BMJ Open

Study protocol for the POPART study – Prophylactic Oropharyngeal surfactant for Preterm infants: A Randomised Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035994
Article Type:	Protocol
Date Submitted by the Author:	25-Nov-2019
Complete List of Authors:	murphy, madeleine; National Maternity Hospital, Neonatology; National Children's Research Centre, National Children's Research Centre, Our Lady's Children's Hospital Galligan, Marie; University College Dublin School of Medicine and Medical Science, School of Medicine Molloy, Brenda; University College Dublin School of Medicine and Medical Science, School of Medicine Hussain, Rabia; University College Dublin School of Medicine and Medical Science, School of Medicine Doran, Peter; University College Dublin School of Medicine and Medical Science, School of Medicine ODonnell, Colm; The National Maternity Hospital, Dublin, Ireland, Neonatal Intensive Care Unit
Keywords:	NEONATOLOGY, PAEDIATRICS, PERINATOLOGY

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

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

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

Study protocol for the POPART study – Prophylactic Oropharyngeal surfactant for Preterm infants: A Randomised Trial

Madeleine C. Murphy,[1-3] Marie Galligan,[3] Brenda Molloy,[3] Rabia Hussain,[3] Peter Doran,[3] Colm P.F. O'Donnell[1-3]

1. National Maternity Hospital, Dublin, Ireland
2. National Children's Research Centre, Dublin, Ireland
3. School of Medicine, University College Dublin, Ireland

Word count 3972 Abstract 299 Figures/Tables 4 References 45

Trial registration

Protocol identification (code or reference number): UCDCRC/16/003

EudraCT number: 2016-004198-41

Protocol version 2.0, dated 19.07.19

Trial sponsor

University College Dublin

Corresponding Author

Address Prof. Colm O'Donnell, Department of Neonatology, National Maternity Hospital, Holles Street, Dublin 2, Ireland

Tel +353 1 6373100

Email codonnell@nmh.ie

Key words: Infant, newborn; oropharyngeal surfactant; respiratory distress syndrome; intubation; randomised controlled trial

Author Contributions: COD conceived and designed the trial protocol, co-wrote the first draft and revised the manuscript for intellectual content. MCM helped design the trial protocol, co-wrote the first draft and revised the manuscript for intellectual content. MG, BM, RH, and PD helped design the trial protocol and revised the manuscript for intellectual content. MG designed the statistical analysis plan. All authors approved the final manuscript prior to submission.

Funding:

Chiesi Farmaceutici, manufacturers of poractant alpha (Curosurf), supply the study drug free of charge; they had no role in study design; have no role in study conduct; and will have no role in data collection, analysis or interpretation. Further, they will have no role in the decision to present, publish or otherwise report results.

Madeleine Murphy is the recipient of a Clinical Research Fellowship by the National Children's Research Centre, Dublin (R17637)

Pediatric Clinical Research Infrastructure Network (PedCRIN), a Project of the European Union Horizon 2020 programme designed to support the extension of clinical drug trials in children throughout Europe, also support the study.

Competing interests: Chiesi Farmaceutici, manufacturers of poractant alpha (Curosurf), supply the study drug free of charge; they had no role in study design; have no role in study conduct; and will have no role in data collection, analysis or interpretation. Further, they will have no role in the decision to present, publish or otherwise report results.

Ethics approval: Research Ethics Committee, The National Maternity Hospital, Dublin, Ireland

Acknowledgements: We would like to acknowledge the administrative staff at UCD for their advice, and support with the trial thus far. We wish to thank the members of PedCRIN and the Principal Investigators and members of the Clinical Trials Units at all our European sites for facilitating extension of our trial to Europe. POPART Trial Investigators: Jan Miletin, Coombe Women and Infants University Hospital, Dublin, Ireland; Claus Klingenberg, University Northern Norway, Tromsø, Norway; Hans Jørgen Guthe, Haukeland University Hospital, Bergen, Norway; Richard Plavka, Charles University, Prague, Czech Republic; Tomas Juren, University Hospital Brno, Brno, Czech Republic; Vincent Rigo, Le Centre Hospitalier Universitaire, Liege, Belgium; Kajsa Bohlin, Karolinska Institutet, Stockholm, Sweden; and Almerinda Pereira, Hospital de Braga, Braga, Portugal.

Data statement: Members of the Trial Steering Committee will have access to the final dataset. Data will be available on request.

Abstract

Introduction: Many preterm infants develop respiratory distress syndrome (RDS), a condition characterised by a relative lack of surfactant. Endotracheal surfactant therapy revolutionised the care of preterm infants in the 1990s. However, supporting newborns with RDS with continuous positive airway pressure (CPAP) and reserving endotracheal surfactant for those who develop respiratory failure despite CPAP yields better results than intubating all infants for surfactant. Half of preterm infants initially managed with CPAP are intubated for surfactant. Intubation is difficult to learn and associated with adverse effects. Surfactant administration into the oropharynx has been reported in preterm animals and humans and may be effective. We wished to determine whether giving oropharyngeal surfactant at birth reduces the rate of endotracheal intubation for respiratory failure in preterm infants within 120 hours of birth.

Methods and analysis: POPART (Prophylactic Oropharyngeal surfactant for Preterm infants: A Randomised Trial) is an investigator-led, unblinded, multicentre, randomised, parallel group, controlled trial. Infants are eligible if born at a participating centre before 29 weeks gestational age and there is a plan to offer intensive care. Infants are excluded if they have major congenital anomalies. Infants are randomised to treatment with oropharyngeal surfactant in addition to CPAP or CPAP alone at birth. The primary outcome is intubation within 120 hours of birth, for bradycardia and/or apnoea despite respiratory support in the delivery room or respiratory failure in the intensive care unit. Secondary outcomes include incidence of mechanical ventilation, endotracheal surfactant use, chronic lung disease, and death before hospital discharge.

Ethics and dissemination: Approval for the study has been granted by the Research Ethics Committees at the National Maternity Hospital, Dublin, Ireland (EC31.2016), and at each

participating site. The trial is being conducted at 9 centres in 6 European countries. The study results will be submitted for publication in a peer-reviewed journal.

Article summary

Strengths and limitations of this study

- This is the first randomised study to examine the efficacy of giving oropharyngeal surfactant at birth to preterm infants at high risk of developing respiratory distress syndrome.
- Oropharyngeal administration is less invasive and easier to perform than endotracheal administration and avoids the short- and longer-term adverse effects of intubation.
- The study will determine whether prophylactic oropharyngeal surfactant reduces the rate of endotracheal intubation for respiratory failure within 120 hours of birth among infants born before 29 weeks of gestation.
- The multicentre nature of this study will increase the generalisability of its findings.
- We were unable to credibly mask the intervention.

Background

All newly-born infants have fluid-filled lungs. Within a short time after birth, they must stop producing this liquid, clear it from their lungs, and replace it with air. Respiratory distress syndrome (RDS) is a lung condition characterised by difficulty in recruiting and maintaining an adequate volume of gas in the lungs. It manifests with increasing signs of respiratory distress and evidence of respiratory failure in newborns at or shortly after birth. The risk of RDS is inversely related to gestational age (GA). Infants with RDS have structural and functional immaturity of their lungs. They also have a relative lack of surfactant,[1] an endogenously produced substance that enables alveoli to expand more easily to recruit and maintain gas within the lung.

Exogenous surfactant[2 3] is frequently used to treat newborns with RDS and has led to improved outcomes for infants worldwide. Randomised controlled trials (RCTs) in the 1980s – 1990s[4-7] demonstrated that surfactant, given by endotracheal tube (ETT), reduced mortality and air leak among premature infants who were intubated for respiratory failure due to RDS. This led to the widespread practice of intubating all extremely preterm infants for surfactant and ventilation ("prophylactic surfactant").[5] Prior to the introduction of surfactant into clinical practice, concerns were raised that premature infants who were intubated for respiratory support had worse respiratory outcomes than infants who were managed with the non-invasive respiratory support, nasal continuous positive airway pressure (CPAP).[8] These concerns persisted after the widespread introduction of surfactant.[9] Multicentre RCTs found that starting infants on CPAP may be beneficial when compared with intubation and positive pressure ventilation (PPV); the studies reported decreased duration of mechanical ventilation with potential benefits of reduction of death and or bronchopulmonary dysplasia (BPD).[10-12] Managing premature newborns initially with CPAP and reserving intubation, mechanical ventilation and surfactant for those infants with worsening respiratory failure despite CPAP yields better results than intubating all infants for surfactant

administration.[13] About half of premature infants initially managed with CPAP for RDS are ultimately intubated for surfactant and ventilation.[14]

Intubation is a procedure that is difficult to learn and is associated with adverse effects, both short[15-19] and longer-term.[20-22] This has led many clinicians to investigate alternative methods of surfactant delivery.[23] Giving nebulised surfactant to spontaneously breathing infants has met with limited success.[24-27] Progress has been slow due to the technical difficulties encountered in aerosolising such large molecules, the expense of the equipment needed to do so and the cost of the large amount of surfactant needed to form an aerosol. Interest has largely focussed on less-invasive methods of surfactant administration. The "minimally invasive" techniques have involved introducing either a feeding tube or vascular catheter into the trachea of a spontaneously breathing infant under direct vision with a laryngoscope.[28-31] These techniques may reduce the need for mechanical ventilation among preterm infants. However, they appear more difficult than intubation and the many short-term adverse effects of intubation that are due to laryngoscopy are not avoided. The laryngeal mask airway, a supraglottic airway device, may be used as an interface to deliver surfactant.[32-35] However there is currently no device available for use in very low birth weight infants, who constitute the majority of infants diagnosed with RDS.

Direct administration of surfactant into the pharynx of human infants has been described in randomised[7] and prospective cohort studies.[36 37] It is apparently effective and is an easier technique to perform than endotracheal intubation or passing a feeding tube or vascular catheter into the trachea. Advantages of pharyngeal surfactant use are that it is an easy and cheaper method of administering surfactant and likely causes less discomfort to infants as it avoids the use of a laryngoscope. Giving surfactant early, prior to ventilation, delivers surfactant to a fluid-filled lung, which is spread via a fluid-air interface when the infant starts breathing. Animal studies report that surfactant is distributed more uniformly,[38] and lung function and compliance is better[39] if surfactant

is delivered prior to ventilation. If shown to be effective, it may reduce the adverse effects, and additional associated costs, of ventilation.

A Cochrane review of pharyngeal surfactant[40] did not identify any eligible trials to assess whether pharyngeal installation of surfactant before the first breath prevented morbidity and mortality in infants at risk of RDS. Large well conducted RCTs are needed, due to the evidence from animal[41 42] and observational human studies[36 37] suggesting that pharyngeal surfactant administration is potentially safe, feasible, and may be effective.

Objective

We will perform a study to establish whether giving preterm infants surfactant into their oropharynx at birth in addition to CPAP compared with CPAP alone reduces their need for subsequent intubation in the first 5 days of life.

Methods

Trial design

The POPART trial is an investigator-led, unblinded, multicentre, randomised parallel-group controlled trial. It aims to determine whether administering oropharyngeal surfactant to premature infants at birth in addition to CPAP compared to CPAP alone reduces the rate of intubation for respiratory failure in the first 5 days of life. The trial will recruit 250 infants born <29 weeks GA at participating centres. A schedule of events is seen in figure 1.

Setting

The trial is being conducted at 9 neonatal intensive care units (NICUs) in 6 European countries [Ireland (National Maternity Hospital (NMH), Dublin; Coombe Women and Infants University Hospital (CWIUH) Dublin); Norway (University Northern Norway, Tromsø; Haukeland University Hospital, Bergen); Czech Republic (Charles University, Prague; University Hospital Brno, Brno), Belgium (Le Centre Hospitalier Universitaire (CHU), Liege); Sweden (Karolinska Institutet, Stockholm); and Portugal (Hospital de Braga, Braga). All data collected pertaining to the primary and secondary outcomes will be collected as part of the infants' hospital course.

Participants

Inclusion and exclusion criteria

Trial subjects will be premature infants at risk of RDS. Infants born less than 29 weeks GA will be included if the treating physician plans to offer intensive care. Infants will be excluded if they have major congenital anomalies (including neural tube defects, major structural cardiac anomalies (excluding patent ductus arteriosus, ventricular septal defect, atrioventricular septal defect), abdominal wall defects, congenital diaphragmatic hernia and major dysmorphic features with an abnormal karyotype) and if the treating physician does not plan to offer intensive care. Written informed consent from parent/legal guardian(s) will be obtained before delivery. Infants of multiple gestation and of either sex are eligible to be enrolled.

Outcome measures

Primary outcome

The primary outcome is the incidence of endotracheal intubation for respiratory failure within 120 hours of birth. Enrolled infants will be intubated for persistent apnoea and/or bradycardia (HR <100bpm) in the delivery room (DR), or for respiratory failure in the NICU defined as ≥ 2 of:

- Clinical signs – worsening tachypnoea; grunting; subcostal, intercostal and/or sternal recession
- Acidosis – pH < 7.2 on 2 blood gases (arterial or capillary) ≥ 30 minutes apart
- Hypoxaemia – FiO_2 > 0.4 to keep oxygen saturation (SpO_2) ≥ 90% for > 30 minutes
- Hypercarbia – PCO_2 > 9.0 kPa on 2 blood gases (arterial or capillary) ≥ 30 minutes apart
- Apnoea – recurrent apnoea treated with mask ventilation

Secondary outcomes

The secondary outcomes are as follows:

1. Intubation in the DR
2. Number of attempts taken to successfully intubate in the DR
3. Chest compressions in the DR
4. Adrenaline administration in the DR
5. Rectal temperature on admission to the NICU
6. NICU intubation
7. Surfactant use before death or hospital discharge
    a. Number of doses, including total dose
    b. Intra-tracheal surfactant received post-intervention
    c. Doses of post-intervention surfactant
8. Respiratory distress syndrome
    a. Clinical evidence and radiological evidence of respiratory distress
9. Incidence of pneumothorax
    a. Incidence of pneumothorax on chest x-ray

10. Incidence of pulmonary haemorrhage
    a. Clinical evidence of pulmonary haemorrhage
11. Mechanical ventilation
12. Days of mechanical ventilation
13. Use of postnatal corticosteroids for ventilator dependence
14. Days of duration of respiratory support (endotracheal ventilation, high-frequency oscillatory ventilation, CPAP, heated humidified high-flow nasal cannula O_2, low flow nasal cannula O_2)
15. BPD – supplemental O_2 at 28 days of life
16. Chronic lung disease of prematurity (CLD) – need for supplemental O_2 at 36 weeks corrected GA determined by physiological oxygen reduction test
17. Medical treatment for a patent ductus arteriosus (PDA)
    a. Administration of ibuprofen or paracetemol for PDA
18. Surgical treatment for a PDA
19. Proven necrotising enterocolitis (≥ Bell's stage 2)
20. Incidence of Intraventricular haemorrhage (IVH) (any and severe: IVH grade ≥ 3)
    a. Evidence on surveillance cranial ultrasounds performed as standard of care
21. Incidence of cystic periventricular leukomalacia
    a. Evidence on surveillance cranial ultrasounds performed as standard of care
22. Retinopathy of prematurity treated with laser photocoagulation or intravitreal injections
    a. Evidence on surveillance ophthalmology review performed as standard of care
23. Death before hospital discharge
24. Survival without BPD at hospital discharge
25. Survival without CLD at hospital discharge
26. Duration of hospitalisation
27. Use of home oxygen therapy
    a. Discharged home on oxygen therapy

Intervention arm: Oropharyngeal surfactant

Infants randomised to oropharyngeal surfactant will receive a dose of surfactant (Curosurf, Chiesi Farmaceutici, Parma, Italy) immediately after birth, ideally before the cord is clamped e.g. 60 seconds. If it is given after the cord is clamped, it will be given once the infant is placed on the resuscitaire. It will be given within 5 minutes of birth in all cases.

The surfactant will be warmed prior to being drawn up in a sterile syringe as per manufacturer's recommendation. This will be done by opening the mouth gently and administering the surfactant as a single bolus into the oropharynx using surfactant tubing attached to the syringe.

Infants will not be weighed prior to enrolment. The 50th centile for birth weight (BW) for boys and girls according to GA is shown in table 1. In our study, infants < 26 weeks will receive a full 120mg vial of Curosurf. We estimate that this will provide dosing in the range as indicated in table 2. In our study, infants 26 – 28 weeks will receive a full 240mg vial of Curosurf, and we estimate that this will provide dosing in the range as indicated in table 3.

Control group: CPAP

Infants randomised to the control group will not have anything injected into their oropharynx and will be stabilised on CPAP in the DR as per routine practice.

Clinical management

After the initial intervention, infants will then receive standard care with CPAP, regardless of their group assignment. DR care will be carried out by the neonatal team who will be trained in neonatal resuscitation as per the recommendations of the International Liaison Committee on Resuscitation (ILCOR). Infants in both groups will be intubated in the DR for persistent apnoea and/or bradycardia despite PPV by mask as per ILCOR recommendations. Infants will not be intubated in the DR solely for surfactant administration. Further surfactant administration and all other aspects of neonatal intensive care will be at the discretion of the treating physicians. Infants in both groups will be treated equally; they will be closely watched to see if they need extra treatment for their RDS at any stage, including surfactant given endotracheally. The frequency of blood gas monitoring is based on the decision of the treating physician. Enrolled infants will be intubated if they reach the pre-determined criteria for respiratory failure. After giving endotracheal surfactant for the treatment of RDS, attending clinicians may attempt to extubate the babies immediately or they may elect to ventilate the babies for a longer period at their discretion.

Investigational medicinal product

Poractant alpha (Curosurf, Chiesi Farmaceutici, Parma, Italy) is a natural surfactant prepared from porcine lungs. It is licensed for ET use for the prevention and treatment of RDS in preterm infants. The dosing recommendations for treatment with Curosurf when given by ETT are 200mg/kg for established RDS and 100 – 200mg/kg for prophylaxis. Further doses of 100mg/kg Curosurf may be given to infants who have persistent respiratory distress despite treatment with surfactant (maximum recommended dose 400mg/kg). It is currently not licensed for oropharyngeal administration, and therefore this study will examine the off-label use of a licensed product. The timing or dosage of ET surfactant will not be affected by oropharyngeal surfactant. If an infant is felt to need ET surfactant following initial oropharyngeal administration, then they will receive the standard initial dose via ETT.

Randomisation

Infants will be randomised (1:1) to receive oropharyngeal surfactant in addition to CPAP or CPAP alone using variable block randomisation, with block sizes of 4, 6 and 8. Randomisation will be stratified by participating centre and GA (<26 weeks and 26-28^{+6} weeks inclusive). Infants of multiple gestations will be randomised as individuals.

A computer-generated randomisation schedule using sequential 6-digit randomisation codes will be prepared by an independent statistician who will not be involved with subsequent data analysis or interpretation and stored securely on a password-protected computer. Each participating centre will be provided with two separate boxes for the two GA strata with consecutively numbered, sealed opaque randomisation envelopes containing the assigned treatment allocation. The boxes containing the envelopes will be stored securely in the NICU. An envelope from the appropriate box will be opened immediately before birth.

Blinding

This is an open-label study. The study will not be blinded to investigators, subjects, or medical or nursing staff. We are not using a placebo, and in the event of the infant being randomised to the 'CONTROL' arm, then they will be commenced on CPAP immediately after birth. The trial statistician will be blinded for data analysis and will be kept unaware of treatment group assignments. We defined objective criteria for the primary outcome to minimise potential bias.

Data management

Data will be collected by the on-site investigators from the patient's clinical notes. This will be recorded on a data worksheet and transferred to an electronic Case Report Form (CRF) to be stored in a secure, dedicated, password-protected electronic database. The clinical study monitor and representative of the regulatory authority can directly access source documents for comparison of such data with the data in the electronic CRFs and can verify that the study is carried out in compliance with the protocol and local regulatory requirements.

The investigators will adhere to national and hospital protocols on data use and storage. Data will be coded. It will be stored in a locked filing cabinet then uploaded onto a password-protected computer in a locked office. Documents will be stored safely in confidential conditions. On all study-specific documents other than the signed consent, the subject will be referred to by the study subject identification code.

Description of statistical methods

Trial results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT). The flow of patients through the trial will be represented on a CONSORT flow diagram, and the number included in the primary and secondary analyses as well as all reasons for exclusions will be reported per trial arm. Analysis of efficacy endpoints will be carried-out following the Intention-To-Treat principle. A Per-Protocol analysis will also be carried out on the primary endpoint, excluding infants with incomplete data on the primary outcome and infants with any major protocol deviations.

Demographic and baseline data will be summarised by treatment group to evaluate comparability.

Primary outcome analysis

The primary outcome will be summarised per group. Ratios of relative risk will be reported with 95% confidence intervals. A two-sided, two-proportion Z test will be carried out to investigate whether the rate of endotracheal intubation differs between intervention and standard-of-care. This analysis will be carried out both on the intention-to-treat set and on the per protocol set.

A completing risks model will be fitted to investigate the effect of the intervention on the primary endpoint, adjusting for competing outcomes (e.g. mortality) that may impact on observation of the primary endpoint.

The sensitivity of the estimated intervention effect to measured covariates of interest, including centre, GA, birth weight, gender, mode of delivery and antenatal corticosteroid treatment, will be evaluated with regression analysis.

Secondary outcome analysis

Categorical outcomes will be summarised per treatment group, with between-group differences expressed as a relative risk with 95% confidence intervals. A two-sided, two-proportion Z test will be carried out for each categorical outcome to investigate whether the proportion differs between intervention and standard of care. For the important secondary endpoint of death before hospital discharge, regression analysis will be employed to determine sensitivity of the estimated intervention effect to potentially relevant covariates (as specified above for the primary outcome).

Numeric secondary outcomes will be summarised by treatment group and between-group differences will be presented with a 95% confidence interval. A superiority hypothesis test will be

carried out to test for a difference in the outcome between control and intervention, using a t-test or a Mann-Whitney U test where relevant.

Subgroup analyses

Subgroup analysis of the primary outcome and the important secondary outcome of death before hospital discharge will be carried out by regression modelling to determine differences in the intervention effect for infants of different GA strata, and infants from different participating centres.

Missing data

Any missing data or data anomalies will be communicated to the study site(s) for prompt clarification and resolution. For outcomes missing more than 5% of data in either treatment group, missing data methods will be employed in analysis. For categorical outcomes with censored data, Kaplan-Meier analyses will be used to estimate treatment effect. For other missing data, a suitable imputation method will be selected during blind review of the data.

Sample size and power

The sample size calculation assumed a rate of endotracheal intubation of 46% for infants treated with CPAP alone, and a rate of 28% for infants receiving oropharyngeal surfactant and CPAP. The former was informed by published RCTs showing a rate of mechanical ventilation in the days after birth among preterm infants treated with CPAP alone from 40– 60%[10-12] and rates of CPAP failure of 43% reported in a cohort of preterm infants 25 – 28 weeks' gestation initially commenced on CPAP.[14] The latter was informed by a cohort of infants born 26 – 28 weeks' gestation reporting that minimally invasive surfactant techniques reduced the rate of mechanical ventilation to from 46% to 28%.[28] Sample size was calculated in G*power based on a two-sided, two-proportion Z test. A

sample size of 125 infants per arm will be required to give a statistical power of 80% at a significance level of 5%, adjusted for an anticipated death rate of 10% (estimated from local data (NMH, Neonatal Clinical Report, 2015).

Safety analyses

Adverse events following administration of oropharyngeal surfactant will be documented. Safety analyses will be carried out on the Safety Set, defined as patients in the intervention arm who received oropharyngeal surfactant and patients who received CPAP only. The frequency of adverse events and the number and percentage of infants reported as having at least one emergent adverse event, will be reported by system organ class and preferred term, by treatment received. The same description will be performed for serious adverse events (SAE), severe AE, AE treatment-related and AE leading to IMP withdrawal. Defined SAEs for the study are important medical events, and death before hospital discharge.

Safety monitoring and interim analysis

A data safety monitoring board (DSMB) will be established to perform ongoing safety surveillance and to perform interim analyses on the study data. The DSMB will be an independent committee, composed of a minimum of three members; at least two will be clinicians with expertise in clinical trials; at least one member will be a clinician with expertise in neonatology.

The DSMB will meet on a 6-monthly basis after start of the trial and will review the frequency and severity of AEs in both treatment groups. If they observe any significant excess of SAEs in the intervention group associated with the intervention, they may recommend premature termination of the trial on the basis of safety concerns.

The DSMB will conduct interim analysis to determine whether the data provide overwhelming evidence of efficacy or futility, defined as a highly statistically significant difference in the primary outcome or a highly statistically significant difference in the important secondary outcome of death before hospital discharge. The type I error rate for interim analysis will be set to 0.001 in accordance with the Haybittle-Peto stopping boundary. For final analysis, the type I error rate will remain at 0.05. Interim analysis will be carried out after approximately 50% of participants (n=126) have completed the study. The DSMB may recommend early termination of the trial due to efficacy or futility; or for unanticipated concerns for the safety of enrolled infants. Standard procedures for reporting AEs will be used in accordance with Good Clinical Practice guidelines.

Ethics and dissemination

The study was initially approved by the Research Ethics Committee at NMH, Dublin, and the Health Products Regulatory Authority of Ireland. Approval was also obtained at the research ethics committees at each participating site and at the relevant competent authority for each participating country. All bodies must be informed in writing of any substantial changes to the protocol, prior to any such changes being implemented. University College Dublin, Ireland is the sponsor for this study.

Screening and consent

Prior to the delivery a member of the research team or other senior doctor will approach parent(s)/guardian(s) of eligible infants to inform them about the study. The team member will explain the purpose and nature of the study and provide written information for the parent(s)/guardian(s) to keep. If the local language is not their first language, they will be offered the opportunity to have an interpreter present while the study is explained. Written consent for enrolment of the infant in the study will then be sought. Parents will be informed that they may withdraw their child from the study at any time should they so wish; and that a decision not to

consent to their infants' participation in the study or to withdraw their infant from the study once enrolled will not affect their infant's access to the best available treatment and care.

Patient and public involvement (PPI)

We liaised with the Irish Neonatal Health Alliance for assistance when designing the parent information leaflet and consent form. Parent focus groups were held via PedCRIN prior to expansion of the study to European sites.

Recruitment

Though the enrolment rates to our studies amongst eligible infants are excellent, we believe it will be necessary to enrol infants at multiple sites in order to enrol our planned target sample of 250 infants in a timely fashion. We have a track record enlisting the help of collaborators nationally[43] and internationally[44 45] to perform our studies. We believe that with their help, we can enrol these infants in 3 years.

Current status

The trial began recruitment in December 2017, with additional sites joining subsequently. It is currently recruiting in 9 centres in 6 European countries. It is expected that recruitment for the study will be completed by December 2020.

Publication of results

The authors intend to publish the results of this trial in a high-quality, peer-reviewed journal upon completion of data collection and analysis.

Discussion

Oropharyngeal surfactant given immediately after birth to preterm infants at risk of RDS has the potential to reduce the risk of intubation and ventilation. Endotracheal intubation is invasive and unpleasant for newborns that is associated with adverse short- and long-term effects. It is also a skill that is difficult for clinicians to learn and maintain. In contrast, giving surfactant into the oropharynx is easy and avoids the adverse effects associated with intubation. There is evidence from animal studies and from case series in humans that it may be effective. This is an attractive proposition, because it could avoid harms associated with intubation for babies and raises the possibility of giving surfactant in contexts where it is not currently feasible (e.g. non-tertiary settings, developing countries). We were unable to credibly mask the intervention and acknowledge this lack of blinding as a limitation of the study. We tried to minimise potential bias by setting predefined objective treatment failure criteria, which were agreed on by all participating sites.

Figure 1. Schedule of events

Procedures	**Screening** Screening	**Allocation** Day of Birth	**Post-allocation** 120 hours after birth	**Close-out** Discharge home
ENROLMENT				
Inclusion/Exclusion Criteria	X			
Informed consent	X			
Allocation		x		
INTERVENTIONS				
Oropharyngeal surfactant		x		
Standard care - CPAP		x		
ASSESSMENTS				
Baseline variables		x		
Primary outcome			x	
Other outcomes			x	x

Table 1. 50th centile for birth weight (BW) for boys and girls according to gestational age (GA)

GA (weeks)	Girls BW (kg)	Boys BW (kg)
23	0.550	0.600
24	0.650	0.700
25	0.775	0.800
26	0.850	0.900
27	0.975	1.050
28	1.100	1.150

Table 2. Infants < 26 weeks estimated dosing range, following 120mg vial of Curosurf

GA (weeks)	Girls BW (kg)	Dose (mg/kg)	Boys BW (kg)	Dose (mg/kg)
23	0.550	218	0.600	200
24	0.650	185	0.700	171
25	0.775	155	0.800	150

Table 3. Infants 26-28^{+6} weeks estimating dosing range, following 240mg vial Curosurf

GA (weeks)	Girls BW (kg)	Dose (mg/kg)	Boys BW (kg)	Dose (mg/kg)
26	0.850	282	0.900	267
27	0.975	246	1.050	229
28	1.100	218	1.150	209

References:

1. Avery ME, Mead J. Surface properties in relation to atelectasis and hyaline membrane disease. *AMA J Dis Child* 1959;97(5, Part 1):517-23. [published Online First: 1959/05/01]
2. Fujiwara T MH, Chida S, Morita T, Watabe Y, Abe T. Artificial surfactant therapy in hyaline-membrane disease. *Lancet (London, England)* 1980;1(8159):55-59.
3. Halliday HL. Surfactants: past, present and future. *Journal of perinatology : official journal of the California Perinatal Association* 2008;28 Suppl 1:S47-56. doi: 10.1038/jp.2008.50 [published Online First: 2008/06/18]
4. Enhorning G, Shennan A, Possmayer F, et al. Prevention of neonatal respiratory distress syndrome by tracheal instillation of surfactant: a randomized clinical trial. *Pediatrics* 1985;76(2):145-53. [published Online First: 1985/08/01]
5. Merritt TA, Hallman M, Bloom BT, et al. Prophylactic treatment of very premature infants with human surfactant. *The New England journal of medicine* 1986;315(13):785-90. doi: 10.1056/nejm198609253151301 [published Online First: 1986/09/25]
6. Hallman M, Merritt TA, Jarvenpaa AL, et al. Exogenous human surfactant for treatment of severe respiratory distress syndrome: a randomized prospective clinical trial. *J Pediatr* 1985;106(6):963-9. [published Online First: 1985/06/01]
7. Ten centre trial of artificial surfactant (artificial lung expanding compound) in very premature babies. Ten Centre Study Group. *British medical journal (Clinical research ed)* 1987;294(6578):991-6. [published Online First: 1987/04/18]
8. Avery ME, Tooley WH, Keller JB, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. *Pediatrics* 1987;79(1):26-30. [published Online First: 1987/01/01]
9. Van Marter LJ, Allred EN, Pagano M, et al. Do clinical markers of barotrauma and oxygen toxicity explain interhospital variation in rates of chronic lung disease? The Neonatology Committee for the Developmental Network. *Pediatrics* 2000;105(6):1194-201. doi: 10.1542/peds.105.6.1194 [published Online First: 2000/06/02]
10. Morley CJ, Davis PG, Doyle LW, et al. Nasal CPAP or intubation at birth for very preterm infants. *The New England journal of medicine* 2008;358(7):700-8. doi: 10.1056/NEJMoa072788 [published Online First: 2008/02/15]
11. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *The New England journal of medicine* 2010;362(21):1970-9. doi: 10.1056/NEJMoa0911783 [published Online First: 2010/05/18]
12. Dunn MS, Kaempf J, de Klerk A, et al. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. *Pediatrics* 2011;128(5):e1069-76. doi: 10.1542/peds.2010-3848 [published Online First: 2011/10/26]
13. Rojas-Reyes MX, Morley CJ, Soll R. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *The Cochrane database of systematic reviews* 2012(3):Cd000510. doi: 10.1002/14651858.CD000510.pub2 [published Online First: 2012/03/16]
14. Dargaville PA, Gerber A, Johansson S, et al. Incidence and Outcome of CPAP Failure in Preterm Infants. *Pediatrics* 2016;138(1) doi: 10.1542/peds.2015-3985 [published Online First: 2016/07/02]

15. Kelly MA, Finer NN. Nasotracheal intubation in the neonate: physiologic responses and effects of atropine and pancuronium. *The Journal of pediatrics* 1984;105(2):303-9. [published Online First: 1984/08/01]
16. Shangle CE, Haas RH, Vaida F, et al. Effects of endotracheal intubation and surfactant on a 3-channel neonatal electroencephalogram. *The Journal of pediatrics* 2012;161(2):252-7. doi: 10.1016/j.jpeds.2012.02.014 [published Online First: 2012/03/20]
17. Marshall TA, Deeder R, Pai S, et al. Physiologic changes associated with endotracheal intubation in preterm infants. *Critical care medicine* 1984;12(6):501-3. doi: 10.1097/00003246-198406000-00006 [published Online First: 1984/06/01]
18. Friesen RH, Honda AT, Thieme RE. Changes in anterior fontanel pressure in preterm neonates during tracheal intubation. *Anesthesia and analgesia* 1987;66(9):874-8. [published Online First: 1987/09/01]
19. Barrington KJ, Finer NN, Etches PC. Succinylcholine and atropine for premedication of the newborn infant before nasotracheal intubation: a randomized, controlled trial. *Critical care medicine* 1989;17(12):1293-6. doi: 10.1097/00003246-198912000-00009 [published Online First: 1989/12/01]
20. Parkin JL, Stevens MH, Jung AL. Acquired and congenital subglottic stenosis in the infant. *The Annals of otology, rhinology, and laryngology* 1976;85(5 Pt.1):573-81. doi: 10.1177/000348947608500503 [published Online First: 1976/09/01]
21. Jobe AH IM. Lung development and function in preterm infants in the surfactant treatment era. *Annu Rev Physiol* 2000;62(825-46)
22. Bjorklund LJ IJ, Curstedt T, John J, Robertson B, Werner O, Vilstrup CT. Manual ventilation with a few large breaths at birth compromises the therapeutic effect of subsequent surfactant replacement in immature lambs. *Pediatr Res* 1997;42(3):348-55.
23. More K, Sakhuja P, Shah PS. Minimally invasive surfactant administration in preterm infants: a meta-narrative review. *JAMA pediatrics* 2014;168(10):901-8. doi: 10.1001/jamapediatrics.2014.1148 [published Online First: 2014/08/05]
24. Berggren E, Liljedahl M, Winbladh B, et al. Pilot study of nebulized surfactant therapy for neonatal respiratory distress syndrome. *Acta paediatrica (Oslo, Norway : 1992)* 2000;89(4):460-4. [published Online First: 2000/06/01]
25. Finer NN MT, Bernstein G, Job L, Mazela J, Segal R. An open label, pilot study of Aerosurf combined with nCPAP to prevent RDS in preterm neonates. *J Aerosol Med Pulm Drug Deliv* 2010;23(5):303-09.
26. Minocchieri S, Berry CA, Pillow JJ. Nebulised surfactant to reduce severity of respiratory distress: a blinded, parallel, randomised controlled trial. *Archives of disease in childhood Fetal and neonatal edition* 2019;104(3):F313-f19. doi: 10.1136/archdischild-2018-315051 [published Online First: 2018/07/28]
27. Abdel-Latif ME, Osborn DA. Nebulised surfactant in preterm infants with or at risk of respiratory distress syndrome. *The Cochrane database of systematic reviews* 2012;10:Cd008310. doi: 10.1002/14651858.CD008310.pub2 [published Online First: 2012/10/19]
28. Gopel W, Kribs A, Ziegler A, et al. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. *Lancet (London, England)* 2011;378(9803):1627-34. doi: 10.1016/s0140-6736(11)60986-0 [published Online First: 2011/10/04]

29. Dargaville PA, Aiyappan A, De Paoli AG, et al. Minimally-invasive surfactant therapy in preterm infants on continuous positive airway pressure. *Archives of disease in childhood Fetal and neonatal edition* 2013;98(2):F122-6. doi: 10.1136/archdischild-2011-301314 [published Online First: 2012/06/12]
30. Kanmaz HG, Erdeve O, Canpolat FE, et al. Surfactant administration via thin catheter during spontaneous breathing: randomized controlled trial. *Pediatrics* 2013;131(2):e502-9. doi: 10.1542/peds.2012-0603 [published Online First: 2013/01/30]
31. Kribs A, Roll C, Gopel W, et al. Nonintubated Surfactant Application vs Conventional Therapy in Extremely Preterm Infants: A Randomized Clinical Trial. *JAMA pediatrics* 2015;169(8):723-30. doi: 10.1001/jamapediatrics.2015.0504 [published Online First: 2015/06/09]
32. Attridge JT SC, Stukenborg GJ, Kattwinkel J. Administration of rescue surfactant by laryngeal mask airway: lessons from a pilot trial. *American journal of perinatology* 2013;30(3):201-06.
33. Barbosa RF, Simoes ESAC, Silva YP. A randomized controlled trial of the laryngeal mask airway for surfactant administration in neonates. *Jornal de pediatria* 2017;93(4):343-50. doi: 10.1016/j.jped.2016.08.007 [published Online First: 2017/01/29]
34. Roberts KD, Brown R, Lampland AL, et al. Laryngeal Mask Airway for Surfactant Administration in Neonates: A Randomized, Controlled Trial. *The Journal of pediatrics* 2018;193:40-46.e1. doi: 10.1016/j.jpeds.2017.09.068 [published Online First: 2017/11/28]
35. Abdel-Latif ME, Osborn DA. Laryngeal mask airway surfactant administration for prevention of morbidity and mortality in preterm infants with or at risk of respiratory distress syndrome. *The Cochrane database of systematic reviews* 2011(7):Cd008309. doi: 10.1002/14651858.CD008309.pub2 [published Online First: 2011/07/08]
36. Kattwinkel J, Robinson M, Bloom BT, et al. Technique for intrapartum administration of surfactant without requirement for an endotracheal tube. *Journal of perinatology : official journal of the California Perinatal Association* 2004;24(6):360-5. doi: 10.1038/sj.jp.7211103 [published Online First: 2004/04/16]
37. Lamberska T, Settelmayerova E, Smisek J, et al. Oropharyngeal surfactant can improve initial stabilisation and reduce rescue intubation in infants born below 25 weeks of gestation. *Acta paediatrica (Oslo, Norway : 1992)* 2018;107(1):73-78. doi: 10.1111/apa.14060 [published Online First: 2017/09/06]
38. Jobe A, Ikegami M, Jacobs H, et al. Surfactant and pulmonary blood flow distributions following treatment of premature lambs with natural surfactant. *The Journal of clinical investigation* 1984;73(3):848-56. doi: 10.1172/jci111280 [published Online First: 1984/03/01]
39. Cummings JJ, Holm BA, Nickerson PA, et al. Pre- versus post-ventilatory surfactant treatment in surfactant-deficient preterm lambs. *Reproduction, fertility, and development* 1995;7(5):1333-8. [published Online First: 1995/01/01]
40. Abdel-Latif ME, Osborn DA. Pharyngeal instillation of surfactant before the first breath for prevention of morbidity and mortality in preterm infants at risk of respiratory distress syndrome. *The Cochrane database of systematic reviews* 2011(3):Cd008311. doi: 10.1002/14651858.CD008311.pub2 [published Online First: 2011/03/18]

41. Enhorning G, Grossmann G, Robertson B. Pharyngeal deposition of surfactant in the premature rabbit fetus. *Biology of the neonate* 1973;22(1):126-32. [published Online First: 1973/01/01]
42. Enhorning G, Robertson B, Milne E, et al. Radiologic evaluation of the premature newborn rabbit after pharyngeal deposition of surfactant. *American journal of obstetrics and gynecology* 1975;121(4):475-80. [published Online First: 1975/02/15]
43. Kieran EA, O'Sullivan A, Miletin J, et al. 2% chlorhexidine-70% isopropyl alcohol versus 10% povidone-iodine for insertion site cleaning before central line insertion in preterm infants: a randomised trial. *Archives of disease in childhood Fetal and neonatal edition* 2018;103(2):F101-f06. doi: 10.1136/archdischild-2016-312193 [published Online First: 2017/10/28]
44. Stenke E, Kieran EA, McCarthy LK, et al. A randomised trial of placing preterm infants on their back or left side after birth. *Archives of disease in childhood Fetal and neonatal edition* 2016;101(5):F397-400. doi: 10.1136/archdischild-2015-309842 [published Online First: 2016/02/06]
45. Murphy MC, Heiring C, Doglioni N, et al. Effect of Needle Aspiration of Pneumothorax on Subsequent Chest Drain Insertion in Newborns: A Randomized Clinical Trial. *JAMA pediatrics* 2018;172(7):664-69. doi: 10.1001/jamapediatrics.2018.0623 [published Online First: 2018/05/26]

BMJ Open

Study protocol for the POPART study – Prophylactic Oropharyngeal surfactant for Preterm infants: A Randomised Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035994.R1
Article Type:	Protocol
Date Submitted by the Author:	04-Mar-2020
Complete List of Authors:	murphy, madeleine; National Maternity Hospital, Neonatology; National Children's Research Centre, National Children's Research Centre, Our Lady's Children's Hospital Galligan, Marie; University College Dublin School of Medicine and Medical Science, School of Medicine Molloy, Brenda; University College Dublin School of Medicine and Medical Science, School of Medicine Hussain, Rabia; University College Dublin School of Medicine and Medical Science, School of Medicine Doran, Peter; University College Dublin School of Medicine and Medical Science, School of Medicine ODonnell, Colm; The National Maternity Hospital, Dublin, Ireland, Neonatal Intensive Care Unit
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Research methods, Paediatrics
Keywords:	NEONATOLOGY, PAEDIATRICS, PERINATOLOGY

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

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

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

Study protocol for the POPART study – Prophylactic Oropharyngeal surfactant for Preterm infants: A Randomised Trial

Madeleine C. Murphy,[1-3] Marie Galligan,[3] Brenda Molloy,[3] Rabia Hussain,[3] Peter Doran,[3] Colm P.F. O'Donnell[1-3]

1. National Maternity Hospital, Dublin, Ireland
2. National Children's Research Centre, Dublin, Ireland
3. School of Medicine, University College Dublin, Ireland

Word count 4308 Abstract 318 Figures/Tables 4 References 55

Trial registration

Protocol identification (code or reference number): UCDCRC/16/003

EudraCT number: 2016-004198-41

Protocol version 2.0, dated 19.07.19

Trial sponsor

University College Dublin

Corresponding Author

Address Prof. Colm O'Donnell, Department of Neonatology, National Maternity Hospital, Holles Street, Dublin 2, Ireland

Tel +353 1 6373100

Email codonnell@nmh.ie

Key words: Infant, newborn; oropharyngeal surfactant; respiratory distress syndrome; intubation; randomised controlled trial

Author Contributions: COD conceived and designed the trial protocol, co-wrote the first draft and revised the manuscript for intellectual content. MCM helped design the trial protocol, co-wrote the first draft and revised the manuscript for intellectual content. MG, BM, RH, and PD helped design the trial protocol and revised the manuscript for intellectual content. MG designed the statistical analysis plan. All authors approved the final manuscript prior to submission.

Funding:

Chiesi Farmaceutici, manufacturers of poractant alfa (Curosurf), supply the study drug free of charge; they had no role in study design; have no role in study conduct; and will have no role in data collection, analysis or interpretation. Further, they will have no role in the decision to present, publish or otherwise report results.

Madeleine Murphy is the recipient of a Clinical Research Fellowship by the National Children's Research Centre, Dublin (R17637)

Pediatric Clinical Research Infrastructure Network (PedCRIN), a Project of the European Union Horizon 2020 programme designed to support the extension of clinical drug trials in children throughout Europe, also support the study.

Competing interests: None declared

Ethics approval:

Ireland: Research Ethics Committee, The National Maternity Hospital, Dublin, Ireland; Research Ethics Committee, Coombe Women and Infants University Hospital

Belgium: Le Comité d'Ethique du CHR Citadelle

Czech Republic: Etická komise, Všeobecné fakultní nemocnice (VFN) v Praze (Ethics Committee of the General University Hospital, Prague)

Norway: Regional komité for medisinsk og helsefaglig forskningsetikk (REK nord) (Regional Ethics Committee, REK, nord)

Portugal: Comissão de Ética para a Investigação Clínica, CEIC (National Ethics Committee for Clinical Research)

Sweden: Stockholm Regional Ethics Review Board

Acknowledgements: We would like to acknowledge the administrative staff at UCD for their advice, and support with the trial thus far. We wish to thank the members of PedCRIN and the Principal Investigators and members of the Clinical Trials Units at all our European sites for facilitating extension of our trial to Europe. POPART Trial Investigators: Jan Miletin, Coombe Women and Infants University Hospital, Dublin, Ireland; Claus Klingenberg, University Northern Norway, Tromsø, Norway; Hans Jørgen Guthe, Haukeland University Hospital, Bergen, Norway; Richard Plavka, Charles University, Prague, Czech Republic; Tomas Juren, University Hospital Brno, Brno, Czech Republic; Vincent Rigo, Le Centre Hospitalier Universitaire, Liege, Belgium; Kajsa Bohlin, Karolinska Institutet, Stockholm, Sweden; and Almerinda Pereira, Hospital de Braga, Braga, Portugal.

Data statement: Members of the Trial Steering Committee will have access to the final dataset. Data will be available on request.

Abstract

Introduction: Many preterm infants develop respiratory distress syndrome (RDS), a condition characterised by a relative lack of surfactant. Endotracheal surfactant therapy revolutionised the care of preterm infants in the 1990s. However, supporting newborns with RDS with continuous positive airway pressure (CPAP) and reserving endotracheal surfactant for those who develop respiratory failure despite CPAP yields better results than intubating all infants for surfactant. Half of preterm infants born before 29 weeks' gestation initially managed with CPAP are intubated for surfactant. Intubation is difficult to learn and associated with adverse effects. Surfactant administration into the oropharynx has been reported in preterm animals and humans and may be effective. We wished to determine whether giving oropharyngeal surfactant at birth reduces the rate of endotracheal intubation for respiratory failure in preterm infants within 120 hours of birth.

Methods and analysis: POPART (Prophylactic Oropharyngeal surfactant for Preterm infants: A Randomised Trial) is an investigator-led, unblinded, multicentre, randomised, parallel group, controlled trial. Infants are eligible if born at a participating centre before 29 weeks gestational age (GA) and there is a plan to offer intensive care. Infants are excluded if they have major congenital anomalies. Infants are randomised at birth to treatment with oropharyngeal surfactant [120mg vial <26 weeks GA stratum; 240mg vial 26 – 28+6 weeks GA stratum] in addition to CPAP or CPAP alone. The primary outcome is intubation within 120 hours of birth, for bradycardia and/or apnoea despite respiratory support in the delivery room or respiratory failure in the intensive care unit. Secondary outcomes include incidence of mechanical ventilation, endotracheal surfactant use, chronic lung disease, and death before hospital discharge.

Ethics and dissemination: Approval for the study has been granted by the Research Ethics Committees at the National Maternity Hospital, Dublin, Ireland (EC31.2016), and at each

participating site. The trial is being conducted at 9 centres in 6 European countries. The study results will be submitted for publication in a peer-reviewed journal.

Article summary

Strengths and limitations of this study

- This is the first randomised study to specifically examine the efficacy of giving oropharyngeal surfactant at birth to preterm infants at high risk of developing respiratory distress syndrome.
- We are enrolling infants < 29 weeks' gestation, including infants at 23 and 24 weeks' gestation, who are most at risk of respiratory distress syndrome.
- We were unable to credibly mask the intervention.
- To reduce the risk of bias we used objective criteria for our primary outcome i.e. intubation within 120 hours of life.
- The multicentre nature of this study will increase the generalisability of its findings.

Background

Respiratory distress syndrome (RDS) is a lung condition of the preterm infant. The risk of RDS is inversely related to gestational age (GA). Infants with RDS have structural and functional immaturity of their lungs. They also have a relative lack of surfactant,[1] an endogenously produced substance that enables alveoli to expand more easily to recruit and maintain gas within the lung.

Exogenous surfactant[2 3] is frequently used to treat newborns with RDS and has led to improved outcomes for infants worldwide. Randomised controlled trials (RCTs) in the 1980s – 1990s[4-7] demonstrated that surfactant, given by endotracheal tube (ETT), reduced mortality and air leak among premature infants who were intubated for respiratory failure due to RDS. This led to the widespread practice of intubating all extremely preterm infants for surfactant and ventilation ("prophylactic surfactant").[5] Prior to the introduction of surfactant into clinical practice, concerns were raised that premature infants who were intubated for respiratory support had worse respiratory outcomes than infants who were managed with the non-invasive respiratory support, nasal continuous positive airway pressure (CPAP).[8] These concerns persisted after the widespread introduction of surfactant.[9] Multicentre RCTs found that starting infants on CPAP may be beneficial when compared with intubation and positive pressure ventilation (PPV); the studies reported decreased duration of mechanical ventilation with potential benefits of reduction of death and or bronchopulmonary dysplasia (BPD).[10-12] Managing premature newborns initially with CPAP and reserving intubation, mechanical ventilation and surfactant for those infants with worsening respiratory failure despite CPAP yields better results than intubating all infants for surfactant administration.[13] About half of premature infants born before 29 weeks' gestation initially managed with CPAP for RDS are ultimately intubated for surfactant and ventilation.[14]

Intubation is a procedure that is difficult to learn and is associated with adverse effects, both short[15-19] and longer-term.[20-22] This has led many clinicians to investigate alternative methods of surfactant delivery.[23] Giving nebulised surfactant to spontaneously breathing infants has met with limited success.[24-27] Progress has been slow due to the technical difficulties encountered in aerosolising such large molecules, the expense of the equipment needed to do so and the cost of the large amount of surfactant needed to form an aerosol. Interest has largely focussed on less-invasive methods of surfactant administration.

Less invasive surfactant administration (LISA) techniques involve introducing either a feeding tube or vascular catheter into the trachea of a spontaneously breathing infant at laryngoscopy.[28-31] LISA is associated with lower rates of mechanical ventilation among preterm infants in randomised[28 31] observational studies.[32] Two year follow up outcomes for infants enrolled in the randomised trial Avoid Mechanical Ventilation,[28] where infants were randomised to surfactant via LISA or to standard care with CPAP and ET instillation of surfactant if necessary, are similar between groups.[33] However, the technique appears more difficult than intubation and the short-term adverse effects of laryngoscopy are not avoided. The procedure is becoming more widely used, but rates vary between countries.[34-37] Concerns regarding the validity and risk of bias within studies, a lack of familiarity with the technique, and patient discomfort have been reported as reasons for not using LISA.[36] Use of sedation and analgesia prior to laryngoscopy is not standard for the LISA procedure.[28] While meta-analyses report that the LISA technique is associated with less death or BPD,[38-40] further RCTs are needed. The Optimist-A trial,[41] evaluating minimally invasive surfactant therapy in preterm infants born between 25 – 28 weeks' gestation is ongoing.

The laryngeal mask airway, a supraglottic airway device, may be used as an interface to deliver surfactant.[42-45] However there is currently no device available for use in very low birth weight infants, who constitute the majority of infants diagnosed with RDS.

Direct administration of surfactant into the pharynx of human infants has been described in randomised[7] and prospective cohort studies.[46 47] It is apparently effective and is an easier technique to perform than endotracheal intubation or passing a feeding tube or vascular catheter into the trachea. Advantages of pharyngeal surfactant use are that it is an easy and cheaper method of administering surfactant and likely causes less discomfort to infants as it avoids the use of a laryngoscope. Giving surfactant early, prior to ventilation, delivers surfactant to a fluid-filled lung, which is spread via a fluid-air interface when the infant starts breathing. Animal studies report that surfactant is distributed more uniformly,[48] and lung function and compliance is better[49] if surfactant is delivered prior to ventilation. If shown to be effective, it may reduce the adverse effects, and additional associated costs, of ventilation.

A Cochrane review of pharyngeal surfactant[50] did not identify any eligible trials to assess whether pharyngeal installation of surfactant before the first breath prevented morbidity and mortality in infants at risk of RDS. The Ten Centre Study randomised 328 infants born between 25 – 29 weeks' gestation to artificial surfactant therapy or saline. For those randomised to surfactant therapy, the first dose was given via the oropharynx, with subsequent doses given via an ETT if the infant was intubated, however the outcomes of infants who received pharyngeal surfactant alone were not reported. Large well conducted RCTs are needed, due to the evidence from animal[51 52] and observational human studies[46 47] suggesting that pharyngeal surfactant administration is potentially safe, feasible, and may be effective.

Objective

We are performing a study to establish whether giving preterm infants surfactant into their oropharynx at birth in addition to CPAP compared with CPAP alone reduces their need for subsequent intubation in the first 5 days of life.

Methods

Trial design

The POPART trial is an investigator-led, unblinded, multicentre, randomised parallel-group controlled trial. It aims to determine whether administering oropharyngeal surfactant to premature infants at birth in addition to CPAP compared to CPAP alone reduces the rate of intubation for respiratory failure in the first 5 days of life. The trial will recruit 250 infants born <29 weeks GA at participating centres. A schedule of events is seen in figure 1.

Setting

The trial is being conducted at 9 neonatal intensive care units (NICUs) in 6 European countries [Ireland (National Maternity Hospital (NMH), Dublin; Coombe Women and Infants University Hospital (CWIUH) Dublin); Norway (University Northern Norway, Tromsø; Haukeland University Hospital, Bergen); Czech Republic (Charles University, Prague; University Hospital Brno, Brno), Belgium (Le Centre Hospitalier Universitaire (CHU), Liege); Sweden (Karolinska Institutet, Stockholm); and Portugal (Hospital de Braga, Braga).

Participants

Inclusion and exclusion criteria

Trial subjects are premature infants at risk of RDS. Infants born less than 29 weeks GA are included if the treating physician plans to offer intensive care. Infants are excluded if they have major

congenital anomalies (including neural tube defects, major structural cardiac anomalies (excluding patent ductus arteriosus, ventricular septal defect, atrioventricular septal defect), abdominal wall defects, congenital diaphragmatic hernia and major dysmorphic features with an abnormal karyotype) and if the treating physician does not plan to offer intensive care. If there is a known anomaly prenatally, families are not approached for consent. In the event of a postnatal diagnosis of the aforementioned conditions, these infants meet criteria for post-randomisation exclusion. Written informed consent from parent/legal guardian(s) is obtained before delivery. Infants of multiple gestation and of either sex are eligible to be enrolled.

Screening and consent

Prior to the delivery a member of the research team or other senior doctor approaches parent(s)/guardian(s) of eligible infants to inform them about the study. The team member explains the purpose and nature of the study and provides written information for the parent(s)/guardian(s) to keep. If the local language is not their first language, they are offered the opportunity to have an interpreter present while the study is explained. Written consent for enrolment of the infant in the study is then sought. Parents are informed that they may withdraw their child from the study at any time should they so wish; and that a decision not to consent to their infants' participation in the study or to withdraw their infant from the study once enrolled does not affect their infant's access to the best available treatment and care.

Outcome measures

Primary outcome

The primary outcome is the incidence of endotracheal intubation for respiratory failure within 120 hours of birth. Enrolled infants are intubated for persistent apnoea and/or bradycardia (HR <100bpm) in the delivery room (DR), or for respiratory failure in the NICU defined as ≥ 2 of:

- Clinical signs – worsening tachypnoea; grunting; subcostal, intercostal and/or sternal recession
- Acidosis – pH < 7.2 on 2 blood gases (arterial or capillary) ≥ 30 minutes apart
- Hypoxaemia – FiO_2 > 0.4 to keep oxygen saturation (SpO_2) ≥ 90% for > 30 minutes
- Hypercarbia – PCO_2 > 9.0 kPa on 2 blood gases (arterial or capillary) ≥ 30 minutes apart
- Apnoea – recurrent apnoea treated with mask ventilation

The primary outcome is intubation within 120 hours of birth. For the purpose of the primary outcome, infants are recorded as 'yes' if they were intubated, briefly intubated for surfactant administration e.g. INSURE, and brief tracheal catheterisation for surfactant administration e.g. LISA technique. We record the treatment plan at the time of intubation. We record whether there is a) a plan for intubation with endotracheal tube, surfactant administration, and continued ventilation; b) a plan for "INSURE" – intubation with ETT, surfactant administration, and immediate (<30 minute) extubation; c) a plan for surfactant administration using LISA technique – surfactant administration through a thin endotracheal catheter; or d) other

We acknowledge that not all infants achieving ≥ 2 of the intubation indicators may be intubated.

Secondary outcomes

The secondary outcomes are as follows:

1. Intubation in the DR
2. Number of attempts taken to successfully intubate in the DR

3. Chest compressions in the DR
4. Adrenaline administration in the DR
5. Rectal temperature on admission to the NICU
6. NICU intubation
7. Surfactant use before death or hospital discharge
    a. Number of doses, and total dose
    b. Intra-tracheal surfactant received post-intervention
    c. Doses of post-intervention surfactant
8. Respiratory distress syndrome
    a. Clinical evidence and radiological evidence of respiratory distress at the time of first intubation
9. Incidence of pneumothorax
    a. Incidence of pneumothorax on chest x-ray
    b. Pneumothorax treated with needle aspiration or chest drain insertion
10. Incidence of pulmonary haemorrhage
    a. Clinical evidence of pulmonary haemorrhage
11. Mechanical ventilation
12. Days of mechanical ventilation
13. Use of postnatal corticosteroids for ventilator dependence
14. Days of duration of respiratory support (endotracheal ventilation, high-frequency oscillatory ventilation, CPAP, heated humidified high-flow nasal cannula O_2, low flow nasal cannula O_2)
15. BPD – supplemental O_2 at 28 days of life
16. Chronic lung disease of prematurity (CLD) –O_2 treatment at 36 weeks corrected GA; we are also recording physiological BPD as determined by physiological oxygen reduction test
17. Medical treatment for a patent ductus arteriosus (PDA)
    a. Administration of ibuprofen or paracetemol for PDA

18. Surgical treatment for a PDA
19. Proven necrotising enterocolitis (≥ Bell's stage 2)
20. Incidence of Intraventricular haemorrhage (IVH) (any and severe: IVH grade ≥ 3)
    a. Evidence on surveillance cranial ultrasounds performed as standard of care
21. Incidence of cystic periventricular leukomalacia
    a. Evidence on surveillance cranial ultrasounds performed as standard of care
22. Retinopathy of prematurity treated with laser photocoagulation or intravitreal injections
    a. Evidence on surveillance ophthalmology review performed as standard of care
23. Death before hospital discharge
24. Survival without BPD at hospital discharge
25. Survival without CLD at hospital discharge
26. Duration of first hospitalisation
27. Use of home oxygen therapy
    a. Discharged home on oxygen therapy

Investigational medicinal product (IMP)

Poractant alfa (Curosurf, Chiesi Farmaceutici, Parma, Italy) is a natural surfactant prepared from porcine lungs. It is licensed for ET use and administration via thin catheter for the prevention and treatment of RDS in preterm infants. The dosing recommendations for treatment with Curosurf when given by ETT are 200mg/kg for established RDS and 100 – 200mg/kg for prophylaxis. Further doses of 100mg/kg Curosurf may be given to infants who have persistent respiratory distress despite treatment with surfactant (maximum recommended dose 400mg/kg). It is currently not licensed for oropharyngeal administration, and therefore this study is examining the off-label use of a licensed product. The timing or dosage of ET surfactant is not be affected by oropharyngeal surfactant. If an

infant is felt to need ET surfactant following initial oropharyngeal administration, then they receive the standard initial dose via ETT.

Randomisation

Infants are randomised (1:1) to receive oropharyngeal surfactant in addition to CPAP or CPAP alone using variable block randomisation, with block sizes of 4, 6 and 8. Randomisation is stratified by participating centre and GA (<26 weeks and 26-28^{+6} weeks inclusive). Infants of multiple gestations are randomised as individuals.

A computer-generated randomisation schedule using sequential 6-digit randomisation codes was prepared by an independent statistician who was not be involved with subsequent data analysis or interpretation and stored securely on a password-protected computer. Each participating centre is provided with two separate boxes for the two GA strata with consecutively numbered, sealed opaque randomisation envelopes containing the assigned treatment allocation. The boxes containing the envelopes are stored securely in the NICU. An envelope from the appropriate box is opened immediately before birth.

Blinding

This is an open-label study. The study is not blinded to investigators, subjects, or medical or nursing staff. We are not using a placebo, and in the event of the infant being randomised to the 'CONTROL' arm, then they will be commenced on CPAP immediately after birth. The trial statistician will be blinded for data analysis and will be kept unaware of treatment group assignments. We defined objective criteria for the primary outcome to minimise potential bias.

Intervention arm: Oropharyngeal surfactant

Infants randomised to oropharyngeal surfactant receive a dose of poractant alfa (Curosurf, Chiesi Farmaceutici, Parma, Italy) immediately after birth, ideally before the cord is clamped e.g. 60 seconds. If it is given after the cord is clamped, it is given once the infant is placed on the resuscitaire. It is given within 5 minutes of birth in all cases. We are recording the timing of cord clamping for all patients.

The surfactant is warmed prior to being drawn up in a sterile syringe as per manufacturer's recommendation. Surfactant is administered by opening the mouth gently and giving the surfactant as a single bolus into the oropharynx using a thin flexible catheter attached to the syringe.

Infants are not weighed prior to enrolment. The 50th centile for birth weight (BW) for boys and girls according to GA is shown in table 1. In our study, infants < 26 weeks receive a full 120mg vial of Curosurf. We estimate that this provides dosing in the range as indicated in table 2. In our study, infants 26 – 28 weeks receive a full 240mg vial of Curosurf, and we estimate that this provides dosing in the range as indicated in table 3.

Control group: CPAP

Infants randomised to the control group do not have anything injected into their oropharynx and are stabilised on CPAP in the DR as per routine practice.

Clinical management

After the initial intervention, infants then receive standard care with CPAP, regardless of their group assignment. DR care is carried out by the neonatal team who are trained in neonatal resuscitation as per the recommendations of the International Liaison Committee on Resuscitation (ILCOR). Infants in both groups are intubated in the DR for persistent apnoea and/or bradycardia despite PPV by mask as per ILCOR recommendations. Infants are not intubated in the DR solely for surfactant administration. All other aspects of neonatal intensive care is at the discretion of the treating physicians. Infants in both groups are treated equally. The frequency of blood gas monitoring is based on the decision of the treating physician. Enrolled infants are intubated if they reach the pre-determined criteria for respiratory failure. After giving endotracheal surfactant for the treatment of RDS, attending clinicians may attempt to extubate the babies immediately or they may elect to ventilate the babies for a longer period at their discretion.

Data management

Data is collected by the on-site investigators from the patient's clinical notes. This is recorded on a data worksheet and transferred to an electronic Case Report Form (CRF) to be stored in a secure, dedicated, password-protected electronic database. The clinical study monitor and representative of the regulatory authority can directly access source documents for comparison of such data with the data in the electronic CRFs and can verify that the study is carried out in compliance with the protocol and local regulatory requirements.

The investigators adheres to national and hospital protocols on data use and storage. Data is coded. It is stored in a locked filing cabinet then uploaded onto a password-protected computer in a locked office. Documents are stored safely in confidential conditions. On all study-specific documents other than the signed consent, the subject is referred to by the study subject identification code.

Description of statistical methods

Trial results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT). The flow of patients through the trial will be represented on a CONSORT flow diagram, and the number included in the primary and secondary analyses as well as all reasons for exclusions will be reported per trial arm. Analysis of efficacy endpoints will be carried-out following the Intention-To-Treat principle. A Per-Protocol analysis will also be carried out on the primary endpoint, excluding infants with incomplete data on the primary outcome and infants with any major protocol deviations.

Demographic and baseline data will be summarised by treatment group to evaluate comparability.

Primary outcome analysis

The primary outcome will be summarised per group. Ratios of relative risk will be reported with 95% confidence intervals. A two-sided, two-proportion Z test will be carried out to investigate whether the rate of endotracheal intubation differs between intervention and standard-of-care. This analysis will be carried out both on the intention-to-treat set and on the per protocol set.

A completing risks model will be fitted to investigate the effect of the intervention on the primary endpoint, adjusting for competing outcomes (e.g. mortality) that may impact on observation of the primary endpoint.

The sensitivity of the estimated intervention effect to measured covariates of interest, including centre, GA, birth weight, gender, mode of delivery and antenatal corticosteroid treatment, will be evaluated with regression analysis.

Secondary outcome analysis

Categorical outcomes will be summarised per treatment group, with between-group differences expressed as a relative risk with 95% confidence intervals. A two-sided, two-proportion Z test will be carried out for each categorical outcome to investigate whether the proportion differs between intervention and standard of care. For the important secondary endpoint of death before hospital discharge, regression analysis will be employed to determine sensitivity of the estimated intervention effect to potentially relevant covariates (as specified above for the primary outcome).

Numeric secondary outcomes will be summarised by treatment group and between-group differences will be presented with a 95% confidence interval. A superiority hypothesis test will be carried out to test for a difference in the outcome between control and intervention, using a t-test or a Mann-Whitney U test where relevant.

Subgroup analyses

Subgroups of interest include infants of different gestational age strata (e.g. less than 26 weeks, and 26-28 weeks' gestation at birth), and infants from different participating centres. Subgroup analysis of the primary outcome and the important secondary outcome of death before hospital discharge will be carried out by regression modelling to determine differences in the intervention effect for infants of different GA strata, and infants from different participating centres.

Missing data

Any missing data or data anomalies will be communicated to the study site(s) for prompt clarification and resolution. For outcomes missing more than 5% of data in either treatment group, missing data methods will be employed in analysis. For categorical outcomes with censored data, Kaplan-Meier analyses will be used to estimate treatment effect. For other missing data, a suitable imputation method will be selected during blind review of the data.

Sample size and power

The sample size calculation assumed a rate of endotracheal intubation of 46% for infants treated with CPAP alone, and a rate of 28% for infants receiving oropharyngeal surfactant and CPAP. The former was informed by published RCTs showing a rate of mechanical ventilation in the days after birth among preterm infants treated with CPAP alone from 40– 60%[10-12] and rates of CPAP failure of 43% reported in a cohort of preterm infants 25 – 28 weeks' gestation initially commenced on CPAP.[14] The latter was informed by a cohort of infants born 26 – 28 weeks' gestation reporting that minimally invasive surfactant techniques reduced the rate of mechanical ventilation to from 46% to 28%.[28] Sample size was calculated in G*power based on a two-sided, two-proportion Z test. A sample size of 125 infants per arm will be required to give a statistical power of 80% at a significance level of 5%, adjusted for an anticipated death rate of 10% (estimated from local data (NMH, Neonatal Clinical Report, 2015).

Safety analyses

Adverse events following administration of oropharyngeal surfactant will be documented. Safety analyses will be carried out on the Safety Set, defined as patients in the intervention arm who received oropharyngeal surfactant and patients who received CPAP only. The frequency of adverse events and the number and percentage of infants reported as having at least one emergent adverse

event, will be reported by system organ class and preferred term, by treatment received. The same description will be performed for serious adverse events (SAE), severe AE, AE treatment-related and AE leading to IMP withdrawal. Defined SAEs for the study are important medical events, and death before hospital discharge.

Safety monitoring and interim analysis

A data safety monitoring board (DSMB) will be established to perform ongoing safety surveillance and to perform interim analyses on the study data. The DSMB will be an independent committee, composed of a minimum of three members; at least two will be clinicians with expertise in clinical trials; at least one member will be a clinician with expertise in neonatology. They will not be blinded to the intervention groups.

The DSMB will meet on a 6-monthly basis after start of the trial and will review the frequency and severity of AEs in both treatment groups. If they observe any significant excess of SAEs in the intervention group associated with the intervention, they may recommend premature termination of the trial on the basis of safety concerns.

The DSMB will conduct interim analysis to determine whether the data provide overwhelming evidence of efficacy or futility, defined as a highly statistically significant difference in the primary outcome or a highly statistically significant difference in the important secondary outcome of death before hospital discharge. The type I error rate for interim analysis will be set to 0.001 in accordance with the Haybittle-Peto stopping boundary. For final analysis, the type I error rate will remain at 0.05. Interim analysis will be carried out after approximately 50% of participants (n=126) have completed the study. The DSMB may recommend early termination of the trial due to efficacy or futility; or for unanticipated concerns for the safety of enrolled infants. Standard procedures for

reporting AEs will be used in accordance with Good Clinical Practice guidelines.

Ethics and dissemination

The study was initially approved by the Research Ethics Committee at NMH, Dublin, and the Health Products Regulatory Authority of Ireland. Approval was also obtained at the research ethics committees at each participating site and at the relevant competent authority for each participating country. All bodies are informed in writing of any substantial changes to the protocol, prior to any such changes being implemented. University College Dublin, Ireland is the sponsor for this study.

Patient and public involvement (PPI)

We liaised with the Irish Neonatal Health Alliance for assistance when designing the parent information leaflet and consent form. Parent focus groups were held via Pediatric Clinical Research Infrastructure Network (PedCRIN) prior to expansion of the study to European sites.

Recruitment

The National Maternity Hospital is a stand-alone university maternity hospital with a tertiary NICU to which >150 infants <1500g are admitted annually. Approximately 60 babies <29 weeks' gestation are admitted annually. Though the enrolment rates to our studies amongst eligible infants are consistently excellent (> 80%), we believe it is necessary to enrol infants at multiple sites in order to enrol our planned target sample of 250 infants in a timely fashion. We have a track record enlisting the help of collaborators nationally[53] and internationally[54 55] to perform our studies. We believe that with their help, we can enrol these infants in 3 years.

Current status

The trial began recruitment in December 2017, with additional sites joining subsequently. It is currently recruiting in 9 centres in 6 European countries. It is expected that recruitment for the study will be completed by December 2020.

Publication of results

The authors intend to publish the results of this trial in a high-quality, peer-reviewed journal upon completion of data collection and analysis.

Discussion

Oropharyngeal surfactant given immediately after birth to preterm infants at risk of RDS has the potential to reduce the risk of intubation and ventilation. Endotracheal intubation is invasive and unpleasant for newborns that is associated with adverse short- and long-term effects. It is also a skill that is difficult for clinicians to learn and maintain. In contrast, giving surfactant into the oropharynx is easy and avoids the adverse effects associated with intubation. There is evidence from animal studies and from case series in humans that it may be effective. This is an attractive proposition, because it could avoid harms associated with intubation for babies and raises the possibility of giving surfactant in contexts where it is not currently feasible (e.g. non-tertiary settings, developing countries). We were unable to credibly mask the intervention and acknowledge this lack of blinding as a limitation of the study. We tried to minimise potential bias by setting predefined objective treatment failure criteria, which were agreed on by all participating sites.

Figure 1. Schedule of events

Table 1. 50th centile for birth weight (BW) for boys and girls according to gestational age (GA)

GA (weeks)	Girls BW (kg)	Boys BW (kg)
23	0.550	0.600
24	0.650	0.700
25	0.775	0.800
26	0.850	0.900
27	0.975	1.050
28	1.100	1.150

Table 2. Infants < 26 weeks estimated dosing range, following 120mg vial of Curosurf

GA (weeks)	Girls BW (kg)	Dose (mg/kg)	Boys BW (kg)	Dose (mg/kg)
23	0.550	218	0.600	200
24	0.650	185	0.700	171
25	0.775	155	0.800	150

Table 3. Infants 26-28+6 weeks estimating dosing range, following 240mg vial Curosurf

GA (weeks)	Girls BW (kg)	Dose (mg/kg)	Boys BW (kg)	Dose (mg/kg)
26	0.850	282	0.900	267
27	0.975	246	1.050	229
28	1.100	218	1.150	209

References:

1. Avery ME, Mead J. Surface properties in relation to atelectasis and hyaline membrane disease. *AMA J Dis Child* 1959;97(5, Part 1):517-23. [published Online First: 1959/05/01]
2. Fujiwara T MH, Chida S, Morita T, Watabe Y, Abe T. Artificial surfactant therapy in hyaline-membrane disease. *Lancet (London, England)* 1980;1(8159):55-59.
3. Halliday HL. Surfactants: past, present and future. *Journal of perinatology : official journal of the California Perinatal Association* 2008;28 Suppl 1:S47-56. doi: 10.1038/jp.2008.50 [published Online First: 2008/06/18]
4. Enhorning G, Shennan A, Possmayer F, et al. Prevention of neonatal respiratory distress syndrome by tracheal instillation of surfactant: a randomized clinical trial. *Pediatrics* 1985;76(2):145-53. [published Online First: 1985/08/01]
5. Merritt TA, Hallman M, Bloom BT, et al. Prophylactic treatment of very premature infants with human surfactant. *The New England journal of medicine* 1986;315(13):785-90. doi: 10.1056/nejm198609253151301 [published Online First: 1986/09/25]
6. Hallman M, Merritt TA, Jarvenpaa AL, et al. Exogenous human surfactant for treatment of severe respiratory distress syndrome: a randomized prospective clinical trial. *J Pediatr* 1985;106(6):963-9. [published Online First: 1985/06/01]
7. Ten centre trial of artificial surfactant (artificial lung expanding compound) in very premature babies. Ten Centre Study Group. *British medical journal (Clinical research ed)* 1987;294(6578):991-6. [published Online First: 1987/04/18]
8. Avery ME, Tooley WH, Keller JB, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. *Pediatrics* 1987;79(1):26-30. [published Online First: 1987/01/01]
9. Van Marter LJ, Allred EN, Pagano M, et al. Do clinical markers of barotrauma and oxygen toxicity explain interhospital variation in rates of chronic lung disease? The Neonatology Committee for the Developmental Network. *Pediatrics* 2000;105(6):1194-201. doi: 10.1542/peds.105.6.1194 [published Online First: 2000/06/02]
10. Morley CJ, Davis PG, Doyle LW, et al. Nasal CPAP or intubation at birth for very preterm infants. *The New England journal of medicine* 2008;358(7):700-8. doi: 10.1056/NEJMoa072788 [published Online First: 2008/02/15]
11. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *The New England journal of medicine* 2010;362(21):1970-9. doi: 10.1056/NEJMoa0911783 [published Online First: 2010/05/18]
12. Dunn MS, Kaempf J, de Klerk A, et al. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. *Pediatrics* 2011;128(5):e1069-76. doi: 10.1542/peds.2010-3848 [published Online First: 2011/10/26]

13. Rojas-Reyes MX, Morley CJ, Soll R. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *The Cochrane database of systematic reviews* 2012(3):Cd000510. doi: 10.1002/14651858.CD000510.pub2 [published Online First: 2012/03/16]
14. Dargaville PA, Gerber A, Johansson S, et al. Incidence and Outcome of CPAP Failure in Preterm Infants. *Pediatrics* 2016;138(1) doi: 10.1542/peds.2015-3985 [published Online First: 2016/07/02]
15. Kelly MA, Finer NN. Nasotracheal intubation in the neonate: physiologic responses and effects of atropine and pancuronium. *The Journal of pediatrics* 1984;105(2):303-9. [published Online First: 1984/08/01]
16. Shangle CE, Haas RH, Vaida F, et al. Effects of endotracheal intubation and surfactant on a 3-channel neonatal electroencephalogram. *The Journal of pediatrics* 2012;161(2):252-7. doi: 10.1016/j.jpeds.2012.02.014 [published Online First: 2012/03/20]
17. Marshall TA, Deeder R, Pai S, et al. Physiologic changes associated with endotracheal intubation in preterm infants. *Critical care medicine* 1984;12(6):501-3. doi: 10.1097/00003246-198406000-00006 [published Online First: 1984/06/01]
18. Friesen RH, Honda AT, Thieme RE. Changes in anterior fontanel pressure in preterm neonates during tracheal intubation. *Anesthesia and analgesia* 1987;66(9):874-8. [published Online First: 1987/09/01]
19. Barrington KJ, Finer NN, Etches PC. Succinylcholine and atropine for premedication of the newborn infant before nasotracheal intubation: a randomized, controlled trial. *Critical care medicine* 1989;17(12):1293-6. doi: 10.1097/00003246-198912000-00009 [published Online First: 1989/12/01]
20. Parkin JL, Stevens MH, Jung AL. Acquired and congenital subglottic stenosis in the infant. *The Annals of otology, rhinology, and laryngology* 1976;85(5 Pt.1):573-81. doi: 10.1177/000348947608500503 [published Online First: 1976/09/01]
21. Jobe AH IM. Lung development and function in preterm infants in the surfactant treatment era. *Annu Rev Physiol* 2000;62(825-46)
22. Bjorklund LJ IJ, Curstedt T, John J, Robertson B, Werner O, Vilstrup CT. Manual ventilation with a few large breaths at birth compromises the therapeutic effect of subsequent surfactant replacement in immature lambs. *Pediatr Res* 1997;42(3):348-55.
23. More K, Sakhuja P, Shah PS. Minimally invasive surfactant administration in preterm infants: a meta-narrative review. *JAMA pediatrics* 2014;168(10):901-8. doi: 10.1001/jamapediatrics.2014.1148 [published Online First: 2014/08/05]
24. Berggren E, Liljedahl M, Winbladh B, et al. Pilot study of nebulized surfactant therapy for neonatal respiratory distress syndrome. *Acta paediatrica (Oslo, Norway : 1992)* 2000;89(4):460-4. [published Online First: 2000/06/01]
25. Finer NN MT, Bernstein G, Job L, Mazela J, Segal R. An open label, pilot study of Aerosurf combined with nCPAP to prevent RDS in preterm neonates. *J Aerosol Med Pulm Drug Deliv* 2010;23(5):303-09.
26. Minocchieri S, Berry CA, Pillow JJ. Nebulised surfactant to reduce severity of respiratory distress: a blinded, parallel, randomised controlled trial. *Archives of disease in childhood Fetal and neonatal edition* 2019;104(3):F313-f19. doi: 10.1136/archdischild-2018-315051 [published Online First: 2018/07/28]

27. Abdel-Latif ME, Osborn DA. Nebulised surfactant in preterm infants with or at risk of respiratory distress syndrome. *The Cochrane database of systematic reviews* 2012;10:Cd008310. doi: 10.1002/14651858.CD008310.pub2 [published Online First: 2012/10/19]
28. Gopel W, Kribs A, Ziegler A, et al. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. *Lancet (London, England)* 2011;378(9803):1627-34. doi: 10.1016/s0140-6736(11)60986-0 [published Online First: 2011/10/04]
29. Dargaville PA, Aiyappan A, De Paoli AG, et al. Minimally-invasive surfactant therapy in preterm infants on continuous positive airway pressure. *Archives of disease in childhood Fetal and neonatal edition* 2013;98(2):F122-6. doi: 10.1136/archdischild-2011-301314 [published Online First: 2012/06/12]
30. Kanmaz HG, Erdeve O, Canpolat FE, et al. Surfactant administration via thin catheter during spontaneous breathing: randomized controlled trial. *Pediatrics* 2013;131(2):e502-9. doi: 10.1542/peds.2012-0603 [published Online First: 2013/01/30]
31. Kribs A, Roll C, Gopel W, et al. Nonintubated Surfactant Application vs Conventional Therapy in Extremely Preterm Infants: A Randomized Clinical Trial. *JAMA pediatrics* 2015;169(8):723-30. doi: 10.1001/jamapediatrics.2015.0504 [published Online First: 2015/06/09]
32. Gopel W, Kribs A, Hartel C, et al. Less invasive surfactant administration is associated with improved pulmonary outcomes in spontaneously breathing preterm infants. *Acta paediatrica (Oslo, Norway : 1992)* 2015;104(3):241-6. doi: 10.1111/apa.12883 [published Online First: 2014/12/05]
33. Herting E, Kribs A, Hartel C, et al. Two-year outcome data suggest that less invasive surfactant administration (LISA) is safe. Results from the follow-up of the randomized controlled AMV (avoid mechanical ventilation) study. *European journal of pediatrics* 2020 doi: 10.1007/s00431-020-03572-0 [published Online First: 2020/02/19]
34. Klotz D, Porcaro U, Fleck T, et al. European perspective on less invasive surfactant administration-a survey. *European journal of pediatrics* 2017;176(2):147-54. doi: 10.1007/s00431-016-2812-9 [published Online First: 2016/12/13]
35. Beltempo M, Isayama T, Vento M, et al. Respiratory Management of Extremely Preterm Infants: An International Survey. *Neonatology* 2018;114(1):28-36. doi: 10.1159/000487987 [published Online First: 2018/04/16]
36. Heiring C, Jonsson B, Andersson S, et al. Survey shows large differences between the Nordic countries in the use of less invasive surfactant administration. *Acta paediatrica (Oslo, Norway : 1992)* 2017;106(3):382-86. doi: 10.1111/apa.13694 [published Online First: 2016/12/20]
37. Kurepa D, Perveen S, Lipener Y, et al. The use of less invasive surfactant administration (LISA) in the United States with review of the literature. *Journal of perinatology : official journal of the California Perinatal Association* 2019;39(3):426-32. doi: 10.1038/s41372-018-0302-9 [published Online First: 2019/01/13]
38. Rigo V, Lefebvre C, Broux I. Surfactant instillation in spontaneously breathing preterm infants: a systematic review and meta-analysis. *European journal of pediatrics* 2016;175(12):1933-42. doi: 10.1007/s00431-016-2789-4 [published Online First: 2016/09/30]

39. Isayama T, Iwami H, McDonald S, et al. Association of Noninvasive Ventilation Strategies With Mortality and Bronchopulmonary Dysplasia Among Preterm Infants: A Systematic Review and Meta-analysis. *Jama* 2016;316(6):611-24. doi: 10.1001/jama.2016.10708 [published Online First: 2016/08/18]
40. Aldana-Aguirre JC, Pinto M, Featherstone RM, et al. Less invasive surfactant administration versus intubation for surfactant delivery in preterm infants with respiratory distress syndrome: a systematic review and meta-analysis. *Archives of disease in childhood Fetal and neonatal edition* 2017;102(1):F17-f23. doi: 10.1136/archdischild-2015-310299 [published Online First: 2016/11/18]
41. Dargaville PA, Kamlin CO, De Paoli AG, et al. The OPTIMIST-A trial: evaluation of minimally-invasive surfactant therapy in preterm infants 25-28 weeks gestation. *BMC pediatrics* 2014;14:213. doi: 10.1186/1471-2431-14-213 [published Online First: 2014/08/29]
42. Attridge JT SC, Stukenborg GJ, Kattwinkel J. Administration of rescue surfactant by laryngeal mask airway: lessons from a pilot trial. *American journal of perinatology* 2013;30(3):201-06.
43. Barbosa RF, Simoes ESAC, Silva YP. A randomized controlled trial of the laryngeal mask airway for surfactant administration in neonates. *Jornal de pediatria* 2017;93(4):343-50. doi: 10.1016/j.jped.2016.08.007 [published Online First: 2017/01/29]
44. Roberts KD, Brown R, Lampland AL, et al. Laryngeal Mask Airway for Surfactant Administration in Neonates: A Randomized, Controlled Trial. *The Journal of pediatrics* 2018;193:40-46.e1. doi: 10.1016/j.jpeds.2017.09.068 [published Online First: 2017/11/28]
45. Abdel-Latif ME, Osborn DA. Laryngeal mask airway surfactant administration for prevention of morbidity and mortality in preterm infants with or at risk of respiratory distress syndrome. *The Cochrane database of systematic reviews* 2011(7):Cd008309. doi: 10.1002/14651858.CD008309.pub2 [published Online First: 2011/07/08]
46. Kattwinkel J, Robinson M, Bloom BT, et al. Technique for intrapartum administration of surfactant without requirement for an endotracheal tube. *Journal of perinatology : official journal of the California Perinatal Association* 2004;24(6):360-5. doi: 10.1038/sj.jp.7211103 [published Online First: 2004/04/16]
47. Lamberska T, Settelmayerova E, Smisek J, et al. Oropharyngeal surfactant can improve initial stabilisation and reduce rescue intubation in infants born below 25 weeks of gestation. *Acta paediatrica (Oslo, Norway : 1992)* 2018;107(1):73-78. doi: 10.1111/apa.14060 [published Online First: 2017/09/06]
48. Jobe A, Ikegami M, Jacobs H, et al. Surfactant and pulmonary blood flow distributions following treatment of premature lambs with natural surfactant. *The Journal of clinical investigation* 1984;73(3):848-56. doi: 10.1172/jci111280 [published Online First: 1984/03/01]
49. Cummings JJ, Holm BA, Nickerson PA, et al. Pre- versus post-ventilatory surfactant treatment in surfactant-deficient preterm lambs. *Reproduction, fertility, and development* 1995;7(5):1333-8. [published Online First: 1995/01/01]
50. Abdel-Latif ME, Osborn DA. Pharyngeal instillation of surfactant before the first breath for prevention of morbidity and mortality in preterm infants at risk of respiratory distress syndrome. *The Cochrane database of systematic reviews* 2011(3):Cd008311. doi: 10.1002/14651858.CD008311.pub2 [published Online First: 2011/03/18]

51. Enhorning G, Grossmann G, Robertson B. Pharyngeal deposition of surfactant in the premature rabbit fetus. *Biology of the neonate* 1973;22(1):126-32. [published Online First: 1973/01/01]
52. Enhorning G, Robertson B, Milne E, et al. Radiologic evaluation of the premature newborn rabbit after pharyngeal deposition of surfactant. *American journal of obstetrics and gynecology* 1975;121(4):475-80. [published Online First: 1975/02/15]
53. Kieran EA, O'Sullivan A, Miletin J, et al. 2% chlorhexidine-70% isopropyl alcohol versus 10% povidone-iodine for insertion site cleaning before central line insertion in preterm infants: a randomised trial. *Archives of disease in childhood Fetal and neonatal edition* 2018;103(2):F101-f06. doi: 10.1136/archdischild-2016-312193 [published Online First: 2017/10/28]
54. Stenke E, Kieran EA, McCarthy LK, et al. A randomised trial of placing preterm infants on their back or left side after birth. *Archives of disease in childhood Fetal and neonatal edition* 2016;101(5):F397-400. doi: 10.1136/archdischild-2015-309842 [published Online First: 2016/02/06]
55. Murphy MC, Heiring C, Doglioni N, et al. Effect of Needle Aspiration of Pneumothorax on Subsequent Chest Drain Insertion in Newborns: A Randomized Clinical Trial. *JAMA pediatrics* 2018;172(7):664-69. doi: 10.1001/jamapediatrics.2018.0623 [published Online First: 2018/05/26]

Procedures	Screening Screening	Allocation Day of Birth	Post-allocation 120 hours after birth	Close-out Discharge home
ENROLMENT				
Inclusion/Exclusion Criteria	X			
Informed consent	X			
Allocation		x		
INTERVENTIONS				
Oropharyngeal surfactant		x		
Standard care - CPAP		x		
ASSESSMENTS				
Baseline variables		x		
Primary outcome			x	
Other outcomes			x	x

Schedule of events

150x82mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title Page 1	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration P1, line 12	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version P1 line 15	3	Date and version identifier
Funding Pg 2 line 7	4	Sources and types of financial, material, and other support
Roles and responsibilities Page 1 Line 17 Page 2 + 3	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	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
	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)
Introduction		
Background and rationale Page 7	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
	6b	Explanation for choice of comparators
Objectives Page 9 Line 22	7	Specific objectives or hypotheses
Trial design Page 10 line 6	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting Page 10 Line 12	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
Eligibility criteria Page 10 Line 23	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions Page 15 Line 1	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	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)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes Page 11 Line 24	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
Participant timeline Page 10 Line 10 (Page 22 Line 15)	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)
Sample size Page 20 Line 7	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
Recruitment Page 12 Line 15	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation Page 15 Line 4	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

Allocation concealment mechanism Page 15 Line 15	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
Implementation Page 15 Line 14	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking) Page 15 Line 19	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods P17 Line 16	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
P19 Line 25	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
Data management Page 17 Line 22	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
Statistical methods P19 Line 2	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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	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)
Methods: Monitoring		
Data monitoring Page 21 Line 6	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

	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
Harms Page 20 Line 23	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing Page 17 Line 18	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval Page 22 Line 2 and Page 2 Line 20	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments Page 22 Line 6	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent Page 11 Line 10	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality Page 17 Line 24	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests Page 2 Line 7	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data Page 3 Line 16	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care N/A	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy Page 22 Line 2 Page 18 Line 6	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
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Study protocol for the POPART study – Prophylactic Oropharyngeal surfactant for Preterm infants: A Randomised Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035994.R2
Article Type:	Protocol
Date Submitted by the Author:	07-Apr-2020
Complete List of Authors:	murphy, madeleine; National Maternity Hospital, Neonatology; National Children's Research Centre, National Children's Research Centre, Our Lady's Children's Hospital Galligan, Marie; University College Dublin School of Medicine and Medical Science, School of Medicine Molloy, Brenda; University College Dublin School of Medicine and Medical Science, School of Medicine Hussain, Rabia; University College Dublin School of Medicine and Medical Science, School of Medicine Doran, Peter; University College Dublin School of Medicine and Medical Science, School of Medicine ODonnell, Colm; The National Maternity Hospital, Dublin, Ireland, Neonatal Intensive Care Unit
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Research methods, Paediatrics
Keywords:	NEONATOLOGY, PAEDIATRICS, PERINATOLOGY

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

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

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

Study protocol for the POPART study – Prophylactic Oropharyngeal surfactant for Preterm infants: A Randomised Trial

Madeleine C. Murphy,[1-3] Marie Galligan,[3] Brenda Molloy,[3] Rabia Hussain,[3] Peter Doran,[3] Colm P.F. O'Donnell[1-3]

1. National Maternity Hospital, Dublin, Ireland
2. National Children's Research Centre, Dublin, Ireland
3. School of Medicine, University College Dublin, Ireland

Word count 4308 Abstract 318 Figures/Tables 4 References 55

Trial registration

Protocol identification (code or reference number): UCDCRC/16/003

EudraCT number: 2016-004198-41

Protocol version 2.0, dated 19.07.19

Trial sponsor

University College Dublin

Corresponding Author

Address Prof. Colm O'Donnell, Department of Neonatology, National Maternity Hospital, Holles Street, Dublin 2, Ireland

Tel +353 1 6373100

Email codonnell@nmh.ie

Key words: Infant, newborn; oropharyngeal surfactant; respiratory distress syndrome; intubation; randomised controlled trial

Author Contributions: COD conceived and designed the trial protocol, co-wrote the first draft and revised the manuscript for intellectual content. MCM helped design the trial protocol, co-wrote the first draft and revised the manuscript for intellectual content. MG, BM, RH, and PD helped design the trial protocol and revised the manuscript for intellectual content. MG designed the statistical analysis plan. All authors approved the final manuscript prior to submission.

Funding:

Chiesi Farmaceutici, manufacturers of poractant alfa (Curosurf), supply the study drug free of charge; they had no role in study design; have no role in study conduct; and will have no role in data collection, analysis or interpretation. Further, they will have no role in the decision to present, publish or otherwise report results.

Madeleine Murphy is the recipient of a Clinical Research Fellowship by the National Children's Research Centre, Dublin (R17637)

Pediatric Clinical Research Infrastructure Network (PedCRIN), a Project of the European Union Horizon 2020 programme designed to support the extension of clinical drug trials in children throughout Europe, also support the study.

Competing interests: None declared

Ethics approval:

Ireland: Research Ethics Committee, The National Maternity Hospital, Dublin, Ireland; Research Ethics Committee, Coombe Women and Infants University Hospital

Belgium: Le Comité d'Ethique du CHR Citadelle

Czech Republic: Etická komise, Všeobecné fakultní nemocnice (VFN) v Praze (Ethics Committee of the General University Hospital, Prague)

Norway: Regional komité for medisinsk og helsefaglig forskningsetikk (REK nord) (Regional Ethics Committee, REK, nord)

Portugal: Comissão de Ética para a Investigação Clínica, CEIC (National Ethics Committee for Clinical Research)

Sweden: Stockholm Regional Ethics Review Board

Acknowledgements: We would like to acknowledge the administrative staff at UCD for their advice, and support with the trial thus far. We wish to thank the members of PedCRIN and the Principal Investigators and members of the Clinical Trials Units at all our European sites for facilitating extension of our trial to Europe. POPART Trial Investigators: Jan Miletin, Coombe Women and Infants University Hospital, Dublin, Ireland; Claus Klingenberg, University Northern Norway, Tromsø, Norway; Hans Jørgen Guthe, Haukeland University Hospital, Bergen, Norway; Richard Plavka, Charles University, Prague, Czech Republic; Tomas Juren, University Hospital Brno, Brno, Czech Republic; Vincent Rigo, Le Centre Hospitalier Universitaire, Liege, Belgium; Kajsa Bohlin, Karolinska Institutet, Stockholm, Sweden; and Almerinda Pereira, Hospital de Braga, Braga, Portugal.

Data statement: Members of the Trial Steering Committee will have access to the final dataset. Data will be available on request.

Abstract

Introduction: Many preterm infants develop respiratory distress syndrome (RDS), a condition characterised by a relative lack of surfactant. Endotracheal surfactant therapy revolutionised the care of preterm infants in the 1990s. However, supporting newborns with RDS with continuous positive airway pressure (CPAP) and reserving endotracheal surfactant for those who develop respiratory failure despite CPAP yields better results than intubating all infants for surfactant. Half of preterm infants born before 29 weeks' gestation initially managed with CPAP are intubated for surfactant. Intubation is difficult to learn and associated with adverse effects. Surfactant administration into the oropharynx has been reported in preterm animals and humans and may be effective. We wished to determine whether giving oropharyngeal surfactant at birth reduces the rate of endotracheal intubation for respiratory failure in preterm infants within 120 hours of birth.

Methods and analysis: POPART (Prophylactic Oropharyngeal surfactant for Preterm infants: A Randomised Trial) is an investigator-led, unblinded, multicentre, randomised, parallel group, controlled trial. Infants are eligible if born at a participating centre before 29 weeks gestational age (GA) and there is a plan to offer intensive care. Infants are excluded if they have major congenital anomalies. Infants are randomised at birth to treatment with oropharyngeal surfactant [120mg vial <26 weeks GA stratum; 240mg vial 26 – 28+6 weeks GA stratum] in addition to CPAP or CPAP alone. The primary outcome is intubation within 120 hours of birth, for bradycardia and/or apnoea despite respiratory support in the delivery room or respiratory failure in the intensive care unit. Secondary outcomes include incidence of mechanical ventilation, endotracheal surfactant use, chronic lung disease, and death before hospital discharge.

Ethics and dissemination: Approval for the study has been granted by the Research Ethics Committees at the National Maternity Hospital, Dublin, Ireland (EC31.2016), and at each

participating site. The trial is being conducted at 9 centres in 6 European countries. The study results will be submitted for publication in a peer-reviewed journal.

Article summary

Strengths and limitations of this study

- This is the first randomised study to specifically examine the efficacy of giving oropharyngeal surfactant at birth to preterm infants at high risk of developing respiratory distress syndrome.
- We are enrolling infants < 29 weeks' gestation, including infants at 23 and 24 weeks' gestation, who are most at risk of respiratory distress syndrome.
- We were unable to credibly mask the intervention.
- To reduce the risk of bias we used objective criteria for our primary outcome i.e. intubation within 120 hours of life.
- The multicentre nature of this study will increase the generalisability of its findings.

Background

Respiratory distress syndrome (RDS) is a lung condition of the preterm infant. The risk of RDS is inversely related to gestational age (GA). Infants with RDS have structural and functional immaturity of their lungs. They also have a relative lack of surfactant,[1] an endogenously produced substance that enables alveoli to expand more easily to recruit and maintain gas within the lung.

Exogenous surfactant[2 3] is frequently used to treat newborns with RDS and has led to improved outcomes for infants worldwide. Randomised controlled trials (RCTs) in the 1980s – 1990s[4-7] demonstrated that surfactant, given by endotracheal tube (ETT), reduced mortality and air leak among premature infants who were intubated for respiratory failure due to RDS. This led to the widespread practice of intubating all extremely preterm infants for surfactant and ventilation ("prophylactic surfactant").[5] Prior to the introduction of surfactant into clinical practice, concerns were raised that premature infants who were intubated for respiratory support had worse respiratory outcomes than infants who were managed with the non-invasive respiratory support, nasal continuous positive airway pressure (CPAP).[8] These concerns persisted after the widespread introduction of surfactant.[9] Multicentre RCTs found that starting infants on CPAP may be beneficial when compared with intubation and positive pressure ventilation (PPV); the studies reported decreased duration of mechanical ventilation with potential benefits of reduction of death and or bronchopulmonary dysplasia (BPD).[10-12] Managing premature newborns initially with CPAP and reserving intubation, mechanical ventilation and surfactant for those infants with worsening respiratory failure despite CPAP yields better results than intubating all infants for surfactant administration.[13] About half of premature infants born before 29 weeks' gestation initially managed with CPAP for RDS are ultimately intubated for surfactant and ventilation.[14]

Intubation is a procedure that is difficult to learn and is associated with adverse effects, both short[15-19] and longer-term.[20-22] This has led many clinicians to investigate alternative methods of surfactant delivery.[23] Giving nebulised surfactant to spontaneously breathing infants has met with limited success.[24-27] Progress has been slow due to the technical difficulties encountered in aerosolising such large molecules, the expense of the equipment needed to do so and the cost of the large amount of surfactant needed to form an aerosol. Interest has largely focussed on less-invasive methods of surfactant administration.

Less invasive surfactant administration (LISA) techniques involve introducing either a feeding tube or vascular catheter into the trachea of a spontaneously breathing infant at laryngoscopy.[28-31] LISA is associated with lower rates of mechanical ventilation among preterm infants in randomised[28 31] and observational studies.[32] Two year follow up outcomes for infants enrolled in the randomised trial Avoid Mechanical Ventilation,[28] where infants were randomised to surfactant via LISA or to standard care with CPAP and ET instillation of surfactant if necessary, are similar between groups.[33] The procedure is becoming more widely used, but rates vary between countries.[34-37] Concerns regarding the validity and risk of bias within studies, a lack of familiarity with the technique, and patient discomfort have been reported as reasons for not using LISA.[36] Use of sedation and analgesia prior to laryngoscopy is not standard for the LISA procedure,[28] and the short-term adverse effects of laryngoscopy are not avoided. While meta-analyses report that the LISA technique is associated with less death or BPD,[38-40] further RCTs are needed. The Optimist-A trial,[41] evaluating minimally invasive surfactant therapy in preterm infants born between 25 – 28 weeks' gestation is ongoing.

The laryngeal mask airway, a supraglottic airway device, may be used as an interface to deliver surfactant.[42-45] However there is currently no device available for use in very low birth weight infants, who constitute the majority of infants diagnosed with RDS.

Direct administration of surfactant into the pharynx of human infants has been described in randomised[7] and prospective cohort studies.[46 47] It is apparently effective and is an easier technique

to perform than endotracheal intubation or passing a feeding tube or vascular catheter into the trachea. Advantages of pharyngeal surfactant use are that it is an easy and cheaper method of administering surfactant and likely causes less discomfort to infants as it avoids the use of a laryngoscope. Giving surfactant early, prior to ventilation, delivers surfactant to a fluid-filled lung, which is spread via a fluid-air interface when the infant starts breathing. Animal studies report that surfactant is distributed more uniformly,[48] and lung function and compliance is better[49] if surfactant is delivered prior to ventilation. If shown to be effective, it may reduce the adverse effects, and additional associated costs, of ventilation.

A Cochrane review of pharyngeal surfactant[50] did not identify any eligible trials to assess whether pharyngeal installation of surfactant before the first breath prevented morbidity and mortality in infants at risk of RDS. The Ten Centre Study randomised 328 infants born between 25 – 29 weeks' gestation to artificial surfactant therapy or saline. For those randomised to surfactant therapy, the first dose was given via the oropharynx, with subsequent doses given via an ETT if the infant was intubated, however the outcomes of infants who received pharyngeal surfactant alone were not reported. Large well conducted RCTs are needed, due to the evidence from animal[51 52] and observational human studies[46 47] suggesting that pharyngeal surfactant administration is potentially safe, feasible, and may be effective.

Objective

We are performing a study to establish whether giving preterm infants surfactant into their oropharynx at birth in addition to CPAP compared with CPAP alone reduces their need for subsequent intubation in the first 5 days of life.

Methods

Trial design

The POPART trial is an investigator-led, unblinded, multicentre, randomised parallel-group controlled trial. It aims to determine whether administering oropharyngeal surfactant to premature infants at birth in addition to CPAP compared to CPAP alone reduces the rate of intubation for respiratory failure in the first 5 days of life. The trial will recruit 250 infants born <29 weeks GA at participating centres. A schedule of events is seen in figure 1.

Setting

The trial is being conducted at 9 neonatal intensive care units (NICUs) in 6 European countries [Ireland (National Maternity Hospital (NMH), Dublin; Coombe Women and Infants University Hospital (CWIUH) Dublin); Norway (University Northern Norway, Tromsø; Haukeland University Hospital, Bergen); Czech Republic (Charles University, Prague; University Hospital Brno, Brno), Belgium (Le Centre Hospitalier Universitaire (CHU), Liege); Sweden (Karolinska Institutet, Stockholm); and Portugal (Hospital de Braga, Braga).

Participants

Inclusion and exclusion criteria

Trial subjects are premature infants at risk of RDS. Infants born less than 29 weeks GA are included if the treating physician plans to offer intensive care. Infants are excluded if they have major congenital anomalies (including neural tube defects, major structural cardiac anomalies (excluding patent ductus arteriosus, ventricular septal defect, atrioventricular septal defect), abdominal wall

defects, congenital diaphragmatic hernia and major dysmorphic features with an abnormal karyotype) and if the treating physician does not plan to offer intensive care. If there is a known anomaly prenatally, families are not approached for consent. In the event of a postnatal diagnosis of the aforementioned conditions, these infants meet criteria for post-randomisation exclusion. Written informed consent from parent/legal guardian(s) is obtained before delivery. Infants of multiple gestation and of either sex are eligible to be enrolled.

Screening and consent

Prior to the delivery a member of the research team or other senior doctor approaches parent(s)/guardian(s) of eligible infants to inform them about the study. The team member explains the purpose and nature of the study and provides written information for the parent(s)/guardian(s) to keep. If the local language is not their first language, they are offered the opportunity to have an interpreter present while the study is explained. Written consent for enrolment of the infant in the study is then sought. Parents are informed that they may withdraw their child from the study at any time should they so wish; and that a decision not to consent to their infants' participation in the study or to withdraw their infant from the study once enrolled does not affect their infant's access to the best available treatment and care.

Outcome measures

Primary outcome

The primary outcome is the incidence of endotracheal intubation for respiratory failure within 120 hours of birth. Enrolled infants are intubated for persistent apnoea and/or bradycardia (HR <100bpm) in the delivery room (DR), or for respiratory failure in the NICU defined as ≥ 2 of:

- Clinical signs – worsening tachypnoea; grunting; subcostal, intercostal and/or sternal recession
- Acidosis – pH < 7.2 on 2 blood gases (arterial or capillary) ≥ 30 minutes apart
- Hypoxaemia – FiO_2 > 0.4 to keep oxygen saturation (SpO_2) ≥ 90% for > 30 minutes
- Hypercarbia – PCO_2 > 9.0 kPa on 2 blood gases (arterial or capillary) ≥ 30 minutes apart
- Apnoea – recurrent apnoea treated with mask ventilation

The primary outcome is intubation within 120 hours of birth. For the purpose of the primary outcome, infants are recorded as 'yes' if they were intubated, briefly intubated for surfactant administration e.g. INSURE, and brief tracheal catheterisation for surfactant administration e.g. LISA technique.

We record the treatment plan at the time of intubation. We record whether there is a) a plan for intubation with endotracheal tube, surfactant administration, and continued ventilation; b) a plan for "INSURE" – intubation with ETT, surfactant administration, and immediate (<30 minute) extubation; c) a plan for surfactant administration using LISA technique – surfactant administration through a thin endotracheal catheter; or d) other

We acknowledge that not all infants achieving ≥ 2 of the intubation indicators may be intubated.

Secondary outcomes

The secondary outcomes are as follows:

1. Intubation in the DR
2. Number of attempts taken to successfully intubate in the DR
3. Chest compressions in the DR

4. Adrenaline administration in the DR
5. Rectal temperature on admission to the NICU
6. NICU intubation
7. Surfactant use before death or hospital discharge
    a. Number of doses, and total dose
    b. Intra-tracheal surfactant received post-intervention
    c. Doses of post-intervention surfactant
8. Respiratory distress syndrome
    a. Clinical evidence and radiological evidence of respiratory distress at the time of first intubation
9. Incidence of pneumothorax
    a. Incidence of pneumothorax on chest x-ray
    b. Pneumothorax treated with needle aspiration or chest drain insertion
10. Incidence of pulmonary haemorrhage
    a. Clinical evidence of pulmonary haemorrhage
11. Mechanical ventilation
12. Days of mechanical ventilation
13. Use of postnatal corticosteroids for ventilator dependence
14. Days of duration of respiratory support (endotracheal ventilation, high-frequency oscillatory ventilation, CPAP, heated humidified high-flow nasal cannula O_2, low flow nasal cannula O_2)
15. BPD – supplemental O_2 at 28 days of life
16. Chronic lung disease of prematurity (CLD) –O_2 treatment at 36 weeks corrected GA; we are also recording physiological BPD as determined by physiological oxygen reduction test
17. Medical treatment for a patent ductus arteriosus (PDA)
    a. Administration of ibuprofen or paracetemol for PDA
18. Surgical treatment for a PDA

19. Proven necrotising enterocolitis (≥ Bell's stage 2)
20. Incidence of Intraventricular haemorrhage (IVH) (any and severe: IVH grade ≥ 3)
    a. Evidence on surveillance cranial ultrasounds performed as standard of care
21. Incidence of cystic periventricular leukomalacia
    a. Evidence on surveillance cranial ultrasounds performed as standard of care
22. Retinopathy of prematurity treated with laser photocoagulation or intravitreal injections
    a. Evidence on surveillance ophthalmology review performed as standard of care
23. Death before hospital discharge
24. Survival without BPD at hospital discharge
25. Survival without CLD at hospital discharge
26. Duration of first hospitalisation
27. Use of home oxygen therapy
    a. Discharged home on oxygen therapy

Investigational medicinal product (IMP)

Poractant alfa (Curosurf, Chiesi Farmaceutici, Parma, Italy) is a natural surfactant prepared from porcine lungs. It is licensed for ET use and administration via thin catheter for the prevention and treatment of RDS in preterm infants. The dosing recommendations for treatment with Curosurf when given by ETT are 200mg/kg for established RDS and 100 – 200mg/kg for prophylaxis. Further doses of 100mg/kg Curosurf may be given to infants who have persistent respiratory distress despite treatment with surfactant (maximum recommended dose 400mg/kg). It is currently not licensed for oropharyngeal administration, and therefore this study is examining the off-label use of a licensed product. The timing or dosage of ET surfactant is not be affected by oropharyngeal surfactant. If an infant is felt to need ET surfactant following initial oropharyngeal administration, then they receive

the standard initial dose via ETT. Additional doses are given at the discretion of the attending physician.

Randomisation

Infants are randomised (1:1) to receive oropharyngeal surfactant in addition to CPAP or CPAP alone using variable block randomisation, with block sizes of 4, 6 and 8. Randomisation is stratified by participating centre and GA (<26 weeks and 26-28^{+6} weeks inclusive). Infants of multiple gestations are randomised as individuals.

A computer-generated randomisation schedule using sequential 6-digit randomisation codes was prepared by an independent statistician who was not be involved with subsequent data analysis or interpretation and stored securely on a password-protected computer. Each participating centre is provided with two separate boxes for the two GA strata with consecutively numbered, sealed opaque randomisation envelopes containing the assigned treatment allocation. The boxes containing the envelopes are stored securely in the NICU. An envelope from the appropriate box is opened immediately before birth.

Blinding

This is an open-label study. The study is not blinded to investigators, subjects, or medical or nursing staff. We are not using a placebo, and in the event of the infant being randomised to the 'CONTROL' arm, then they will be commenced on CPAP immediately after birth. The trial statistician will be blinded for data analysis and will be kept unaware of treatment group assignments. We defined objective criteria for the primary outcome to minimise potential bias.

Intervention arm: Oropharyngeal surfactant

Infants randomised to oropharyngeal surfactant receive a dose of poractant alfa (Curosurf, Chiesi Farmaceutici, Parma, Italy) immediately after birth, ideally before the cord is clamped e.g. 60 seconds, and are then commenced on CPAP as per routine practice. If it is given after the cord is clamped, it is given once the infant is placed on the resuscitaire. It is given within 5 minutes of birth in all cases. We are recording the timing of cord clamping for all patients.

The surfactant is warmed prior to being drawn up in a sterile syringe as per manufacturer's recommendation. Surfactant is administered by opening the mouth gently and giving the surfactant as a single bolus into the oropharynx using a thin flexible catheter attached to the syringe.

Infants are not weighed prior to enrolment. The 50th centile for birth weight (BW) for boys and girls according to GA is shown in table 1. In our study, infants < 26 weeks receive a full 120mg vial of Curosurf. We estimate that this provides dosing in the range as indicated in table 2. In our study, infants 26 – 28 weeks receive a full 240mg vial of Curosurf, and we estimate that this provides dosing in the range as indicated in table 3.

Control group: CPAP

Infants randomised to the control group do not have anything injected into their oropharynx and are stabilised on CPAP in the DR as per routine practice.

Clinical management

After the initial intervention, infants then receive standard care with CPAP, regardless of their group assignment. DR care is carried out by the neonatal team who are trained in neonatal resuscitation as per the recommendations of the International Liaison Committee on Resuscitation (ILCOR). Infants in both groups are intubated in the DR for persistent apnoea and/or bradycardia despite PPV by mask as per ILCOR recommendations. Infants are not intubated in the DR solely for surfactant administration. All other aspects of neonatal intensive care is at the discretion of the treating physicians. Infants in both groups are treated equally. The frequency of blood gas monitoring is based on the decision of the treating physician. Enrolled infants are intubated if they reach the pre-determined criteria for respiratory failure. After giving endotracheal surfactant for the treatment of RDS, attending clinicians may attempt to extubate the babies immediately or they may elect to ventilate the babies for a longer period at their discretion.

Data management

Data is collected by the on-site investigators from the patient's clinical notes. This is recorded on a data worksheet and transferred to an electronic Case Report Form (CRF) to be stored in a secure, dedicated, password-protected electronic database. The clinical study monitor and representative of the regulatory authority can directly access source documents for comparison of such data with the data in the electronic CRFs and can verify that the study is carried out in compliance with the protocol and local regulatory requirements.

The investigators adheres to national and hospital protocols on data use and storage. Data is coded. It is stored in a locked filing cabinet then uploaded onto a password-protected computer in a locked office. Documents are stored safely in confidential conditions. On all study-specific documents other than the signed consent, the subject is referred to by the study subject identification code.

Description of statistical methods

Trial results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT). The flow of patients through the trial will be represented on a CONSORT flow diagram, and the number included in the primary and secondary analyses as well as all reasons for exclusions will be reported per trial arm. Analysis of efficacy endpoints will be carried-out following the Intention-To-Treat principle. A Per-Protocol analysis will also be carried out on the primary endpoint, excluding infants with incomplete data on the primary outcome and infants with any major protocol deviations.

Demographic and baseline data will be summarised by treatment group to evaluate comparability.

Primary outcome analysis

The primary outcome will be summarised per group. Ratios of relative risk will be reported with 95% confidence intervals. A two-sided, two-proportion Z test will be carried out to investigate whether the rate of endotracheal intubation differs between intervention and standard-of-care. This analysis will be carried out both on the intention-to-treat set and on the per protocol set.

A completing risks model will be fitted to investigate the effect of the intervention on the primary endpoint, adjusting for competing outcomes (e.g. mortality) that may impact on observation of the primary endpoint.

The sensitivity of the estimated intervention effect to measured covariates of interest, including centre, GA, birth weight, gender, mode of delivery and antenatal corticosteroid treatment, will be evaluated with regression analysis.

Secondary outcome analysis

Categorical outcomes will be summarised per treatment group, with between-group differences expressed as a relative risk with 95% confidence intervals. A two-sided, two-proportion Z test will be carried out for each categorical outcome to investigate whether the proportion differs between intervention and standard of care. For the important secondary endpoint of death before hospital discharge, regression analysis will be employed to determine sensitivity of the estimated intervention effect to potentially relevant covariates (as specified above for the primary outcome).

Numeric secondary outcomes will be summarised by treatment group and between-group differences will be presented with a 95% confidence interval. A superiority hypothesis test will be carried out to test for a difference in the outcome between control and intervention, using a t-test or a Mann-Whitney U test where relevant.

Subgroup analyses

Subgroups of interest include infants of different gestational age strata (e.g. less than 26 weeks, and 26-28 weeks' gestation at birth), and infants from different participating centres. Subgroup analysis of the primary outcome and the important secondary outcome of death before hospital discharge will be carried out by regression modelling to determine differences in the intervention effect for infants of different GA strata, and infants from different participating centres.

Missing data

Any missing data or data anomalies will be communicated to the study site(s) for prompt clarification and resolution. For outcomes missing more than 5% of data in either treatment group, missing data methods will be employed in analysis. For categorical outcomes with censored data, Kaplan-Meier analyses will be used to estimate treatment effect. For other missing data, a suitable imputation method will be selected during blind review of the data.

Sample size and power

The sample size calculation assumed a rate of endotracheal intubation of 46% for infants treated with CPAP alone, and a rate of 28% for infants receiving oropharyngeal surfactant and CPAP. The former was informed by published RCTs showing a rate of mechanical ventilation in the days after birth among preterm infants treated with CPAP alone from 40– 60%[10-12] and rates of CPAP failure of 43% reported in a cohort of preterm infants 25 – 28 weeks' gestation initially commenced on CPAP.[14] The latter was informed by a cohort of infants born 26 – 28 weeks' gestation reporting that minimally invasive surfactant techniques reduced the rate of mechanical ventilation to from 46% to 28%.[28] Sample size was calculated in G*power based on a two-sided, two-proportion Z test. A sample size of 125 infants per arm will be required to give a statistical power of 80% at a significance level of 5%, adjusted for an anticipated death rate of 10% (estimated from local data (NMH, Neonatal Clinical Report, 2015).

Safety analyses

Adverse events following administration of oropharyngeal surfactant will be documented. Safety analyses will be carried out on the Safety Set, defined as patients in the intervention arm who received oropharyngeal surfactant and patients who received CPAP only. The frequency of adverse events and the number and percentage of infants reported as having at least one emergent adverse

event, will be reported by system organ class and preferred term, by treatment received. The same description will be performed for serious adverse events (SAE), severe AE, AE treatment-related and AE leading to IMP withdrawal. Defined SAEs for the study are important medical events, and death before hospital discharge.

Safety monitoring and interim analysis

A data safety monitoring board (DSMB) will be established to perform ongoing safety surveillance and to perform interim analyses on the study data. The DSMB will be an independent committee, composed of a minimum of three members; at least two will be clinicians with expertise in clinical trials; at least one member will be a clinician with expertise in neonatology. They will not be blinded to the intervention groups.

The DSMB will meet on a 6-monthly basis after start of the trial and will review the frequency and severity of AEs in both treatment groups. If they observe any significant excess of SAEs in the intervention group associated with the intervention, they may recommend premature termination of the trial on the basis of safety concerns.

The DSMB will conduct interim analysis to determine whether the data provide overwhelming evidence of efficacy or futility, defined as a highly statistically significant difference in the primary outcome or a highly statistically significant difference in the important secondary outcome of death before hospital discharge. The type I error rate for interim analysis will be set to 0.001 in accordance with the Haybittle-Peto stopping boundary. For final analysis, the type I error rate will remain at 0.05. Interim analysis will be carried out after approximately 50% of participants (n=126) have completed the study. The DSMB may recommend early termination of the trial due to efficacy or futility; or for unanticipated concerns for the safety of enrolled infants. Standard procedures for

reporting AEs will be used in accordance with Good Clinical Practice guidelines.

Ethics and dissemination

The study was initially approved by the Research Ethics Committee at NMH, Dublin, and the Health Products Regulatory Authority of Ireland. Approval was also obtained at the research ethics committees at each participating site and at the relevant competent authority for each participating country. All bodies are informed in writing of any substantial changes to the protocol, prior to any such changes being implemented. University College Dublin, Ireland is the sponsor for this study.

Patient and public involvement (PPI)

We liaised with the Irish Neonatal Health Alliance for assistance when designing the parent information leaflet and consent form. Parent focus groups were held via Pediatric Clinical Research Infrastructure Network (PedCRIN) prior to expansion of the study to European sites.

Recruitment

The National Maternity Hospital is a stand-alone university maternity hospital with a tertiary NICU to which >150 infants <1500g are admitted annually. Approximately 60 babies <29 weeks' gestation are admitted annually. Though the enrolment rates to our studies amongst eligible infants are consistently excellent (> 80%), we believe it is necessary to enrol infants at multiple sites in order to enrol our planned target sample of 250 infants in a timely fashion. We have a track record enlisting the help of collaborators nationally[53] and internationally[54 55] to perform our studies. We believe that with their help, we can enrol these infants in 3 years.

Current status

The trial began recruitment in December 2017, with additional sites joining subsequently. It is currently recruiting in 9 centres in 6 European countries. It is expected that recruitment for the study will be completed by December 2020.

Publication of results

The authors intend to publish the results of this trial in a high-quality, peer-reviewed journal upon completion of data collection and analysis.

Discussion

Oropharyngeal surfactant given immediately after birth to preterm infants at risk of RDS has the potential to reduce the risk of intubation and ventilation. Endotracheal intubation is invasive and unpleasant for newborns that is associated with adverse short- and long-term effects. It is also a skill that is difficult for clinicians to learn and maintain. In contrast, giving surfactant into the oropharynx is easy and avoids the adverse effects associated with intubation. There is evidence from animal studies and from case series in humans that it may be effective. This is an attractive proposition, because it could avoid harms associated with intubation for babies and raises the possibility of giving surfactant in contexts where it is not currently feasible (e.g. non-tertiary settings, developing countries). We were unable to credibly mask the intervention and acknowledge this lack of blinding as a limitation of the study. We tried to minimise potential bias by setting predefined objective treatment failure criteria, which were agreed on by all participating sites.

Figure 1. Schedule of events

Table 1. 50th centile for birth weight (BW) for boys and girls according to gestational age (GA)

GA (weeks)	Girls BW (kg)	Boys BW (kg)
23	0.550	0.600
24	0.650	0.700
25	0.775	0.800
26	0.850	0.900
27	0.975	1.050
28	1.100	1.150

Table 2. Infants < 26 weeks estimated dosing range, following 120mg vial of Curosurf

GA (weeks)	Girls BW (kg)	Dose (mg/kg)	Boys BW (kg)	Dose (mg/kg)
23	0.550	218	0.600	200
24	0.650	185	0.700	171
25	0.775	155	0.800	150

Table 3. Infants 26-28+6 weeks estimating dosing range, following 240mg vial Curosurf

GA (weeks)	Girls BW (kg)	Dose (mg/kg)	Boys BW (kg)	Dose (mg/kg)
26	0.850	282	0.900	267
27	0.975	246	1.050	229
28	1.100	218	1.150	209

References:

1. Avery ME, Mead J. Surface properties in relation to atelectasis and hyaline membrane disease. *AMA J Dis Child* 1959;97(5, Part 1):517-23. [published Online First: 1959/05/01]
2. Fujiwara T MH, Chida S, Morita T, Watabe Y, Abe T. Artificial surfactant therapy in hyaline-membrane disease. *Lancet (London, England)* 1980;1(8159):55-59.
3. Halliday HL. Surfactants: past, present and future. *Journal of perinatology : official journal of the California Perinatal Association* 2008;28 Suppl 1:S47-56. doi: 10.1038/jp.2008.50 [published Online First: 2008/06/18]
4. Enhorning G, Shennan A, Possmayer F, et al. Prevention of neonatal respiratory distress syndrome by tracheal instillation of surfactant: a randomized clinical trial. *Pediatrics* 1985;76(2):145-53. [published Online First: 1985/08/01]
5. Merritt TA, Hallman M, Bloom BT, et al. Prophylactic treatment of very premature infants with human surfactant. *The New England journal of medicine* 1986;315(13):785-90. doi: 10.1056/nejm198609253151301 [published Online First: 1986/09/25]
6. Hallman M, Merritt TA, Jarvenpaa AL, et al. Exogenous human surfactant for treatment of severe respiratory distress syndrome: a randomized prospective clinical trial. *J Pediatr* 1985;106(6):963-9. [published Online First: 1985/06/01]
7. Ten centre trial of artificial surfactant (artificial lung expanding compound) in very premature babies. Ten Centre Study Group. *British medical journal (Clinical research ed)* 1987;294(6578):991-6. [published Online First: 1987/04/18]
8. Avery ME, Tooley WH, Keller JB, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. *Pediatrics* 1987;79(1):26-30. [published Online First: 1987/01/01]
9. Van Marter LJ, Allred EN, Pagano M, et al. Do clinical markers of barotrauma and oxygen toxicity explain interhospital variation in rates of chronic lung disease? The Neonatology Committee for the Developmental Network. *Pediatrics* 2000;105(6):1194-201. doi: 10.1542/peds.105.6.1194 [published Online First: 2000/06/02]
10. Morley CJ, Davis PG, Doyle LW, et al. Nasal CPAP or intubation at birth for very preterm infants. *The New England journal of medicine* 2008;358(7):700-8. doi: 10.1056/NEJMoa072788 [published Online First: 2008/02/15]
11. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *The New England journal of medicine* 2010;362(21):1970-9. doi: 10.1056/NEJMoa0911783 [published Online First: 2010/05/18]
12. Dunn MS, Kaempf J, de Klerk A, et al. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. *Pediatrics* 2011;128(5):e1069-76. doi: 10.1542/peds.2010-3848 [published Online First: 2011/10/26]

13. Rojas-Reyes MX, Morley CJ, Soll R. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *The Cochrane database of systematic reviews* 2012(3):Cd000510. doi: 10.1002/14651858.CD000510.pub2 [published Online First: 2012/03/16]
14. Dargaville PA, Gerber A, Johansson S, et al. Incidence and Outcome of CPAP Failure in Preterm Infants. *Pediatrics* 2016;138(1) doi: 10.1542/peds.2015-3985 [published Online First: 2016/07/02]
15. Kelly MA, Finer NN. Nasotracheal intubation in the neonate: physiologic responses and effects of atropine and pancuronium. *The Journal of pediatrics* 1984;105(2):303-9. [published Online First: 1984/08/01]
16. Shangle CE, Haas RH, Vaida F, et al. Effects of endotracheal intubation and surfactant on a 3-channel neonatal electroencephalogram. *The Journal of pediatrics* 2012;161(2):252-7. doi: 10.1016/j.jpeds.2012.02.014 [published Online First: 2012/03/20]
17. Marshall TA, Deeder R, Pai S, et al. Physiologic changes associated with endotracheal intubation in preterm infants. *Critical care medicine* 1984;12(6):501-3. doi: 10.1097/00003246-198406000-00006 [published Online First: 1984/06/01]
18. Friesen RH, Honda AT, Thieme RE. Changes in anterior fontanel pressure in preterm neonates during tracheal intubation. *Anesthesia and analgesia* 1987;66(9):874-8. [published Online First: 1987/09/01]
19. Barrington KJ, Finer NN, Etches PC. Succinylcholine and atropine for premedication of the newborn infant before nasotracheal intubation: a randomized, controlled trial. *Critical care medicine* 1989;17(12):1293-6. doi: 10.1097/00003246-198912000-00009 [published Online First: 1989/12/01]
20. Parkin JL, Stevens MH, Jung AL. Acquired and congenital subglottic stenosis in the infant. *The Annals of otology, rhinology, and laryngology* 1976;85(5 Pt.1):573-81. doi: 10.1177/000348947608500503 [published Online First: 1976/09/01]
21. Jobe AH IM. Lung development and function in preterm infants in the surfactant treatment era. *Annu Rev Physiol* 2000;62(825-46)
22. Bjorklund LJ IJ, Curstedt T, John J, Robertson B, Werner O, Vilstrup CT. Manual ventilation with a few large breaths at birth compromises the therapeutic effect of subsequent surfactant replacement in immature lambs. *Pediatr Res* 1997;42(3):348-55.
23. More K, Sakhuja P, Shah PS. Minimally invasive surfactant administration in preterm infants: a meta-narrative review. *JAMA pediatrics* 2014;168(10):901-8. doi: 10.1001/jamapediatrics.2014.1148 [published Online First: 2014/08/05]
24. Berggren E, Liljedahl M, Winbladh B, et al. Pilot study of nebulized surfactant therapy for neonatal respiratory distress syndrome. *Acta paediatrica (Oslo, Norway : 1992)* 2000;89(4):460-4. [published Online First: 2000/06/01]
25. Finer NN MT, Bernstein G, Job L, Mazela J, Segal R. An open label, pilot study of Aerosurf combined with nCPAP to prevent RDS in preterm neonates. *J Aerosol Med Pulm Drug Deliv* 2010;23(5):303-09.
26. Minocchieri S, Berry CA, Pillow JJ. Nebulised surfactant to reduce severity of respiratory distress: a blinded, parallel, randomised controlled trial. *Archives of disease in childhood Fetal and neonatal edition* 2019;104(3):F313-f19. doi: 10.1136/archdischild-2018-315051 [published Online First: 2018/07/28]

27. Abdel-Latif ME, Osborn DA. Nebulised surfactant in preterm infants with or at risk of respiratory distress syndrome. *The Cochrane database of systematic reviews* 2012;10:Cd008310. doi: 10.1002/14651858.CD008310.pub2 [published Online First: 2012/10/19]
28. Gopel W, Kribs A, Ziegler A, et al. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. *Lancet (London, England)* 2011;378(9803):1627-34. doi: 10.1016/s0140-6736(11)60986-0 [published Online First: 2011/10/04]
29. Dargaville PA, Aiyappan A, De Paoli AG, et al. Minimally-invasive surfactant therapy in preterm infants on continuous positive airway pressure. *Archives of disease in childhood Fetal and neonatal edition* 2013;98(2):F122-6. doi: 10.1136/archdischild-2011-301314 [published Online First: 2012/06/12]
30. Kanmaz HG, Erdeve O, Canpolat FE, et al. Surfactant administration via thin catheter during spontaneous breathing: randomized controlled trial. *Pediatrics* 2013;131(2):e502-9. doi: 10.1542/peds.2012-0603 [published Online First: 2013/01/30]
31. Kribs A, Roll C, Gopel W, et al. Nonintubated Surfactant Application vs Conventional Therapy in Extremely Preterm Infants: A Randomized Clinical Trial. *JAMA pediatrics* 2015;169(8):723-30. doi: 10.1001/jamapediatrics.2015.0504 [published Online First: 2015/06/09]
32. Gopel W, Kribs A, Hartel C, et al. Less invasive surfactant administration is associated with improved pulmonary outcomes in spontaneously breathing preterm infants. *Acta paediatrica (Oslo, Norway : 1992)* 2015;104(3):241-6. doi: 10.1111/apa.12883 [published Online First: 2014/12/05]
33. Herting E, Kribs A, Hartel C, et al. Two-year outcome data suggest that less invasive surfactant administration (LISA) is safe. Results from the follow-up of the randomized controlled AMV (avoid mechanical ventilation) study. *European journal of pediatrics* 2020 doi: 10.1007/s00431-020-03572-0 [published Online First: 2020/02/19]
34. Klotz D, Porcaro U, Fleck T, et al. European perspective on less invasive surfactant administration-a survey. *European journal of pediatrics* 2017;176(2):147-54. doi: 10.1007/s00431-016-2812-9 [published Online First: 2016/12/13]
35. Beltempo M, Isayama T, Vento M, et al. Respiratory Management of Extremely Preterm Infants: An International Survey. *Neonatology* 2018;114(1):28-36. doi: 10.1159/000487987 [published Online First: 2018/04/16]
36. Heiring C, Jonsson B, Andersson S, et al. Survey shows large differences between the Nordic countries in the use of less invasive surfactant administration. *Acta paediatrica (Oslo, Norway : 1992)* 2017;106(3):382-86. doi: 10.1111/apa.13694 [published Online First: 2016/12/20]
37. Kurepa D, Perveen S, Lipener Y, et al. The use of less invasive surfactant administration (LISA) in the United States with review of the literature. *Journal of perinatology : official journal of the California Perinatal Association* 2019;39(3):426-32. doi: 10.1038/s41372-018-0302-9 [published Online First: 2019/01/13]
38. Rigo V, Lefebvre C, Broux I. Surfactant instillation in spontaneously breathing preterm infants: a systematic review and meta-analysis. *European journal of pediatrics* 2016;175(12):1933-42. doi: 10.1007/s00431-016-2789-4 [published Online First: 2016/09/30]

39. Isayama T, Iwami H, McDonald S, et al. Association of Noninvasive Ventilation Strategies With Mortality and Bronchopulmonary Dysplasia Among Preterm Infants: A Systematic Review and Meta-analysis. *Jama* 2016;316(6):611-24. doi: 10.1001/jama.2016.10708 [published Online First: 2016/08/18]
40. Aldana-Aguirre JC, Pinto M, Featherstone RM, et al. Less invasive surfactant administration versus intubation for surfactant delivery in preterm infants with respiratory distress syndrome: a systematic review and meta-analysis. *Archives of disease in childhood Fetal and neonatal edition* 2017;102(1):F17-f23. doi: 10.1136/archdischild-2015-310299 [published Online First: 2016/11/18]
41. Dargaville PA, Kamlin CO, De Paoli AG, et al. The OPTIMIST-A trial: evaluation of minimally-invasive surfactant therapy in preterm infants 25-28 weeks gestation. *BMC pediatrics* 2014;14:213. doi: 10.1186/1471-2431-14-213 [published Online First: 2014/08/29]
42. Attridge JT SC, Stukenborg GJ, Kattwinkel J. Administration of rescue surfactant by laryngeal mask airway: lessons from a pilot trial. *American journal of perinatology* 2013;30(3):201-06.
43. Barbosa RF, Simoes ESAC, Silva YP. A randomized controlled trial of the laryngeal mask airway for surfactant administration in neonates. *Jornal de pediatria* 2017;93(4):343-50. doi: 10.1016/j.jped.2016.08.007 [published Online First: 2017/01/29]
44. Roberts KD, Brown R, Lampland AL, et al. Laryngeal Mask Airway for Surfactant Administration in Neonates: A Randomized, Controlled Trial. *The Journal of pediatrics* 2018;193:40-46.e1. doi: 10.1016/j.jpeds.2017.09.068 [published Online First: 2017/11/28]
45. Abdel-Latif ME, Osborn DA. Laryngeal mask airway surfactant administration for prevention of morbidity and mortality in preterm infants with or at risk of respiratory distress syndrome. *The Cochrane database of systematic reviews* 2011(7):Cd008309. doi: 10.1002/14651858.CD008309.pub2 [published Online First: 2011/07/08]
46. Kattwinkel J, Robinson M, Bloom BT, et al. Technique for intrapartum administration of surfactant without requirement for an endotracheal tube. *Journal of perinatology : official journal of the California Perinatal Association* 2004;24(6):360-5. doi: 10.1038/sj.jp.7211103 [published Online First: 2004/04/16]
47. Lamberska T, Settelmayerova E, Smisek J, et al. Oropharyngeal surfactant can improve initial stabilisation and reduce rescue intubation in infants born below 25 weeks of gestation. *Acta paediatrica (Oslo, Norway : 1992)* 2018;107(1):73-78. doi: 10.1111/apa.14060 [published Online First: 2017/09/06]
48. Jobe A, Ikegami M, Jacobs H, et al. Surfactant and pulmonary blood flow distributions following treatment of premature lambs with natural surfactant. *The Journal of clinical investigation* 1984;73(3):848-56. doi: 10.1172/jci111280 [published Online First: 1984/03/01]
49. Cummings JJ, Holm BA, Nickerson PA, et al. Pre- versus post-ventilatory surfactant treatment in surfactant-deficient preterm lambs. *Reproduction, fertility, and development* 1995;7(5):1333-8. [published Online First: 1995/01/01]
50. Abdel-Latif ME, Osborn DA. Pharyngeal instillation of surfactant before the first breath for prevention of morbidity and mortality in preterm infants at risk of respiratory distress syndrome. *The Cochrane database of systematic reviews* 2011(3):Cd008311. doi: 10.1002/14651858.CD008311.pub2 [published Online First: 2011/03/18]

51. Enhorning G, Grossmann G, Robertson B. Pharyngeal deposition of surfactant in the premature rabbit fetus. *Biology of the neonate* 1973;22(1):126-32. [published Online First: 1973/01/01]
52. Enhorning G, Robertson B, Milne E, et al. Radiologic evaluation of the premature newborn rabbit after pharyngeal deposition of surfactant. *American journal of obstetrics and gynecology* 1975;121(4):475-80. [published Online First: 1975/02/15]
53. Kieran EA, O'Sullivan A, Miletin J, et al. 2% chlorhexidine-70% isopropyl alcohol versus 10% povidone-iodine for insertion site cleaning before central line insertion in preterm infants: a randomised trial. *Archives of disease in childhood Fetal and neonatal edition* 2018;103(2):F101-f06. doi: 10.1136/archdischild-2016-312193 [published Online First: 2017/10/28]
54. Stenke E, Kieran EA, McCarthy LK, et al. A randomised trial of placing preterm infants on their back or left side after birth. *Archives of disease in childhood Fetal and neonatal edition* 2016;101(5):F397-400. doi: 10.1136/archdischild-2015-309842 [published Online First: 2016/02/06]
55. Murphy MC, Heiring C, Doglioni N, et al. Effect of Needle Aspiration of Pneumothorax on Subsequent Chest Drain Insertion in Newborns: A Randomized Clinical Trial. *JAMA pediatrics* 2018;172(7):664-69. doi: 10.1001/jamapediatrics.2018.0623 [published Online First: 2018/05/26]

Procedures	Screening Screening	Allocation Day of Birth	Post-allocation 120 hours after birth	Close-out Discharge home
ENROLMENT				
Inclusion/Exclusion Criteria	X			
Informed consent	X			
Allocation		x		
INTERVENTIONS				
Oropharyngeal surfactant		x		
Standard care - CPAP		x		
ASSESSMENTS				
Baseline variables		x		
Primary outcome			x	
Other outcomes			x	x

Schedule of events

150x82mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title Page 1	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration P1, line 12	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version P1 line 15	3	Date and version identifier
Funding Pg 2 line 7	4	Sources and types of financial, material, and other support
Roles and responsibilities Page 1 Line 17 Page 2 + 3	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	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
	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)
Introduction		
Background and rationale Page 7	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
	6b	Explanation for choice of comparators
Objectives Page 9 Line 22	7	Specific objectives or hypotheses
Trial design Page 10 line 6	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting Page 10 Line 12	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
Eligibility criteria Page 10 Line 23	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions Page 15 Line 1	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	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)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes Page 11 Line 24	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
Participant timeline Page 10 Line 10 (Page 22 Line 15)	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)
Sample size Page 20 Line 7	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
Recruitment Page 12 Line 15	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation Page 15 Line 4	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

Allocation concealment mechanism Page 15 Line 15	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
Implementation Page 15 Line 14	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking) Page 15 Line 19	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods P17 Line 16	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
P19 Line 25	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
Data management Page 17 Line 22	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
Statistical methods P19 Line 2	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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	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)
Methods: Monitoring		
Data monitoring Page 21 Line 6	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

	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
Harms Page 20 Line 23	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing Page 17 Line 18	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval Page 22 Line 2 and Page 2 Line 20	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments Page 22 Line 6	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent Page 11 Line 10	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality Page 17 Line 24	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests Page 2 Line 7	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data Page 3 Line 16	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care N/A	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy Page 22 Line 2 Page 18 Line 6	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
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.