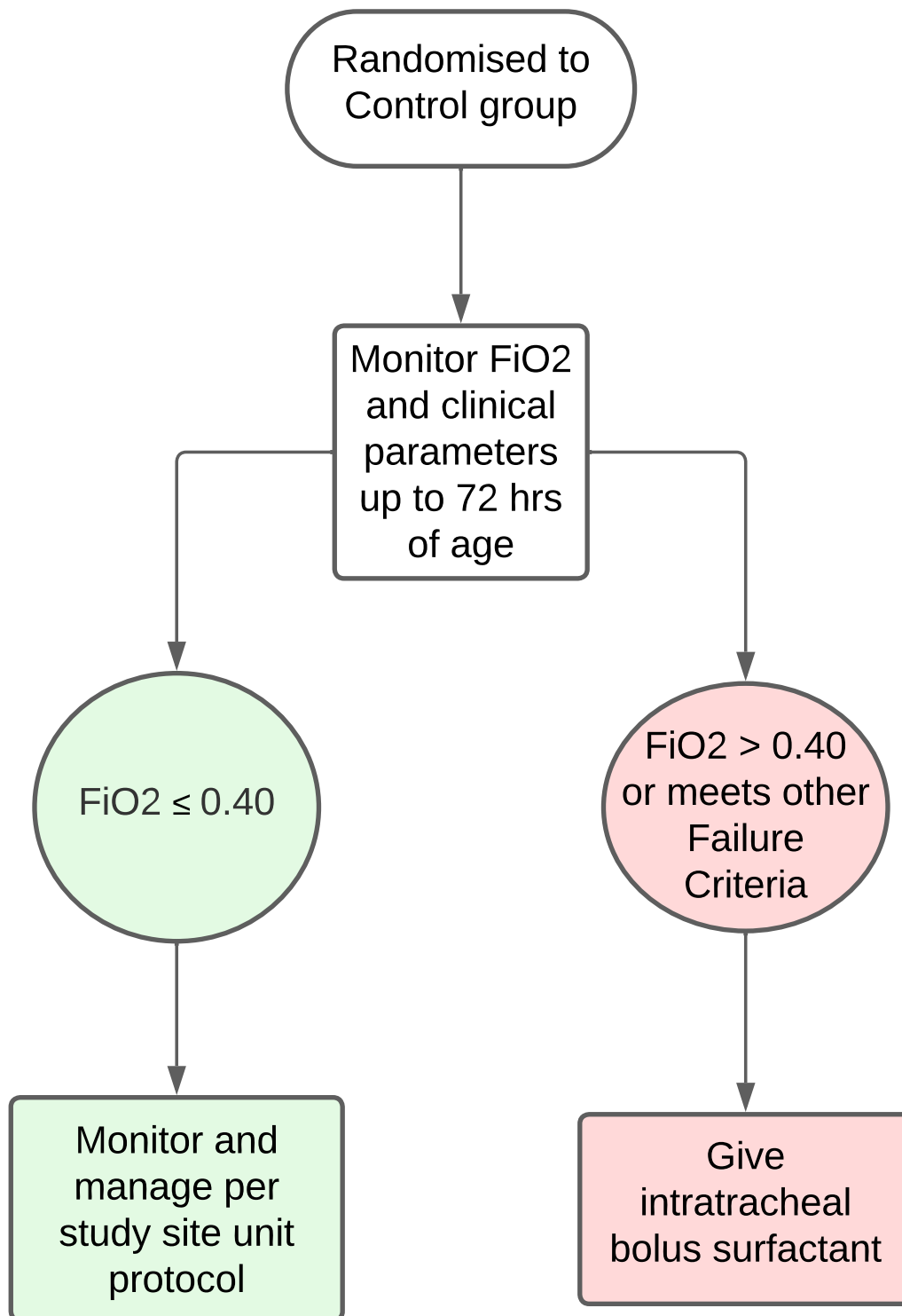
At each site, an  $\text{FiO}_2 > 0.40$  is consistent with the unit protocol to administer intratracheal bolus surfactant and aligns with the current South African standard of care. Beractant 100 mg/kg (Survanta) or Poractant Alfa 100 mg/kg (Curosurf) may be administered by LISA, INSURE or intubation for surfactant delivery followed by mechanical ventilation. The method of administration and the choice of surfactant used is at the discretion of the treating clinician.

### Concomitant therapy

At all sites, all infants < 32 weeks' gestation will receive a loading dose of caffeine on admission to the neonatal unit, and a maintenance dose as prophylaxis for apnoea of prematurity. Caffeine will be discontinued if infants have reached 34 weeks' gestation and have had no apnoeas for one week. Caffeine continuation beyond



**Fig. 1** Intervention and redosing flow chart



**Fig. 2** Control group flow chart

34 weeks' gestation is at the treating clinician's discretion and reasons for continuation must be appropriately documented. Only caffeine use will be standardised across all

three sites. All other concomitant therapies used in neonatal medicine are allowed and their use is indicated per study site protocol. These concomitant therapies do not

have to be standardised across sites but must be the same between intervention and control groups at each site.

### Outcomes

The primary outcome is the proportion of infants requiring intratracheal bolus surfactant administration in the first 72 h of age in each study group.

Secondary outcomes include:

- Proportion of infants meeting failure criteria in the first 72 h of age in each group
- Proportion of infants receiving multiple doses of intratracheal bolus surfactant in each group
- Number of hours on mechanical ventilation during hospital stay between groups
- Number of days on CPAP and/or HFNC, and supplementary oxygen during hospital stay between groups
- Incidence of adverse events and select comorbidities of prematurity between groups (see [Appendix](#) for definitions)
- Incidence of BPD in survivors at 36 weeks' postmenstrual age between groups (see [Appendix](#) for definitions)
- Incidence of BPD or death at 36 weeks' postmenstrual age between groups

### Participant timeline

See Fig. 3 for schedule of assessments. If an infant receives intratracheal bolus surfactant, the following information will be documented:

- Date, time, and age of administration
- Surfactant type, dosing details and method by which it was given (LISA, INSURE, etc.), and
- Respiratory status, including  $\text{FiO}_2$ , oxygen saturation and type of respiratory support, at the time of administration

If an infant meets failure criteria the age at which the infant met failure criteria will be documented.

Serial measurements of respiratory status will be collected at various timepoints from birth to discharge home or death and will include:

- Need for oral/nasal suctioning
- Respiratory status including type and level of support,  $\text{FiO}_2$  requirement and peripheral oxygen saturation

Additional data on the clinical course in hospital will be collected and include the following:

- The incidence of adverse events and selected comorbidities of prematurity (see [Appendix](#) for definitions)
- BPD status assessed at 36 weeks' postmenstrual age (see [Appendix](#) for definition)
- Discharge disposition

Infants who are transferred to another hospital will be followed up by study staff to ascertain their BPD status (if transferred prior to 36 weeks' postmenstrual age) and discharge disposition.

### Sample size

The proportion of infants who will require intratracheal bolus surfactant administration in the control group is estimated to be 45%. Assuming a 40% relative risk reduction to reduce the proportion of infants requiring intratracheal bolus surfactant to 27%, the study will aim to enrol approximately 220 infants (110 infants in each arm). To accommodate for a 5% dropout rate, we will aim to enrol approximately 232 infants (116 infants in each arm) for the study to have a power of 80% to detect a significant difference with a type 1 error of 0.05.

### Recruitment

See Fig. 4 for study enrolment flow chart. All potential study participants will be recruited by dedicated study staff in the NICU and/or high care area at each site. Non-study clinical staff may inform the study staff of potential study participants. Infants will be screened from 2 to 24 h of age to determine if they meet eligibility criteria.

The mother of an eligible infant will be approached by a study staff member to describe the nature of the study and the proposed benefits, and the potential risks associated with study participation. An opportunity to ask questions will be provided. Once all questions and concerns have been addressed by the study staff member, written informed consent will be obtained. See [supplementary material](#) for model informed consent form. A copy of the signed informed consent will be provided to the mother of the infant. Mothers who consent for their infants to take part in the study will be reimbursed for their time, inconvenience, and expenses as per the South African Health Products Regulatory Authority (SAHPRA) suggested compensation model.

### Assignment of interventions

#### Allocation

Randomisation will occur strictly at 2–24 h of age. A web-based system will randomise the eligible infant in a 1:1 manner to receive aerosolized surfactant while on nCPAP (intervention group) or continue on nCPAP alone (control group). The computer-generated, balanced-block randomisation sequence will be stratified by site and by

	Screening 2 – 24 h of age	≤ 4 h after randomisation	> 4 h to ≤ 24 h after randomisation	> 24 h after randomisation to 72 h of age	72 h of age to discharge / death	36 weeks PMA	Discharge / Death
Verify inclusion/exclusion Criteria	X						
Informed consent	X						
Randomisation	X						
Maternal/infant history including delivery and resuscitation details	X						
Weight, length, & head circumference	X				X		X <sup>0</sup>
Concomitant therapies	X	X	X	X	X	X	X
AeroFact™ dose/s (Intervention group only)		X	X	X <sup>1</sup>			
Intratracheal bolus surfactant administration (if needed)		X	X	X			
Respiratory status (oxygenation and respiratory support)	X	X <sup>2</sup>	X <sup>3</sup>	X <sup>4</sup>	X <sup>5</sup>	X <sup>6</sup>	X
Need for oral/nasal suctioning		X					
Incidence of AEs/SAEs including comorbidities of prematurity		X	X	X	X	X	X
Assess BPD status <sup>7</sup>						X <sup>6</sup>	
Disposition							X

**Fig. 3** Schedule of assessments. <sup>0</sup> Weight and head circumference only (excluding length). <sup>1</sup> AeroFact™ dose/s only up to 32 h of age. <sup>2</sup> Respiratory Status assessed every 30 min and other clinically relevant timepoints. <sup>3</sup> Respiratory Status assessed every hour and other clinically relevant timepoints. <sup>4</sup> Respiratory Status assessed every 3 h and other clinically relevant timepoint. <sup>5</sup> Respiratory Status assessed daily. <sup>6</sup> Respiratory Status assessed by telephone if transferred to another hospital prior to 36 weeks postmenstrual age. <sup>7</sup> See Appendix for definitions

weight band (900–1199 g and 1200–1999 g). If twins are enrolled, each infant will be randomised independently.

**Blinding**

The study staff, NICU staff and infant’s mother will not be blinded to the study group allocation. However, several aspects of the study protocol are designed to reduce bias, including:

- Objective failure criteria to be eligible for intratracheal bolus surfactant, based on FiO<sub>2</sub> requirements. These are collected as a secondary endpoint.

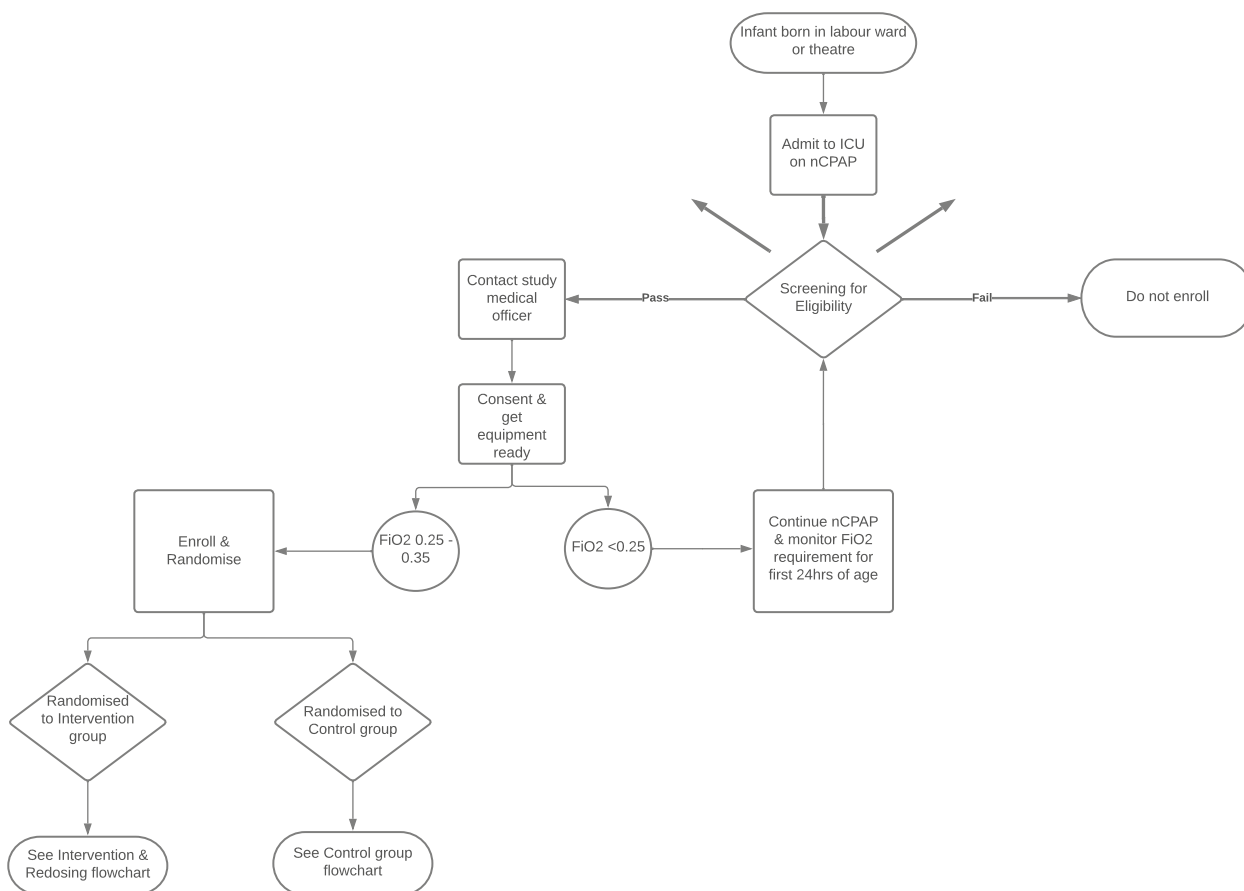
- Consistent policies for use of caffeine between groups at all sites
- Consistent peripheral oxygen saturation targets which drive duration of supplemental oxygen use between groups at all sites
- Consistent criteria for diagnosis of BPD at all sites

**Data collection, management, and analysis**

**Data collection methods**

Trained study staff will enter the information from the infant’s hospital record and source documentation as required by the protocol onto the electronic case report





**Fig. 4** Study enrolment flow chart

form (eCRF) in accordance with the eCRF completion guidelines. See [supplementary material](#) for complete CRE. An infant who is withdrawn from the study for safety or administrative reasons will immediately stop any aerosolization (if in the intervention group) and will have no further data collected for study purposes. However, the infant will remain in the study for data analyses and outcomes measurements, unless the mother specifically requests that their infant’s data not be included.

**Data management**

Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

**Statistical methods**

The primary analysis will be the Intention-to-Treat (ITT) population, defined as all randomised infants, regardless of their adherence with the entry criteria, treatment they received or subsequent withdrawal from treatment, or deviation from the protocol. The Per-Protocol (PP) population is defined as all randomised infants who were not

associated with any major protocol violations. The Safety Population will include all subjects who are randomised and started their allocated treatment.

All study data collected onto the eCRF will be exported for statistical analyses. Continuous variables will be summarized by treatment group and overall using descriptive statistics (n, mean, standard deviation, median, interquartile range, minimum and maximum). Frequencies and percentages will be presented by study group and overall, for categorical variables. All inferential statistical analysis will be based on a two-sided test with a type I error of 0.05. The efficacy analyses of the primary and secondary efficacy endpoints will be conducted on the ITT population. The PP population analyses of primary and secondary endpoints will be considered supportive.

**Data monitoring**

Each site will receive rigorous in-person monitoring of protocol compliance and study data by a clinical research associate (CRA) from OnQ Research, a clinical research organisation. CRAs will periodically visit each investigational site to review the eCRFs for completeness and

accuracy against the source documents. CRAs will highlight any discrepancies found in the documentation of study processes and ensure that appropriate site personnel address the discrepancies. CRAs will also perform investigational product (IP) accountability during the study and prior to study close-out.

### Harms

Safety will be assessed by comparison of the rate of adverse events (AE) between the intervention and control groups. AEs for this study include select co-morbidities of prematurity (see [supplementary material](#)) or any untoward medical occurrence deemed significant by the site principal investigator (PI). An AE does not necessarily have to have a causal relationship with the IP. The PI will be asked to determine the causal relationship of each AE to the investigational drug/device. All AEs will be coded using the Medical Dictionary for Regulatory Affairs and SAEs will be summarized by treatment group, severity, and relationship to study treatment.

An independent Data Safety and Monitoring Board (DSMB) will consist of at least three neonatologists and one statistician who are not investigators in the study nor otherwise associated with the study. The DSMB will periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and make recommendations concerning the continuation, modification, or termination of the trial for safety purposes. The DSMB will establish its own charter, procedures, and criteria for recommendations regarding safety.

### Audit

The database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be documented and returned to the study site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail.

### Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12887-023-04296-4>.

**Additional file 1.** SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents.

**Additional file 2: Appendix A.** Definitions. **Appendix B.** Bacterial pathogens.

**Additional file 3.** Informed Consent Form.

**Additional file 4.** Case Report Form.

### Acknowledgements

Thanks, and appreciation go to:

i) The Aerogen Pharma team, in particular: Jeanette Asselin, Hee-Byung Choe, Andy Clark, Judy Doto, Plamena Entcheva-Dimitrov, Jim Fink, Amanda Redeker and Colin Tefler.

ii) The Bill and Melinda Gates Foundation in particular: Cicely Fadel, Maureen Halligan, and Farhad Imam.

### Patient and public involvement statement

Patients and their families were not directly involved in the planning of this study. However, a recent statement released by the World Health Organization calls for the development, testing and optimization of aerosolized surfactant therapy in infants with RDS born in LMICs [15]. This target product profile has been posted to the public for their comments and insights.

### Authors' contributions

Drs Lategan, Tooke and Zar were involved in the conception and design of the work, the analysis of data and the drafting and revising of the work. Drs Durand, Ehret, Harrison, Horn, Kali, Nakwa, Soll, Van Wyk and Velaphi were involved in the design of the work, the analysis of data, and the drafting and revising of the work. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

### Funding

The funding for development of the protocol was provided by the Bill & Melinda Gates Foundation (INV-026401 & INV-039901). The trial is sponsored by Aerogen Pharma Ltd (16605 Amphlett Boulevard, Suite 360, San Mateo, CA 94402, USA), who have secured a grant from the Bill & Melinda Gates Foundation to sponsor the study.

### Declarations

#### Ethics approval and consent to participate

The sponsor and PIs have obtained approval from the relevant regulatory authorities including SAHPRA (Ref 20221016), University of Cape Town HREC (681/2022), University of the Witwatersrand HREC (insert) and Stellenbosch University (M23/02/004). All major and minor protocol amendments will be submitted to SAHPRA and university ethics committees for approval. Consent to enter the study will be sought from each infant's mother only after a full explanation has been given, and time allowed for consideration. The PIs will preserve the confidentiality of participants taking part in the study as guided by South Africa's data protection law, the Protection of Personal Information (POPI) Act 4 of 2013 and will retain all study records and reports for 10 years following completion of the study. Both the sponsor and the PIs will have access to the final trial anonymised dataset for publication. All authors will meet the ICMJE criteria for authorship and no professional writers will be used. The full protocol will be available online for public access. Any relevant data and results may be published or publicly presented by the investigators.

Post-trial access is not applicable for the following reasons:

- Surfactant is only effective in the first few days of life, thus there will be no long-term treatment requirements.
- Aerosolized surfactant is not currently a standard of care anywhere in the world, and should it not be available post-trial, other forms of surfactant delivery (bolus intratracheal surfactant which is the current standard of care) would still be available.
- Should the intervention of aerosolized surfactant prove beneficial in our setting (proof of concept), then this study would be the first step in the development of a cheaper, more accessible drug-device combination for infants in LMICs.

#### Competing interests

Dr Durand is the chief medical officer at Aerogen Pharma but his contributions to the protocol were of an advisory nature.

#### Author details

<sup>1</sup>Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa. <sup>2</sup>Aerogen Pharma, San Mateo, CA, USA. <sup>3</sup>Groote Schuur Hospital Neonatal Unit, Neonatal Department, Groote Schuur Hospital, Old Main Building, Cape Town, South Africa. <sup>4</sup>Department of Paediatrics and Child Health, University of the Witwatersrand, Johannesburg, South Africa. <sup>5</sup>Chris Hani Baragwanath Hospital Neonatal Unit, Johannesburg, South Africa. <sup>6</sup>Department of Paediatrics and Child Health, Stellenbosch University, Cape

Town, South Africa. <sup>7</sup>Tygerberg Hospital Neonatal Unit, Cape Town, South Africa. <sup>8</sup>Vermont Oxford Network, Burlington, VT, USA. <sup>9</sup>University of Vermont Larner College of Medicine, Pediatrics, Burlington, VT, USA. <sup>10</sup>Unit on Child and Adolescent Health, South African Medical Research Council, Cape Town, South Africa.

Received: 1 August 2023 Accepted: 7 September 2023

Published online: 19 September 2023

## References

1. Bohlin K. RDS–CPAP or surfactant or both. *Acta Paediatr.* 2012;101:24–8.
2. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Te Pas A, et al. European consensus guidelines on the management of respiratory distress syndrome–2019 update. *Neonatology.* 2019;115(4):432–50.
3. Foglia EE, Ades A, Sawyer T, Glass KM, Singh N, Jung P, et al. Neonatal intubation practice and outcomes: an international registry study. *Pediatrics.* 2019;143(1):e20180902.
4. Armstrong L, Harding F, Critchley J, McNarry AF, Myatra SN, Cooper R, et al. An international survey of airway management education in 61 countries. *Br J Anaesth.* 2020;125(1):e54–60.
5. Dani C, Talosi G, Piccinno A, Ginocchio VM, Balla G, Lavizzari A, et al. A randomized, controlled trial to investigate the efficacy of nebulized poractant alfa in premature babies with respiratory distress syndrome. *J Pediatr.* 2022;246:40–47.e5.
6. Jardine L, Lui K, Liley HG, Schindler T, Fink J, Asselin J, et al. Trial of aerosolised surfactant for preterm infants with respiratory distress syndrome. *Arch Dis Child Fetal Neonatal Ed.* 2022;107(1):51–5.
7. Cummings JJ, Gerday E, Minton S, Katheria A, Albert G, Flores-Torres J, et al. Aerosolized calfactant for newborns with respiratory distress: a randomized trial. *Pediatrics.* 2020;146(5):e20193967.
8. Glaser K, Wright CJ. Aerosolized calfactant in infants with RDS: surfactant replacement 2.0? *Pediatrics.* 2020;146(5):e2020021576.
9. Minocchieri S, Berry CA, Pillow JJ. Nebulised surfactant to reduce severity of respiratory distress: a blinded, parallel, randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed.* 2019;104(3):F313–9.
10. Gaertner VD, Thomann J, Bassler D, Rügger CM. Surfactant nebulization to prevent intubation in preterm infants: a systematic review and meta-analysis. *Pediatrics.* 2021;148(5):e2021052504.
11. Tooke L, Ehret DE, Okolo A, Dlamini-Nqeketo S, Joolay Y, Minto'o S, et al. Limited resources restrict the provision of adequate neonatal respiratory care in the countries of Africa. *Acta Paediatr.* 2022;111(2):275–83.
12. Pillow JJ, Minocchieri S. Innovation in surfactant therapy II: surfactant administration by aerosolization. *Neonatology.* 2012;101(4):337–44.
13. Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200–7.
14. Lategan I, Price C, Rhoda NR, Zar HJ, Tooke L. Respiratory interventions for preterm infants in LMICs: a prospective study from Cape Town, South Africa. *Front Glob Women's Health.* 2022;3:817817.
15. WHO. Target product profile for aerosolized surfactant therapy in neonates with respiratory distress syndrome in low- and middle-income countries. <https://www.who.int/publications/i/item/9789240067851>. Accessed 15 June 2023.

## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more [biomedcentral.com/submissions](https://biomedcentral.com/submissions)

