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

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

A Randomised Trial

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Trial sponsor

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3 **Author Contributions:** COD conceived and designed the trial protocol, co-wrote the first draft and
4 revised the manuscript for intellectual content. MCM helped design the trial protocol, co-wrote the
5 first draft and revised the manuscript for intellectual content. MG, BM, RH, and PD helped design
6 the trial protocol and revised the manuscript for intellectual content. MG designed the statistical
7 analysis plan. All authors approved the final manuscript prior to submission.
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16

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20 collection, analysis or interpretation. Further, they will have no role in the decision to present,
21 publish or otherwise report results.
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31
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42 study drug free of charge; they had no role in study design; have no role in study conduct; and will
43 have no role in data collection, analysis or interpretation. Further, they will have no role in the
44 decision to present, publish or otherwise report results.
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2
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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

1
2
3 participating site. The trial is being conducted at 9 centres in 6 European countries. The study results
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5 will be submitted for publication in a peer-reviewed journal.
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For peer review only

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3 Article summary
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7 Strengths and limitations of this study
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- 11
- 12 • This is the first randomised study to examine the efficacy of giving oropharyngeal surfactant
13 at birth to preterm infants at high risk of developing respiratory distress syndrome.
14
 - 15 • Oropharyngeal administration is less invasive and easier to perform than endotracheal
16 administration and avoids the short- and longer-term adverse effects of intubation.
17
 - 18 • The study will determine whether prophylactic oropharyngeal surfactant reduces the rate of
19 endotracheal intubation for respiratory failure within 120 hours of birth among infants born
20 before 29 weeks of gestation.
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 - 22 • The multicentre nature of this study will increase the generalisability of its findings.
23
 - 24 • We were unable to credibly mask the intervention.
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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 – 1990s⁴⁻⁷ 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

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2
3 administration.¹³ About half of premature infants initially managed with CPAP for RDS are ultimately
4
5 intubated for surfactant and ventilation.¹⁴
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10 Intubation is a procedure that is difficult to learn and is associated with adverse effects, both short¹⁵⁻
11
12 ¹⁹ and longer-term.²⁰⁻²² This has led many clinicians to investigate alternative methods of surfactant
13
14 delivery.²³ Giving nebulised surfactant to spontaneously breathing infants has met with limited
15
16 success.²⁴⁻²⁷ Progress has been slow due to the technical difficulties encountered in aerosolising such
17
18 large molecules, the expense of the equipment needed to do so and the cost of the large amount of
19
20 surfactant needed to form an aerosol. Interest has largely focussed on less-invasive methods of
21
22 surfactant administration. The “minimally invasive” techniques have involved introducing either a
23
24 feeding tube or vascular catheter into the trachea of a spontaneously breathing infant under direct
25
26 vision with a laryngoscope.²⁸⁻³¹ These techniques may reduce the need for mechanical ventilation
27
28 among preterm infants. However, they appear more difficult than intubation and the many short-
29
30 term adverse effects of intubation that are due to laryngoscopy are not avoided. The laryngeal mask
31
32 airway, a supraglottic airway device, may be used as an interface to deliver surfactant.³²⁻³⁵ However
33
34 there is currently no device available for use in very low birth weight infants, who constitute the
35
36 majority of infants diagnosed with RDS, who constitute the
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44 Direct administration of surfactant into the pharynx of human infants has been described in
45
46 randomised⁷ and prospective cohort studies.³⁶⁻³⁷ It is apparently effective and is an easier technique
47
48 to perform than endotracheal intubation or passing a feeding tube or vascular catheter into the
49
50 trachea. Advantages of pharyngeal surfactant use are that it is an easy and cheaper method of
51
52 administering surfactant and likely causes less discomfort to infants as it avoids the use of a
53
54 laryngoscope. Giving surfactant early, prior to ventilation, delivers surfactant to a fluid-filled lung,
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56 which is spread via a fluid-air interface when the infant starts breathing. Animal studies report that
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58 surfactant is distributed more uniformly,³⁸ and lung function and compliance is better³⁹ if surfactant
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3 is delivered prior to ventilation. If shown to be effective, it may reduce the adverse effects, and
4
5 additional associated costs, of ventilation.
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10 A Cochrane review of pharyngeal surfactant⁴⁰ did not identify any eligible trials to assess whether
11
12 pharyngeal installation of surfactant before the first breath prevented morbidity and mortality in
13
14 infants at risk of RDS. Large well conducted RCTs are needed, due to the evidence from animal^{41 42}
15
16 and observational human studies^{36 37} suggesting that pharyngeal surfactant administration is
17
18 potentially safe, feasible, and may be effective.
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23 Objective

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

37 Trial design

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45 The POPART trial is an investigator-led, unblinded, multicentre, randomised parallel-group
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47 controlled trial. It aims to determine whether administering oropharyngeal surfactant to premature
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49 infants at birth in addition to CPAP compared to CPAP alone reduces the rate of intubation for
50
51 respiratory failure in the first 5 days of life. The trial will recruit 250 infants born <29 weeks GA at
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53 participating centres. A schedule of events is seen in figure 1.
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59 Setting

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5 The trial is being conducted at 9 neonatal intensive care units (NICUs) in 6 European countries
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7 [Ireland (National Maternity Hospital (NMH), Dublin; Coombe Women and Infants University
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9 Hospital (CWIUH) Dublin); Norway (University Northern Norway, Tromsø; Haukeland University
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11 Hospital, Bergen); Czech Republic (Charles University, Prague; University Hospital Brno, Brno),
12
13 Belgium (Le Centre Hospitalier Universitaire (CHU), Liege); Sweden (Karolinska Institutet,
14
15 Stockholm); and Portugal (Hospital de Braga, Braga). All data collected pertaining to the primary and
16
17 secondary outcomes will be collected as part of the infants' hospital course.
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23 Participants

24 25 26 27 28 Inclusion and exclusion criteria

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32 Trial subjects will be premature infants at risk of RDS. Infants born less than 29 weeks GA will be
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34 included if the treating physician plans to offer intensive care. Infants will be excluded if they have
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36 major congenital anomalies (including neural tube defects, major structural cardiac anomalies
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38 (excluding patent ductus arteriosus, ventricular septal defect, atrioventricular septal defect),
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40 abdominal wall defects, congenital diaphragmatic hernia and major dysmorphic features with an
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42 abnormal karyotype) and if the treating physician does not plan to offer intensive care. Written
43
44 informed consent from parent/legal guardian(s) will be obtained before delivery. Infants of multiple
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46 gestation and of either sex are eligible to be enrolled.
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52 Outcome measures

53 54 55 56 57 Primary outcome

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3 The primary outcome is the incidence of endotracheal intubation for respiratory failure within 120
4 hours of birth. Enrolled infants will be intubated for persistent apnoea and/or bradycardia (HR
5 <100bpm) in the delivery room (DR), or for respiratory failure in the NICU defined as ≥ 2 of:
6
7

- 8 - Clinical signs – worsening tachypnoea; grunting; subcostal, intercostal and/or sternal recession
- 9
- 10 - Acidosis – pH < 7.2 on 2 blood gases (arterial or capillary) ≥ 30 minutes apart
- 11
- 12 - Hypoxaemia – $\text{FiO}_2 > 0.4$ to keep oxygen saturation (SpO_2) $\geq 90\%$ for > 30 minutes
- 13
- 14 - Hypercarbia – $\text{PCO}_2 > 9.0$ kPa on 2 blood gases (arterial or capillary) ≥ 30 minutes apart
- 15
- 16 - Apnoea – recurrent apnoea treated with mask ventilation
- 17
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23 Secondary outcomes

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25
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27 The secondary outcomes are as follows:

- 28 1. Intubation in the DR
 - 29
 - 30 2. Number of attempts taken to successfully intubate in the DR
 - 31
 - 32 3. Chest compressions in the DR
 - 33
 - 34 4. Adrenaline administration in the DR
 - 35
 - 36 5. Rectal temperature on admission to the NICU
 - 37
 - 38 6. NICU intubation
 - 39
 - 40 7. Surfactant use before death or hospital discharge
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- 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

- 1
- 2
- 3 10. Incidence of pulmonary haemorrhage
- 4
- 5 a. Clinical evidence of pulmonary haemorrhage
- 6
- 7 11. Mechanical ventilation
- 8
- 9 12. Days of mechanical ventilation
- 10
- 11 13. Use of postnatal corticosteroids for ventilator dependence
- 12
- 13 14. Days of duration of respiratory support (endotracheal ventilation, high-frequency oscillatory
- 14 ventilation, CPAP, heated humidified high-flow nasal cannula O₂, low flow nasal cannula O₂)
- 15
- 16 15. BPD – supplemental O₂ at 28 days of life
- 17
- 18 16. Chronic lung disease of prematurity (CLD) – need for supplemental O₂ at 36 weeks corrected
- 19 GA determined by physiological oxygen reduction test
- 20
- 21 17. Medical treatment for a patent ductus arteriosus (PDA)
- 22
- 23 a. Administration of ibuprofen or paracetamol for PDA
- 24
- 25 18. Surgical treatment for a PDA
- 26
- 27 19. Proven necrotising enterocolitis (≥ Bell's stage 2)
- 28
- 29 20. Incidence of Intraventricular haemorrhage (IVH) (any and severe: IVH grade ≥ 3)
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- 31 a. Evidence on surveillance cranial ultrasounds performed as standard of care
- 32
- 33 21. Incidence of cystic periventricular leukomalacia
- 34
- 35 a. Evidence on surveillance cranial ultrasounds performed as standard of care
- 36
- 37 22. Retinopathy of prematurity treated with laser photocoagulation or intravitreal injections
- 38
- 39 a. Evidence on surveillance ophthalmology review performed as standard of care
- 40
- 41 23. Death before hospital discharge
- 42
- 43 24. Survival without BPD at hospital discharge
- 44
- 45 25. Survival without CLD at hospital discharge
- 46
- 47 26. Duration of hospitalisation
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- 49 27. Use of home oxygen therapy
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- 51 a. Discharged home on oxygen therapy
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5 Intervention arm: Oropharyngeal surfactant
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10 Infants randomised to oropharyngeal surfactant will receive a dose of surfactant (Curosurf, Chiesi
11 Farmaceutici, Parma, Italy) immediately after birth, ideally before the cord is clamped e.g. 60
12 seconds. If it is given after the cord is clamped, it will be given once the infant is placed on the
13 resuscitaire. It will be given within 5 minutes of birth in all cases.
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21 The surfactant will be warmed prior to being drawn up in a sterile syringe as per manufacturer's
22 recommendation. This will be done by opening the mouth gently and administering the surfactant as
23 a single bolus into the oropharynx using surfactant tubing attached to the syringe.
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30 Infants will not be weighed prior to enrolment. The 50th centile for birth weight (BW) for boys and
31 girls according to GA is shown in table 1. In our study, infants < 26 weeks will receive a full 120mg
32 vial of Curosurf. We estimate that this will provide dosing in the range as indicated in table 2. In our
33 study, infants 26 – 28 weeks will receive a full 240mg vial of Curosurf, and we estimate that this will
34 provide dosing in the range as indicated in table 3.
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43 Control group: CPAP
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48 Infants randomised to the control group will not have anything injected into their oropharynx and
49 will be stabilised on CPAP in the DR as per routine practice.
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54 Clinical management
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3 After the initial intervention, infants will then receive standard care with CPAP, regardless of their
4 group assignment. DR care will be carried out by the neonatal team who will be trained in neonatal
5 resuscitation as per the recommendations of the International Liaison Committee on Resuscitation
6 (ILCOR). Infants in both groups will be intubated in the DR for persistent apnoea and/or bradycardia
7 despite PPV by mask as per ILCOR recommendations. Infants will not be intubated in the DR solely
8 for surfactant administration. Further surfactant administration and all other aspects of neonatal
9 intensive care will be at the discretion of the treating physicians. Infants in both groups will be
10 treated equally; they will be closely watched to see if they need extra treatment for their RDS at any
11 stage, including surfactant given endotracheally. The frequency of blood gas monitoring is based on
12 the decision of the treating physician. Enrolled infants will be intubated if they reach the pre-
13 determined criteria for respiratory failure. After giving endotracheal surfactant for the treatment of
14 RDS, attending clinicians may attempt to extubate the babies immediately or they may elect to
15 ventilate the babies for a longer period at their discretion.

Investigational medicinal product

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19 Poractant alpha (Curosurf, Chiesi Farmaceutici, Parma, Italy) is a natural surfactant prepared from
20 porcine lungs. It is licensed for ET use for the prevention and treatment of RDS in preterm infants.
21 The dosing recommendations for treatment with Curosurf when given by ETT are 200mg/kg for
22 established RDS and 100 – 200mg/kg for prophylaxis. Further doses of 100mg/kg Curosurf may be
23 given to infants who have persistent respiratory distress despite treatment with surfactant
24 (maximum recommended dose 400mg/kg). It is currently not licensed for oropharyngeal
25 administration, and therefore this study will examine the off-label use of a licensed product. The
26 timing or dosage of ET surfactant will not be affected by oropharyngeal surfactant. If an infant is felt
27 to need ET surfactant following initial oropharyngeal administration, then they will receive the
28 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

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3 Data will be collected by the on-site investigators from the patient's clinical notes. This will be
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5 recorded on a data worksheet and transferred to an electronic Case Report Form (CRF) to be stored
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7 in a secure, dedicated, password-protected electronic database. The clinical study monitor and
8
9 representative of the regulatory authority can directly access source documents for comparison of
10
11 such data with the data in the electronic CRFs and can verify that the study is carried out in
12
13 compliance with the protocol and local regulatory requirements.
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18 The investigators will adhere to national and hospital protocols on data use and storage. Data will be
19
20 coded. It will be stored in a locked filing cabinet then uploaded onto a password-protected computer
21
22 in a locked office. Documents will be stored safely in confidential conditions. On all study-specific
23
24 documents other than the signed consent, the subject will be referred to by the study subject
25
26 identification code.
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32 Description of statistical methods 33 34 35 36

37 Trial results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT).
38
39 The flow of patients through the trial will be represented on a CONSORT flow diagram, and the
40
41 number included in the primary and secondary analyses as well as all reasons for exclusions will be
42
43 reported per trial arm. Analysis of efficacy endpoints will be carried-out following the Intention-To-
44
45 Treat principle. A Per-Protocol analysis will also be carried out on the primary endpoint, excluding
46
47 infants with incomplete data on the primary outcome and infants with any major protocol
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49 deviations.
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54 Demographic and baseline data will be summarised by treatment group to evaluate comparability.
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59 Primary outcome analysis 60

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5 The primary outcome will be summarised per group. Ratios of relative risk will be
6
7 reported with 95% confidence intervals. A two-sided, two-proportion Z test will be
8
9 carried out to investigate whether the rate of endotracheal intubation differs between
10
11 intervention and standard-of-care. This analysis will be carried out both on the
12
13 intention-to-treat set and on the per protocol set.
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18 A competing risks model will be fitted to investigate the effect of the intervention on
19
20 the primary endpoint, adjusting for competing outcomes (e.g. mortality) that may
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22 impact on observation of the primary endpoint.
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28 The sensitivity of the estimated intervention effect to measured covariates of interest,
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30 including centre, GA, birth weight, gender, mode of delivery and antenatal
31
32 corticosteroid treatment, will be evaluated with regression analysis.
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36 37 Secondary outcome analysis

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39 Categorical outcomes will be summarised per treatment group, with between-group differences
40
41 expressed as a relative risk with 95% confidence intervals. A two-sided, two-proportion Z test will be
42
43 carried out for each categorical outcome to investigate whether the proportion differs between
44
45 intervention and standard of care. For the important secondary endpoint of death before hospital
46
47 discharge, regression analysis will be employed to determine sensitivity of the estimated
48
49 intervention effect to potentially relevant covariates (as specified above for the primary outcome).
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55 Numeric secondary outcomes will be summarised by treatment group and between-group
56
57 differences will be presented with a 95% confidence interval. A superiority hypothesis test will be
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3 carried out to test for a difference in the outcome between control and intervention, using a t-test
4
5 or a Mann-Whitney U test where relevant.
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10 Subgroup analyses

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12 Subgroup analysis of the primary outcome and the important secondary outcome of death before
13
14 hospital discharge will be carried out by regression modelling to determine differences in the
15
16 intervention effect for infants of different GA strata, and infants from different participating centres.
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21 Missing data

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25 Any missing data or data anomalies will be communicated to the study site(s) for prompt
26
27 clarification and resolution. For outcomes missing more than 5% of data in either treatment group,
28
29 missing data methods will be employed in analysis. For categorical outcomes with censored data,
30
31 Kaplan-Meier analyses will be used to estimate treatment effect. For other missing data, a suitable
32
33 imputation method will be selected during blind review of the data.
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39 Sample size and power

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43 The sample size calculation assumed a rate of endotracheal intubation of 46% for infants treated
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45 with CPAP alone, and a rate of 28% for infants receiving oropharyngeal surfactant and CPAP. The
46
47 former was informed by published RCTs showing a rate of mechanical ventilation in the days after
48
49 birth among preterm infants treated with CPAP alone from 40– 60%¹⁰⁻¹² and rates of CPAP failure of
50
51 43% reported in a cohort of preterm infants 25 – 28 weeks' gestation initially commenced on
52
53 CPAP.¹⁴ The latter was informed by a cohort of infants born 26 – 28 weeks' gestation reporting that
54
55 minimally invasive surfactant techniques reduced the rate of mechanical ventilation to from 46% to
56
57 28%.²⁸ Sample size was calculated in G*power based on a two-sided, two-proportion Z test. A
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3 sample size of 125 infants per arm will be required to give a statistical power of 80% at a significance
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5 level of 5%, adjusted for an anticipated death rate of 10% (estimated from local data (NMH,
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7 Neonatal Clinical Report, 2015).
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10 11 12 Safety analyses 13 14 15

16 Adverse events following administration of oropharyngeal surfactant will be documented. Safety
17
18 analyses will be carried out on the Safety Set, defined as patients in the intervention arm who
19
20 received oropharyngeal surfactant and patients who received CPAP only. The frequency of adverse
21
22 events and the number and percentage of infants reported as having at least one emergent adverse
23
24 event, will be reported by system organ class and preferred term, by treatment received. The same
25
26 description will be performed for serious adverse events (SAE), severe AE, AE treatment-related and
27
28 AE leading to IMP withdrawal. Defined SAEs for the study are important medical events, and death
29
30 before hospital discharge.
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36 37 Safety monitoring and interim analysis 38 39 40

41 A data safety monitoring board (DSMB) will be established to perform ongoing safety surveillance
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43 and to perform interim analyses on the study data. The DSMB will be an independent committee,
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45 composed of a minimum of three members; at least two will be clinicians with expertise in clinical
46
47 trials; at least one member will be a clinician with expertise in neonatology.
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52 The DSMB will meet on a 6-monthly basis after start of the trial and will review the frequency and
53
54 severity of AEs in both treatment groups. If they observe any significant excess of SAEs in the
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56 intervention group associated with the intervention, they may recommend premature termination
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58 of the trial on the basis of safety concerns.
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5 The DSMB will conduct interim analysis to determine whether the data provide overwhelming
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7 evidence of efficacy or futility, defined as a highly statistically significant difference in the primary
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9 outcome or a highly statistically significant difference in the important secondary outcome of death
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11 before hospital discharge. The type I error rate for interim analysis will be set to 0.001 in accordance
12
13 with the Haybittle-Peto stopping boundary. For final analysis, the type I error rate will remain at
14
15 0.05. Interim analysis will be carried out after approximately 50% of participants (n=126) have
16
17 completed the study. The DSMB may recommend early termination of the trial due to efficacy or
18
19 futility; or for unanticipated concerns for the safety of enrolled infants. Standard procedures for
20
21 reporting AEs will be used in accordance with Good Clinical Practice guidelines.
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26 Ethics and dissemination

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30 The study was initially approved by the Research Ethics Committee at NMH, Dublin, and the Health
31
32 Products Regulatory Authority of Ireland. Approval was also obtained at the research ethics
33
34 committees at each participating site and at the relevant competent authority for each participating
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36 country. All bodies must be informed in writing of any substantial changes to the protocol, prior to
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38 any such changes being implemented. University College Dublin, Ireland is the sponsor for this study.
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42 Screening and consent

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46 Prior to the delivery a member of the research team or other senior doctor will approach
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48 parent(s)/guardian(s) of eligible infants to inform them about the study. The team member will
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50 explain the purpose and nature of the study and provide written information for the
51
52 parent(s)/guardian(s) to keep. If the local language is not their first language, they will be offered the
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54 opportunity to have an interpreter present while the study is explained. Written consent for
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56 enrolment of the infant in the study will then be sought. Parents will be informed that they may
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58 withdraw their child from the study at any time should they so wish; and that a decision not to
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3 consent to their infants' participation in the study or to withdraw their infant from the study once
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5 enrolled will not affect their infant's access to the best available treatment and care.
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10 Patient and public involvement (PPI)
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14 We liaised with the Irish Neonatal Health Alliance for assistance when designing the parent
15 information leaflet and consent form. Parent focus groups were held via PedCRIN prior to expansion
16 of the study to European sites.
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23 Recruitment
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28 Though the enrolment rates to our studies amongst eligible infants are excellent, we believe it will
29 be necessary to enrol infants at multiple sites in order to enrol our planned target sample of 250
30 infants in a timely fashion. We have a track record enlisting the help of collaborators nationally⁴³ and
31 internationally^{44 45} to perform our studies. We believe that with their help, we can enrol these
32 infants in 3 years.
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41 Current status
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46 The trial began recruitment in December 2017, with additional sites joining subsequently. It is
47 currently recruiting in 9 centres in 6 European countries. It is expected that recruitment for the study
48 will be completed by December 2020.
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54 Publication of results
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3 The authors intend to publish the results of this trial in a high-quality, peer-reviewed journal upon
4 completion of data collection and analysis.
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8 Discussion 9

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13 Oropharyngeal surfactant given immediately after birth to preterm infants at risk of RDS has the
14 potential to reduce the risk of intubation and ventilation. Endotracheal intubation is invasive and
15 unpleasant for newborns that is associated with adverse short- and long-term effects. It is also a skill
16 that is difficult for clinicians to learn and maintain. In contrast, giving surfactant into the oropharynx
17 is easy and avoids the adverse effects associated with intubation. There is evidence from animal
18 studies and from case series in humans that it may be effective. This is an attractive proposition,
19 because it could avoid harms associated with intubation for babies and raises the possibility of giving
20 surfactant in contexts where it is not currently feasible (e.g. non-tertiary settings, developing
21 countries). We were unable to credibly mask the intervention and acknowledge this lack of blinding
22 as a limitation of the study. We tried to minimise potential bias by setting predefined objective
23 treatment failure criteria, which were agreed on by all participating sites.
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Figure 1. Schedule of events

<u>Procedures</u>	<u>Screening</u>	<u>Allocation</u>	<u>Post-allocation</u>	<u>Close-out</u>
	Screening	Day of Birth	120 hours after birth	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

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BMJ Open

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

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Primary Subject Heading:	Paediatrics
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1
2
3 1 **Study protocol for the POPART study – Prophylactic Oropharyngeal surfactant for Preterm infants:**

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5 2 **A Randomised Trial**

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31 12 **Trial registration**

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58
59 26 **Key words:** Infant, newborn; oropharyngeal surfactant; respiratory distress syndrome; intubation;

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61 27 randomised controlled trial

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4
5 2 revised the manuscript for intellectual content. MCM helped design the trial protocol, co-wrote the
6
7 3 first draft and revised the manuscript for intellectual content. MG, BM, RH, and PD helped design
8
9 4 the trial protocol and revised the manuscript for intellectual content. MG designed the statistical
10
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14 6

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24
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26

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46
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48
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50
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52
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4
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8
9 4 Research)
10
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35 16 **Data statement:** Members of the Trial Steering Committee will have access to the final dataset. Data
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37 17 will be available on request.
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3 1 Abstract
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7 3 Introduction: Many preterm infants develop respiratory distress syndrome (RDS), a condition
8
9 4 characterised by a relative lack of surfactant. Endotracheal surfactant therapy revolutionised the
10
11 5 care of preterm infants in the 1990s. However, supporting newborns with RDS with continuous
12
13 6 positive airway pressure (CPAP) and reserving endotracheal surfactant for those who develop
14
15 7 respiratory failure despite CPAP yields better results than intubating all infants for surfactant. Half of
16
17 8 preterm infants born before 29 weeks' gestation initially managed with CPAP are intubated for
18
19 9 surfactant. Intubation is difficult to learn and associated with adverse effects. Surfactant
20
21 10 administration into the oropharynx has been reported in preterm animals and humans and may be
22
23 11 effective. We wished to determine whether giving oropharyngeal surfactant at birth reduces the
24
25 12 rate of endotracheal intubation for respiratory failure in preterm infants within 120 hours of birth.
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32 14 Methods and analysis: POPART (Prophylactic Oropharyngeal surfactant for Preterm infants: A
33
34 15 Randomised Trial) is an investigator-led, unblinded, multicentre, randomised, parallel group,
35
36 16 controlled trial. Infants are eligible if born at a participating centre before 29 weeks gestational age
37
38 17 (GA) and there is a plan to offer intensive care. Infants are excluded if they have major congenital
39
40 18 anomalies. Infants are randomised at birth to treatment with oropharyngeal surfactant [120mg vial
41
42 19 <26 weeks GA stratum; 240mg vial 26 – 28+6 weeks GA stratum] in addition to CPAP or CPAP alone.
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44
45 20 The primary outcome is intubation within 120 hours of birth, for bradycardia and/or apnoea despite
46
47 21 respiratory support in the delivery room or respiratory failure in the intensive care unit. Secondary
48
49 22 outcomes include incidence of mechanical ventilation, endotracheal surfactant use, chronic lung
50
51 23 disease, and death before hospital discharge.
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57 25 Ethics and dissemination: Approval for the study has been granted by the Research Ethics
58
59 26 Committees at the National Maternity Hospital, Dublin, Ireland (EC31.2016), and at each
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3 1 participating site. The trial is being conducted at 9 centres in 6 European countries. The study results
4
5 2 will be submitted for publication in a peer-reviewed journal.
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For peer review only

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3 1 Article summary
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7 3 Strengths and limitations of this study
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10 5 • This is the first randomised study to specifically examine the efficacy of giving oropharyngeal
11 6 surfactant at birth to preterm infants at high risk of developing respiratory distress
12 7 syndrome.
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15 10 • We are enrolling infants < 29 weeks' gestation, including infants at 23 and 24 weeks'
16 11 gestation, who are most at risk of respiratory distress syndrome.
17 12

18 13

19 14 • We were unable to credibly mask the intervention.
20 15

21 16

22 17 • To reduce the risk of bias we used objective criteria for our primary outcome i.e. intubation
23 18 within 120 hours of life.
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26 21 • The multicentre nature of this study will increase the generalisability of its findings.
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3 1 Background
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8 3 Respiratory distress syndrome (RDS) is a lung condition of the preterm infant. The risk of RDS is
9
10 4 inversely related to gestational age (GA). Infants with RDS have structural and functional immaturity
11
12 5 of their lungs. They also have a relative lack of surfactant,¹ an endogenously produced substance
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14 6 that enables alveoli to expand more easily to recruit and maintain gas within the lung.
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16 7
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18 8 Exogenous surfactant^{2,3} is frequently used to treat newborns with RDS and has led to improved
19
20 9 outcomes for infants worldwide. Randomised controlled trials (RCTs) in the 1980s – 1990s⁴⁻⁷
21
22 10 demonstrated that surfactant, given by endotracheal tube (ETT), reduced mortality and air leak
23
24 11 among premature infants who were intubated for respiratory failure due to RDS. This led to the
25
26 12 widespread practice of intubating all extremely preterm infants for surfactant and ventilation
27
28 13 (“prophylactic surfactant”).⁵ Prior to the introduction of surfactant into clinical practice, concerns
29
30 14 were raised that premature infants who were intubated for respiratory support had worse
31
32 15 respiratory outcomes than infants who were managed with the non-invasive respiratory support,
33
34 16 nasal continuous positive airway pressure (CPAP).⁸ These concerns persisted after the widespread
35
36 17 introduction of surfactant.⁹ Multicentre RCTs found that starting infants on CPAP may be beneficial
37
38 18 when compared with intubation and positive pressure ventilation (PPV); the studies reported
39
40 19 decreased duration of mechanical ventilation with potential benefits of reduction of death and or
41
42 20 bronchopulmonary dysplasia (BPD).¹⁰⁻¹² Managing premature newborns initially with CPAP and
43
44 21 reserving intubation, mechanical ventilation and surfactant for those infants with worsening
45
46 22 respiratory failure despite CPAP yields better results than intubating all infants for surfactant
47
48 23 administration.¹³ About half of premature infants born before 29 weeks’ gestation initially managed
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50 24 with CPAP for RDS are ultimately intubated for surfactant and ventilation.¹⁴
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3 1 Intubation is a procedure that is difficult to learn and is associated with adverse effects, both short¹⁵⁻
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5 2 ¹⁹ and longer-term.²⁰⁻²² This has led many clinicians to investigate alternative methods of surfactant
6
7 3 delivery.²³ Giving nebulised surfactant to spontaneously breathing infants has met with limited
8
9 4 success.²⁴⁻²⁷ Progress has been slow due to the technical difficulties encountered in aerosolising such
10
11 5 large molecules, the expense of the equipment needed to do so and the cost of the large amount of
12
13 6 surfactant needed to form an aerosol. Interest has largely focussed on less-invasive methods of
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15 7 surfactant administration.
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17 8 Less invasive surfactant administration (LISA) techniques involve introducing either a feeding tube or
18
19 9 vascular catheter into the trachea of a spontaneously breathing infant at laryngoscopy.²⁸⁻³¹ LISA is
20
21 10 associated with lower rates of mechanical ventilation among preterm infants in randomised^{28 31}
22
23 11 observational studies.³² Two year follow up outcomes for infants enrolled in the randomised trial
24
25 12 Avoid Mechanical Ventilation,²⁸ where infants were randomised to surfactant via LISA or to standard
26
27 13 care with CPAP and ET instillation of surfactant if necessary, are similar between groups.³³ However,
28
29 14 the technique appears more difficult than intubation and the short-term adverse effects of
30
31 15 laryngoscopy are not avoided. The procedure is becoming more widely used, but rates vary between
32
33 16 countries.³⁴⁻³⁷ Concerns regarding the validity and risk of bias within studies, a lack of familiarity with
34
35 17 the technique, and patient discomfort have been reported as reasons for not using LISA.³⁶ Use of
36
37 18 sedation and analgesia prior to laryngoscopy is not standard for the LISA procedure.²⁸ While meta-
38
39 19 analyses report that the LISA technique is associated with less death or BPD,³⁸⁻⁴⁰ further RCTs are
40
41 20 needed. The Optimist-A trial,⁴¹ evaluating minimally invasive surfactant therapy in preterm infants
42
43 21 born between 25 – 28 weeks' gestation is ongoing.
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45 22 The laryngeal mask airway, a supraglottic airway device, may be used as an interface to deliver
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47 23 surfactant.⁴²⁻⁴⁵ However there is currently no device available for use in very low birth weight
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49 24 infants, who constitute the majority of infants diagnosed with RDS.
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3 1 Direct administration of surfactant into the pharynx of human infants has been described in
4
5 2 randomised⁷ and prospective cohort studies.^{46 47} It is apparently effective and is an easier technique
6
7 3 to perform than endotracheal intubation or passing a feeding tube or vascular catheter into the
8
9 4 trachea. Advantages of pharyngeal surfactant use are that it is an easy and cheaper method of
10
11 5 administering surfactant and likely causes less discomfort to infants as it avoids the use of a
12
13 6 laryngoscope. Giving surfactant early, prior to ventilation, delivers surfactant to a fluid-filled lung,
14
15 7 which is spread via a fluid-air interface when the infant starts breathing. Animal studies report that
16
17 8 surfactant is distributed more uniformly,⁴⁸ and lung function and compliance is better⁴⁹ if surfactant
18
19 9 is delivered prior to ventilation. If shown to be effective, it may reduce the adverse effects, and
20
21 10 additional associated costs, of ventilation.
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28 12 A Cochrane review of pharyngeal surfactant⁵⁰ did not identify any eligible trials to assess whether
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30 13 pharyngeal installation of surfactant before the first breath prevented morbidity and mortality in
31
32 14 infants at risk of RDS. The Ten Centre Study randomised 328 infants born between 25 – 29 weeks'
33
34 15 gestation to artificial surfactant therapy or saline. For those randomised to surfactant therapy, the
35
36 16 first dose was given via the oropharynx, with subsequent doses given via an ETT if the infant was
37
38 17 intubated, however the outcomes of infants who received pharyngeal surfactant alone were not
39
40 18 reported. Large well conducted RCTs are needed, due to the evidence from animal^{51 52} and
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42 19 observational human studies^{46 47} suggesting that pharyngeal surfactant administration is potentially
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44 20 safe, feasible, and may be effective.
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50 22 Objective
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55 24 We are performing a study to establish whether giving preterm infants surfactant into their
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57 25 oropharynx at birth in addition to CPAP compared with CPAP alone reduces their need for
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59 26 subsequent intubation in the first 5 days of life.
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45 2 **Methods**
67 3
89 4 Trial design
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14 6 The POPART trial is an investigator-led, unblinded, multicentre, randomised parallel-group
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16 7 controlled trial. It aims to determine whether administering oropharyngeal surfactant to premature
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18 8 infants at birth in addition to CPAP compared to CPAP alone reduces the rate of intubation for
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20 9 respiratory failure in the first 5 days of life. The trial will recruit 250 infants born <29 weeks GA at
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22 10 participating centres. A schedule of events is seen in figure 1.
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25 11
2627 12 Setting
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2930 13
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32 14 The trial is being conducted at 9 neonatal intensive care units (NICUs) in 6 European countries
33
34 15 [Ireland (National Maternity Hospital (NMH), Dublin; Coombe Women and Infants University
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36 16 Hospital (CWIUH) Dublin); Norway (University Northern Norway, Tromsø; Haukeland University
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38 17 Hospital, Bergen); Czech Republic (Charles University, Prague; University Hospital Brno, Brno),
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40 18 Belgium (Le Centre Hospitalier Universitaire (CHU), Liege); Sweden (Karolinska Institutet,
41
42 19 Stockholm); and Portugal (Hospital de Braga, Braga).
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45 20
4647 21 Participants
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4950 22
5152 23 Inclusion and exclusion criteria
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57 25 Trial subjects are premature infants at risk of RDS. Infants born less than 29 weeks GA are included if
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59 26 the treating physician plans to offer intensive care. Infants are excluded if they have major
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1 congenital anomalies (including neural tube defects, major structural cardiac anomalies (excluding
2 patent ductus arteriosus, ventricular septal defect, atrioventricular septal defect), abdominal wall
3 defects, congenital diaphragmatic hernia and major dysmorphic features with an abnormal
4 karyotype) and if the treating physician does not plan to offer intensive care. If there is a known
5 anomaly prenatally, families are not approached for consent. In the event of a postnatal diagnosis of
6 the aforementioned conditions, these infants meet criteria for post-randomisation exclusion.
7 Written informed consent from parent/legal guardian(s) is obtained before delivery. Infants of
8 multiple gestation and of either sex are eligible to be enrolled.

10 Screening and consent

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

22 Outcome measures

24 Primary outcome

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3 1 The primary outcome is the incidence of endotracheal intubation for respiratory failure within 120
4
5 2 hours of birth. Enrolled infants are intubated for persistent apnoea and/or bradycardia (HR
6
7 3 <100bpm) in the delivery room (DR), or for respiratory failure in the NICU defined as ≥ 2 of:

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10 4 - Clinical signs – worsening tachypnoea; grunting; subcostal, intercostal and/or sternal recession
11
12 5 - Acidosis – pH < 7.2 on 2 blood gases (arterial or capillary) ≥ 30 minutes apart
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14 6 - Hypoxaemia – $\text{FiO}_2 > 0.4$ to keep oxygen saturation (SpO_2) $\geq 90\%$ for > 30 minutes
15
16 7 - Hypercarbia – $\text{PCO}_2 > 9.0$ kPa on 2 blood gases (arterial or capillary) ≥ 30 minutes apart
17
18 8 - Apnoea – recurrent apnoea treated with mask ventilation
19
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21 9

22
23 10 The primary outcome is intubation within 120 hours of birth. For the purpose of the primary
24
25 11 outcome, infants are recorded as ‘yes’ if they were intubated, briefly intubated for surfactant
26
27 12 administration e.g. INSURE, and brief tracheal catheterisation for surfactant administration e.g. LISA
28
29 13 technique. We record the treatment plan at the time of intubation. We record whether there is a) a
30
31 14 plan for intubation with endotracheal tube, surfactant administration, and continued ventilation; b)
32
33 15 a plan for “INSURE” – intubation with ETT, surfactant administration, and immediate (<30 minute)
34
35 16 extubation; c) a plan for surfactant administration using LISA technique – surfactant administration
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37 17 through a thin endotracheal catheter; or d) other
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43 19 We acknowledge that not all infants achieving ≥ 2 of the intubation indicators may be intubated.
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50 22 Secondary outcomes
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54 24 The secondary outcomes are as follows:

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57 25 1. Intubation in the DR
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59 26 2. Number of attempts taken to successfully intubate in the DR
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- 3 1 3. Chest compressions in the DR
- 4
- 5 2 4. Adrenaline administration in the DR
- 6
- 7 3 5. Rectal temperature on admission to the NICU
- 8
- 9 4 6. NICU intubation
- 10
- 11 5 7. Surfactant use before death or hospital discharge
- 12
- 13 6 a. Number of doses, and total dose
- 14
- 15 7 b. Intra-tracheal surfactant received post-intervention
- 16
- 17 8 c. Doses of post-intervention surfactant
- 18
- 19 9 8. Respiratory distress syndrome
- 20
- 21 10 a. Clinical evidence and radiological evidence of respiratory distress at the time of first
- 22
- 23 11 intubation
- 24
- 25 12 9. Incidence of pneumothorax
- 26
- 27 13 a. Incidence of pneumothorax on chest x-ray
- 28
- 29 14 b. Pneumothorax treated with needle aspiration or chest drain insertion
- 30
- 31 15 10. Incidence of pulmonary haemorrhage
- 32
- 33 16 a. Clinical evidence of pulmonary haemorrhage
- 34
- 35 17 11. Mechanical ventilation
- 36
- 37 18 12. Days of mechanical ventilation
- 38
- 39 19 13. Use of postnatal corticosteroids for ventilator dependence
- 40
- 41 20 14. Days of duration of respiratory support (endotracheal ventilation, high-frequency oscillatory
- 42
- 43 21 ventilation, CPAP, heated humidified high-flow nasal cannula O₂, low flow nasal cannula O₂)
- 44
- 45 22 15. BPD – supplemental O₂ at 28 days of life
- 46
- 47 23 16. Chronic lung disease of prematurity (CLD) –O₂ treatment at 36 weeks corrected GA; we are
- 48
- 49 24 also recording physiological BPD as determined by physiological oxygen reduction test
- 50
- 51 25 17. Medical treatment for a patent ductus arteriosus (PDA)
- 52
- 53 26 a. Administration of ibuprofen or paracetamol for PDA
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- 3 1 18. Surgical treatment for a PDA
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- 5 2 19. Proven necrotising enterocolitis (\geq Bell's stage 2)
- 6
- 7 3 20. Incidence of Intraventricular haemorrhage (IVH) (any and severe: IVH grade \geq 3)
- 8
- 9 a. Evidence on surveillance cranial ultrasounds performed as standard of care
- 10 4
- 11
- 12 5 21. Incidence of cystic periventricular leukomalacia
- 13
- 14 6 a. Evidence on surveillance cranial ultrasounds performed as standard of care
- 15
- 16 7 22. Retinopathy of prematurity treated with laser photocoagulation or intravitreal injections
- 17
- 18 8 a. Evidence on surveillance ophthalmology review performed as standard of care
- 19
- 20
- 21 9 23. Death before hospital discharge
- 22
- 23 10 24. Survival without BPD at hospital discharge
- 24
- 25 11 25. Survival without CLD at hospital discharge
- 26
- 27 12 26. Duration of first hospitalisation
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- 29 13 27. Use of home oxygen therapy
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- 32 14 a. Discharged home on oxygen therapy
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36 16 Investigational medicinal product (IMP)

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41 18 Poractant alfa (Curosurf, Chiesi Farmaceutici, Parma, Italy) is a natural surfactant prepared from

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43 19 porcine lungs. It is licensed for ET use and administration via thin catheter for the prevention and

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45 20 treatment of RDS in preterm infants. The dosing recommendations for treatment with Curosurf

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47 21 when given by ETT are 200mg/kg for established RDS and 100 – 200mg/kg for prophylaxis. Further

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49 22 doses of 100mg/kg Curosurf may be given to infants who have persistent respiratory distress despite

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51 23 treatment with surfactant (maximum recommended dose 400mg/kg). It is currently not licensed for

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53 24 oropharyngeal administration, and therefore this study is examining the off-label use of a licensed

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55 25 product. The timing or dosage of ET surfactant is not be affected by oropharyngeal surfactant. If an

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3 1 infant is felt to need ET surfactant following initial oropharyngeal administration, then they receive
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5 2 the standard initial dose via ETT.
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10 4 Randomisation

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13 6 Infants are randomised (1:1) to receive oropharyngeal surfactant in addition to CPAP or CPAP alone
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15 7 using variable block randomisation, with block sizes of 4, 6 and 8. Randomisation is stratified by
16
17 8 participating centre and GA (<26 weeks and 26-28⁺⁶ weeks inclusive). Infants of multiple gestations
18
19 9 are randomised as individuals.
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23 10

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25 11 A computer-generated randomisation schedule using sequential 6-digit randomisation codes was
26
27 12 prepared by an independent statistician who was not be involved with subsequent data analysis or
28
29 13 interpretation and stored securely on a password-protected computer. Each participating centre is
30
31 14 provided with two separate boxes for the two GA strata with consecutively numbered, sealed
32
33 15 opaque randomisation envelopes containing the assigned treatment allocation. The boxes
34
35 16 containing the envelopes are stored securely in the NICU. An envelope from the appropriate box is
36
37 17 opened immediately before birth.
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42 19 Blinding

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47 21 This is an open-label study. The study is not blinded to investigators, subjects, or medical or nursing
48
49 22 staff. We are not using a placebo, and in the event of the infant being randomised to the 'CONTROL'
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51 23 arm, then they will be commenced on CPAP immediately after birth. The trial statistician will be
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53 24 blinded for data analysis and will be kept unaware of treatment group assignments. We defined
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55 25 objective criteria for the primary outcome to minimise potential bias.
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3 1 Intervention arm: Oropharyngeal surfactant
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7 3 Infants randomised to oropharyngeal surfactant receive a dose of poractant alfa (Curosurf, Chiesi
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9 4 Farmaceutici, Parma, Italy) immediately after birth, ideally before the cord is clamped e.g. 60
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11 5 seconds. If it is given after the cord is clamped, it is given once the infant is placed on the
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13 6 resuscitaire. It is given within 5 minutes of birth in all cases. We are recording the timing of cord
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15 7 clamping for all patients.
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20 9 The surfactant is warmed prior to being drawn up in a sterile syringe as per manufacturer's
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22 10 recommendation. Surfactant is administered by opening the mouth gently and giving the surfactant
23

24 11 as a single bolus into the oropharynx using a thin flexible catheter attached to the syringe.
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29 13 Infants are not weighed prior to enrolment. The 50th centile for birth weight (BW) for boys and girls
30

31 14 according to GA is shown in table 1. In our study, infants < 26 weeks receive a full 120mg vial of
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33 15 Curosurf. We estimate that this provides dosing in the range as indicated in table 2. In our study,
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35 16 infants 26 – 28 weeks receive a full 240mg vial of Curosurf, and we estimate that this provides
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37 17 dosing in the range as indicated in table 3.
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42 19 Control group: CPAP
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46 21 Infants randomised to the control group do not have anything injected into their oropharynx and are
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48 22 stabilised on CPAP in the DR as per routine practice.
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53 24 Clinical management
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3 1 After the initial intervention, infants then receive standard care with CPAP, regardless of their group
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5 2 assignment. DR care is carried out by the neonatal team who are trained in neonatal resuscitation as
6
7 3 per the recommendations of the International Liaison Committee on Resuscitation (ILCOR). Infants
8
9 4 in both groups are intubated in the DR for persistent apnoea and/or bradycardia despite PPV by
10
11 5 mask as per ILCOR recommendations. Infants are not intubated in the DR solely for surfactant
12
13 6 administration. All other aspects of neonatal intensive care is at the discretion of the treating
14
15 7 physicians. Infants in both groups are treated equally. The frequency of blood gas monitoring is
16
17 8 based on the decision of the treating physician. Enrolled infants are intubated if they reach the pre-
18
19 9 determined criteria for respiratory failure. After giving endotracheal surfactant for the treatment of
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21 10 RDS, attending clinicians may attempt to extubate the babies immediately or they may elect to
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23 11 ventilate the babies for a longer period at their discretion.
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32 14 Data management

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38 16 Data is collected by the on-site investigators from the patient's clinical notes. This is recorded on a
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40 17 data worksheet and transferred to an electronic Case Report Form (CRF) to be stored in a secure,
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42 18 dedicated, password-protected electronic database. The clinical study monitor and representative of
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44 19 the regulatory authority can directly access source documents for comparison of such data with the
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46 20 data in the electronic CRFs and can verify that the study is carried out in compliance with the
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48 21 protocol and local regulatory requirements.
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52 22 The investigators adheres to national and hospital protocols on data use and storage. Data is coded.
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54 23 It is stored in a locked filing cabinet then uploaded onto a password-protected computer in a locked
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56 24 office. Documents are stored safely in confidential conditions. On all study-specific documents other
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58 25 than the signed consent, the subject is referred to by the study subject identification code.
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45 2 Description of statistical methods
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910 4 Trial results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT).
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12 5 The flow of patients through the trial will be represented on a CONSORT flow diagram, and the
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14 6 number included in the primary and secondary analyses as well as all reasons for exclusions will be
15
16 7 reported per trial arm. Analysis of efficacy endpoints will be carried-out following the Intention-To-
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18 8 Treat principle. A Per-Protocol analysis will also be carried out on the primary endpoint, excluding
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20 9 infants with incomplete data on the primary outcome and infants with any major protocol
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22 10 deviations.
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27 12 Demographic and baseline data will be summarised by treatment group to evaluate comparability.
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29 1330 14 Primary outcome analysis
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36 16 The primary outcome will be summarised per group. Ratios of relative risk will be
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38 17 reported with 95% confidence intervals. A two-sided, two-proportion Z test will be
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40 18 carried out to investigate whether the rate of endotracheal intubation differs between
41
42 19 intervention and standard-of-care. This analysis will be carried out both on the
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44 20 intention-to-treat set and on the per protocol set.
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49 22 A competing risks model will be fitted to investigate the effect of the intervention on
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51 23 the primary endpoint, adjusting for competing outcomes (e.g. mortality) that may
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53 24 impact on observation of the primary endpoint.
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3 1 The sensitivity of the estimated intervention effect to measured covariates of interest,
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5 2 including centre, GA, birth weight, gender, mode of delivery and antenatal
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7 3 corticosteroid treatment, will be evaluated with regression analysis.
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10 5 Secondary outcome analysis

11 6 Categorical outcomes will be summarised per treatment group, with between-group differences
12
13 7 expressed as a relative risk with 95% confidence intervals. A two-sided, two-proportion Z test will be
14
15 8 carried out for each categorical outcome to investigate whether the proportion differs between
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17 9 intervention and standard of care. For the important secondary endpoint of death before hospital
18
19 10 discharge, regression analysis will be employed to determine sensitivity of the estimated
20
21 11 intervention effect to potentially relevant covariates (as specified above for the primary outcome).
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23 12

24 13 Numeric secondary outcomes will be summarised by treatment group and between-group
25
26 14 differences will be presented with a 95% confidence interval. A superiority hypothesis test will be
27
28 15 carried out to test for a difference in the outcome between control and intervention, using a t-test
29
30 16 or a Mann-Whitney U test where relevant.
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32 17

33 18 Subgroup analyses

34 19 Subgroups of interest include infants of different gestational age strata (e.g. less than 26 weeks, and
35
36 20 26-28 weeks' gestation at birth), and infants from different participating centres. Subgroup analysis
37
38 21 of the primary outcome and the important secondary outcome of death before hospital discharge
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40 22 will be carried out by regression modelling to determine differences in the intervention effect for
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42 23 infants of different GA strata, and infants from different participating centres.
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45 25 Missing data

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3 1 Any missing data or data anomalies will be communicated to the study site(s) for prompt
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5 2 clarification and resolution. For outcomes missing more than 5% of data in either treatment group,
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7 3 missing data methods will be employed in analysis. For categorical outcomes with censored data,
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9 4 Kaplan-Meier analyses will be used to estimate treatment effect. For other missing data, a suitable
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11 5 imputation method will be selected during blind review of the data.
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16 7 Sample size and power

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20 9 The sample size calculation assumed a rate of endotracheal intubation of 46% for infants treated
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22 10 with CPAP alone, and a rate of 28% for infants receiving oropharyngeal surfactant and CPAP. The
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24 11 former was informed by published RCTs showing a rate of mechanical ventilation in the days after
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26 12 birth among preterm infants treated with CPAP alone from 40– 60%¹⁰⁻¹² and rates of CPAP failure of
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28 13 43% reported in a cohort of preterm infants 25 – 28 weeks' gestation initially commenced on
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30 14 CPAP.¹⁴ The latter was informed by a cohort of infants born 26 – 28 weeks' gestation reporting that
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32 15 minimally invasive surfactant techniques reduced the rate of mechanical ventilation to from 46% to
33
34 16 28%.²⁸ Sample size was calculated in G*power based on a two-sided, two-proportion Z test. A
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36 17 sample size of 125 infants per arm will be required to give a statistical power of 80% at a significance
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38 18 level of 5%, adjusted for an anticipated death rate of 10% (estimated from local data (NMH,
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40 19 Neonatal Clinical Report, 2015).
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21 Safety analyses

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23 23 Adverse events following administration of oropharyngeal surfactant will be documented. Safety
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25 24 analyses will be carried out on the Safety Set, defined as patients in the intervention arm who
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27 25 received oropharyngeal surfactant and patients who received CPAP only. The frequency of adverse
28
29 26 events and the number and percentage of infants reported as having at least one emergent adverse
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1 event, will be reported by system organ class and preferred term, by treatment received. The same
2 description will be performed for serious adverse events (SAE), severe AE, AE treatment-related and
3 AE leading to IMP withdrawal. Defined SAEs for the study are important medical events, and death
4 before hospital discharge.

6 Safety monitoring and interim analysis

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

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

19 The DSMB will conduct interim analysis to determine whether the data provide overwhelming
20 evidence of efficacy or futility, defined as a highly statistically significant difference in the primary
21 outcome or a highly statistically significant difference in the important secondary outcome of death
22 before hospital discharge. The type I error rate for interim analysis will be set to 0.001 in accordance
23 with the Haybittle-Peto stopping boundary. For final analysis, the type I error rate will remain at
24 0.05. Interim analysis will be carried out after approximately 50% of participants (n=126) have
25 completed the study. The DSMB may recommend early termination of the trial due to efficacy or
26 futility; or for unanticipated concerns for the safety of enrolled infants. Standard procedures for

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3 1 reporting AEs will be used in accordance with Good Clinical Practice guidelines.
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6 2 Ethics and dissemination
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10 3 The study was initially approved by the Research Ethics Committee at NMH, Dublin, and the Health
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12 4 Products Regulatory Authority of Ireland. Approval was also obtained at the research ethics
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14 5 committees at each participating site and at the relevant competent authority for each participating
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16 6 country. All bodies are informed in writing of any substantial changes to the protocol, prior to any
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18 7 such changes being implemented. University College Dublin, Ireland is the sponsor for this study.
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24 9 Patient and public involvement (PPI)
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29 11 We liaised with the Irish Neonatal Health Alliance for assistance when designing the parent
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31 12 information leaflet and consent form. Parent focus groups were held via Pediatric Clinical Research
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33 13 Infrastructure Network (PedCRIN) prior to expansion of the study to European sites.
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38 15 Recruitment
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42 17 The National Maternity Hospital is a stand-alone university maternity hospital with a tertiary NICU to
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44 18 which >150 infants <1500g are admitted annually. Approximately 60 babies <29 weeks' gestation are
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46 19 admitted annually. Though the enrolment rates to our studies amongst eligible infants are
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48 20 consistently excellent (> 80%), we believe it is necessary to enrol infants at multiple sites in order to
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50 21 enrol our planned target sample of 250 infants in a timely fashion. We have a track record enlisting
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52 22 the help of collaborators nationally⁵³ and internationally^{54 55} to perform our studies. We believe that
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55 23 with their help, we can enrol these infants in 3 years.
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60 25 Current status

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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.

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Publication of results

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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

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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.

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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

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<u>Procedures</u>	<u>Screening</u>	<u>Allocation</u>	<u>Post-allocation</u>	<u>Close-out</u>
	Screening	Day of Birth	120 hours after birth	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 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title <i>Page 1</i>	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration <i>P1, line 12</i>	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 <i>P1 line 15</i>	3	Date and version identifier
Funding <i>Page 2 line 7</i>	4	Sources and types of financial, material, and other support
Roles and responsibilities <i>Page 1 Line 17</i> <i>Page 2 + 3</i>	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 <i>Page 7</i>	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 <i>Page 9 line 22</i>	7	Specific objectives or hypotheses
Trial design <i>Page 10 line 6</i>	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

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

Allocation:

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52			
53	Sequence	16a	Method of generating the allocation sequence (eg, computer-
54	generation		generated random numbers), and list of any factors for stratification.
55	Page 15 line 4		To reduce predictability of a random sequence, details of any planned
56			restriction (eg, blocking) should be provided in a separate document
57			that is unavailable to those who enrol participants or assign
58			interventions
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- 1
2 Allocation 16b Mechanism of implementing the allocation sequence (eg, central
3 concealment telephone; sequentially numbered, opaque, sealed envelopes),
4 mechanism describing any steps to conceal the sequence until interventions are
5 assigned
6 *Page 15 Line 15*
- 7 Implementation 16c Who will generate the allocation sequence, who will enrol participants,
8 and who will assign participants to interventions
9 *Page 15 Line 14*
- 10 Blinding 17a Who will be blinded after assignment to interventions (eg, trial
11 (masking) participants, care providers, outcome assessors, data analysts), and
12 how
13 *Page 15*
14 *Line 19*
- 15 17b If blinded, circumstances under which unblinding is permissible, and
16 procedure for revealing a participant's allocated intervention during
17 the trial
18
19

20 **Methods: Data collection, management, and analysis**

- 21 Data collection 18a Plans for assessment and collection of outcome, baseline, and other
22 methods trial data, including any related processes to promote data quality (eg,
23 duplicate measurements, training of assessors) and a description of
24 study instruments (eg, questionnaires, laboratory tests) along with
25 their reliability and validity, if known. Reference to where data
26 collection forms can be found, if not in the protocol
27 *P17 Line 16*
- 28 18b Plans to promote participant retention and complete follow-up,
29 including list of any outcome data to be collected for participants who
30 discontinue or deviate from intervention protocols
31 *P19 Line 25*
- 32 Data 19 Plans for data entry, coding, security, and storage, including any
33 management related processes to promote data quality (eg, double data entry;
34 range checks for data values). Reference to where details of data
35 management procedures can be found, if not in the protocol
36 *Page 17 Line 22*
- 37 Statistical 20a Statistical methods for analysing primary and secondary outcomes.
38 methods Reference to where other details of the statistical analysis plan can be
39 found, if not in the protocol
40 *P18 Line 2*
- 41 20b Methods for any additional analyses (eg, subgroup and adjusted
42 analyses)
43
44 20c Definition of analysis population relating to protocol non-adherence
45 (eg, as randomised analysis), and any statistical methods to handle
46 missing data (eg, multiple imputation)
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52 **Methods: Monitoring**

- 53 Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role
54 and reporting structure; statement of whether it is independent from
55 the sponsor and competing interests; and reference to where further
56 details about its charter can be found, if not in the protocol.
57 Alternatively, an explanation of why a DMC is not needed
58 *Page 21*
59 *Line 6*
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1			
2		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
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7	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
8	<i>Page 20</i>		
9	<i>Line 23</i>		
10			
11	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
12	<i>Page 17</i>		
13	<i>Line 18</i>		
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15			
16	Ethics and dissemination		
17			
18	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
19	<i>Page 22 line 2</i>	<i>and Page 2 line 10</i>	
20	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
21	<i>Page 22</i>		
22	<i>Line 6</i>		
23			
24			
25			
26	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
27	<i>Page 11</i>		
28	<i>Line 10</i>		
29			
30		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
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32			
33	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
34	<i>Page 17</i>		
35	<i>Line 24</i>		
36			
37	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
38	<i>Page 2 line 7</i>		
39	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
40	<i>Page 3 line 16</i>		
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45	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
46	<i>with</i>		
47			
48	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
49	<i>Page 21 line 2</i>		
50	<i>Page 18 line 6</i>		
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54		31b	Authorship eligibility guidelines and any intended use of professional writers
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57		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
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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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-035994.R2
Article Type:	Protocol
Date Submitted by the Author:	07-Apr-2020
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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Research methods, Paediatrics
Keywords:	NEONATOLOGY, PAEDIATRICS, PERINATOLOGY

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2
3 1 **Study protocol for the POPART study – Prophylactic Oropharyngeal surfactant for Preterm infants:**

4
5 2 **A Randomised Trial**

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7 3

8
9 4 Madeleine C. Murphy,¹⁻³ Marie Galligan,³ Brenda Molloy,³ Rabia Hussain,³ Peter Doran,³ Colm P.F.

10
11 5 O'Donnell¹⁻³

12
13 6 1. National Maternity Hospital, Dublin, Ireland

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15 7 2. National Children's Research Centre, Dublin, Ireland

16
17 8 3. School of Medicine, University College Dublin, Ireland

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21 10 Word count 4308

Abstract 318

Figures/Tables 4

References 55

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23 11

24
25 12 **Trial registration**

26
27 13 Protocol identification (code or reference number): UCDCRC/16/003

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29 14 EudraCT number: 2016-004198-41

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31 15 Protocol version 2.0, dated 19.07.19

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34
35 17 **Trial sponsor**

36
37 18 University College Dublin

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40
41 20 **Corresponding Author**

42
43 21 Address Prof. Colm O'Donnell, Department of Neonatology, National Maternity Hospital,
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45 22 Holles Street, Dublin 2, Ireland

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47 23 Tel +353 1 6373100

48
49 24 Email codonnell@nmh.ie

50
51 25

52
53 26 **Key words:** Infant, newborn; oropharyngeal surfactant; respiratory distress syndrome; intubation;

54
55 27 randomised controlled trial

1
2
3 1 **Author Contributions:** COD conceived and designed the trial protocol, co-wrote the first draft and
4
5 2 revised the manuscript for intellectual content. MCM helped design the trial protocol, co-wrote the
6
7 3 first draft and revised the manuscript for intellectual content. MG, BM, RH, and PD helped design
8
9 4 the trial protocol and revised the manuscript for intellectual content. MG designed the statistical
10
11 5 analysis plan. All authors approved the final manuscript prior to submission.
12
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14 6

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16
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22
23 10 collection, analysis or interpretation. Further, they will have no role in the decision to present,
24
25 11 publish or otherwise report results.
26

27
28 12 Madeleine Murphy is the recipient of a Clinical Research Fellowship by the National Children's
29
30 13 Research Centre, Dublin (R17637)
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35
36 16 throughout Europe, also support the study.
37
38
39 17

40
41 18 **Competing interests:** None declared
42
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46 20 **Ethics approval:**

47
48 21 Ireland: Research Ethics Committee, The National Maternity Hospital, Dublin, Ireland; Research
49
50 22 Ethics Committee, Coombe Women and Infants University Hospital
51
52 23 Belgium: Le Comité d'Ethique du CHR Citadelle
53
54 24 Czech Republic: Etická komise, Všeobecné fakultní nemocnice (VFN) v Praze (Ethics Committee of
55
56 25 the General University Hospital, Prague)
57
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59
60

- 1
2
3 1 Norway: Regional komité for medisinsk og helsefaglig forskningsetikk (REK nord) (Regional Ethics
4
5 2 Committee, REK, nord)
6
7 3 Portugal: Comissão de Ética para a Investigação Clínica, CEIC (National Ethics Committee for Clinical
8
9 4 Research)
10
11
12 5 Sweden: Stockholm Regional Ethics Review Board
13
14 6

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25 12 Norway; Hans Jørgen Guthe, Haukeland University Hospital, Bergen, Norway; Richard Plavka, Charles
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28
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30
31 15 Stockholm, Sweden; and Almerinda Pereira, Hospital de Braga, Braga, Portugal.
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35 16 **Data statement:** Members of the Trial Steering Committee will have access to the final dataset. Data
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37 17 will be available on request.
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3 1 Abstract
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7 3 Introduction: Many preterm infants develop respiratory distress syndrome (RDS), a condition
8
9 4 characterised by a relative lack of surfactant. Endotracheal surfactant therapy revolutionised the
10
11 5 care of preterm infants in the 1990s. However, supporting newborns with RDS with continuous
12
13 6 positive airway pressure (CPAP) and reserving endotracheal surfactant for those who develop
14
15 7 respiratory failure despite CPAP yields better results than intubating all infants for surfactant. Half of
16
17 8 preterm infants born before 29 weeks' gestation initially managed with CPAP are intubated for
18
19 9 surfactant. Intubation is difficult to learn and associated with adverse effects. Surfactant
20
21 10 administration into the oropharynx has been reported in preterm animals and humans and may be
22
23 11 effective. We wished to determine whether giving oropharyngeal surfactant at birth reduces the
24
25 12 rate of endotracheal intubation for respiratory failure in preterm infants within 120 hours of birth.
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32 14 Methods and analysis: POPART (Prophylactic Oropharyngeal surfactant for Preterm infants: A
33
34 15 Randomised Trial) is an investigator-led, unblinded, multicentre, randomised, parallel group,
35
36 16 controlled trial. Infants are eligible if born at a participating centre before 29 weeks gestational age
37
38 17 (GA) and there is a plan to offer intensive care. Infants are excluded if they have major congenital
39
40 18 anomalies. Infants are randomised at birth to treatment with oropharyngeal surfactant [120mg vial
41
42 19 <26 weeks GA stratum; 240mg vial 26 – 28+6 weeks GA stratum] in addition to CPAP or CPAP alone.
43
44 20 The primary outcome is intubation within 120 hours of birth, for bradycardia and/or apnoea despite
45
46 21 respiratory support in the delivery room or respiratory failure in the intensive care unit. Secondary
47
48 22 outcomes include incidence of mechanical ventilation, endotracheal surfactant use, chronic lung
49
50 23 disease, and death before hospital discharge.
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57 24
58 25 Ethics and dissemination: Approval for the study has been granted by the Research Ethics
59
60 26 Committees at the National Maternity Hospital, Dublin, Ireland (EC31.2016), and at each

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2
3 1 participating site. The trial is being conducted at 9 centres in 6 European countries. The study results
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5 2 will be submitted for publication in a peer-reviewed journal.
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For peer review only

1
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3 1 Article summary
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7 3 Strengths and limitations of this study
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9 4

10 5 • This is the first randomised study to specifically examine the efficacy of giving oropharyngeal
11 6 surfactant at birth to preterm infants at high risk of developing respiratory distress
12 7 syndrome.
13 8

14 9

15 10 • We are enrolling infants < 29 weeks' gestation, including infants at 23 and 24 weeks'
16 11 gestation, who are most at risk of respiratory distress syndrome.
17 12

18 13

19 14 • We were unable to credibly mask the intervention.
20 15

21 16

22 17 • To reduce the risk of bias we used objective criteria for our primary outcome i.e. intubation
23 18 within 120 hours of life.
24 19

25 20

26 21 • The multicentre nature of this study will increase the generalisability of its findings.
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1 Background

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7
8 Respiratory distress syndrome (RDS) is a lung condition of the preterm infant. The risk of RDS is
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10 inversely related to gestational age (GA). Infants with RDS have structural and functional immaturity
11
12 of their lungs. They also have a relative lack of surfactant,¹ an endogenously produced substance
13
14 that enables alveoli to expand more easily to recruit and maintain gas within the lung.
15
16
17
18 Exogenous surfactant^{2,3} is frequently used to treat newborns with RDS and has led to improved
19
20 outcomes for infants worldwide. Randomised controlled trials (RCTs) in the 1980s – 1990s⁴⁻⁷
21
22 demonstrated that surfactant, given by endotracheal tube (ETT), reduced mortality and air leak
23
24 among premature infants who were intubated for respiratory failure due to RDS. This led to the
25
26 widespread practice of intubating all extremely preterm infants for surfactant and ventilation
27
28 (“prophylactic surfactant”).⁵ Prior to the introduction of surfactant into clinical practice, concerns
29
30 were raised that premature infants who were intubated for respiratory support had worse
31
32 respiratory outcomes than infants who were managed with the non-invasive respiratory support,
33
34 nasal continuous positive airway pressure (CPAP).⁸ These concerns persisted after the widespread
35
36 introduction of surfactant.⁹ Multicentre RCTs found that starting infants on CPAP may be beneficial
37
38 when compared with intubation and positive pressure ventilation (PPV); the studies reported
39
40 decreased duration of mechanical ventilation with potential benefits of reduction of death and or
41
42 bronchopulmonary dysplasia (BPD).¹⁰⁻¹² Managing premature newborns initially with CPAP and
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44 reserving intubation, mechanical ventilation and surfactant for those infants with worsening
45
46 respiratory failure despite CPAP yields better results than intubating all infants for surfactant
47
48 administration.¹³ About half of premature infants born before 29 weeks’ gestation initially managed
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50 with CPAP for RDS are ultimately intubated for surfactant and ventilation.¹⁴
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3 1 Intubation is a procedure that is difficult to learn and is associated with adverse effects, both short¹⁵⁻
4
5 2 ¹⁹ and longer-term.²⁰⁻²² This has led many clinicians to investigate alternative methods of surfactant
6
7 3 delivery.²³ Giving nebulised surfactant to spontaneously breathing infants has met with limited
8
9 4 success.²⁴⁻²⁷ Progress has been slow due to the technical difficulties encountered in aerosolising such
10
11 5 large molecules, the expense of the equipment needed to do so and the cost of the large amount of
12
13 6 surfactant needed to form an aerosol. Interest has largely focussed on less-invasive methods of
14
15 7 surfactant administration.
16
17 8 Less invasive surfactant administration (LISA) techniques involve introducing either a feeding tube or
18
19 9 vascular catheter into the trachea of a spontaneously breathing infant at laryngoscopy.²⁸⁻³¹ LISA is
20
21 10 associated with lower rates of mechanical ventilation among preterm infants in randomised^{28 31} and
22
23 11 observational studies.³² Two year follow up outcomes for infants enrolled in the randomised trial
24
25 12 Avoid Mechanical Ventilation,²⁸ where infants were randomised to surfactant via LISA or to standard
26
27 13 care with CPAP and ET instillation of surfactant if necessary, are similar between groups.³³ The
28
29 14 procedure is becoming more widely used, but rates vary between countries.³⁴⁻³⁷ Concerns regarding
30
31 15 the validity and risk of bias within studies, a lack of familiarity with the technique, and patient
32
33 16 discomfort have been reported as reasons for not using LISA.³⁶ Use of sedation and analgesia prior
34
35 17 to laryngoscopy is not standard for the LISA procedure,²⁸ and the short-term adverse effects of
36
37 18 laryngoscopy are not avoided. While meta-analyses report that the LISA technique is associated with
38
39 19 less death or BPD,³⁸⁻⁴⁰ further RCTs are needed. The Optimist-A trial,⁴¹ evaluating minimally invasive
40
41 20 surfactant therapy in preterm infants born between 25 – 28 weeks' gestation is ongoing.
42
43 21 The laryngeal mask airway, a supraglottic airway device, may be used as an interface to deliver
44
45 22 surfactant.⁴²⁻⁴⁵ However there is currently no device available for use in very low birth weight
46
47 23 infants, who constitute the majority of infants diagnosed with RDS.
48
49 24
50
51 25 Direct administration of surfactant into the pharynx of human infants has been described in
52
53 26 randomised⁷ and prospective cohort studies.^{46 47} It is apparently effective and is an easier technique
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1 to perform than endotracheal intubation or passing a feeding tube or vascular catheter into the
2 trachea. Advantages of pharyngeal surfactant use are that it is an easy and cheaper method of
3 administering surfactant and likely causes less discomfort to infants as it avoids the use of a
4 laryngoscope. Giving surfactant early, prior to ventilation, delivers surfactant to a fluid-filled lung,
5 which is spread via a fluid-air interface when the infant starts breathing. Animal studies report that
6 surfactant is distributed more uniformly,⁴⁸ and lung function and compliance is better⁴⁹ if surfactant
7 is delivered prior to ventilation. If shown to be effective, it may reduce the adverse effects, and
8 additional associated costs, of ventilation.

9
10 A Cochrane review of pharyngeal surfactant⁵⁰ did not identify any eligible trials to assess whether
11 pharyngeal installation of surfactant before the first breath prevented morbidity and mortality in
12 infants at risk of RDS. The Ten Centre Study randomised 328 infants born between 25 – 29 weeks'
13 gestation to artificial surfactant therapy or saline. For those randomised to surfactant therapy, the
14 first dose was given via the oropharynx, with subsequent doses given via an ETT if the infant was
15 intubated, however the outcomes of infants who received pharyngeal surfactant alone were not
16 reported. Large well conducted RCTs are needed, due to the evidence from animal^{51 52} and
17 observational human studies^{46 47} suggesting that pharyngeal surfactant administration is potentially
18 safe, feasible, and may be effective.

20 Objective

21
22 We are performing a study to establish whether giving preterm infants surfactant into their
23 oropharynx at birth in addition to CPAP compared with CPAP alone reduces their need for
24 subsequent intubation in the first 5 days of life.

26 Methods

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3 1
45 2 Trial design
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10 4 The POPART trial is an investigator-led, unblinded, multicentre, randomised parallel-group
11
12 5 controlled trial. It aims to determine whether administering oropharyngeal surfactant to premature
13
14 6 infants at birth in addition to CPAP compared to CPAP alone reduces the rate of intubation for
15
16 7 respiratory failure in the first 5 days of life. The trial will recruit 250 infants born <29 weeks GA at
17
18 8 participating centres. A schedule of events is seen in figure 1.
19

20
21 9
2223 10 Setting
2425 11
26

27
28 12 The trial is being conducted at 9 neonatal intensive care units (NICUs) in 6 European countries
29
30 13 [Ireland (National Maternity Hospital (NMH), Dublin; Coombe Women and Infants University
31
32 14 Hospital (CWIUH) Dublin); Norway (University Northern Norway, Tromsø; Haukeland University
33
34 15 Hospital, Bergen); Czech Republic (Charles University, Prague; University Hospital Brno, Brno),
35
36 16 Belgium (Le Centre Hospitalier Universitaire (CHU), Liege); Sweden (Karolinska Institutet,
37
38 17 Stockholm); and Portugal (Hospital de Braga, Braga).
39

40
41 18
4243 19 Participants
4445 20
4647 21 Inclusion and exclusion criteria
4849 22
50

51
52 23 Trial subjects are premature infants at risk of RDS. Infants born less than 29 weeks GA are included if
53
54 24 the treating physician plans to offer intensive care. Infants are excluded if they have major
55
56 25 congenital anomalies (including neural tube defects, major structural cardiac anomalies (excluding
57
58 26 patent ductus arteriosus, ventricular septal defect, atrioventricular septal defect), abdominal wall
59
60

1
2
3 1 defects, congenital diaphragmatic hernia and major dysmorphic features with an abnormal
4
5 2 karyotype) and if the treating physician does not plan to offer intensive care. If there is a known
6
7 3 anomaly prenatally, families are not approached for consent. In the event of a postnatal diagnosis of
8
9 4 the aforementioned conditions, these infants meet criteria for post-randomisation exclusion.
10
11 5 Written informed consent from parent/legal guardian(s) is obtained before delivery. Infants of
12
13 6 multiple gestation and of either sex are eligible to be enrolled.
14
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18

19 8 Screening and consent

20
21 9
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23 10 Prior to the delivery a member of the research team or other senior doctor approaches
24
25 11 parent(s)/guardian(s) of eligible infants to inform them about the study. The team member explains
26
27 12 the purpose and nature of the study and provides written information for the parent(s)/guardian(s)
28
29 13 to keep. If the local language is not their first language, they are offered the opportunity to have an
30
31 14 interpreter present while the study is explained. Written consent for enrolment of the infant in the
32
33 15 study is then sought. Parents are informed that they may withdraw their child from the study at any
34
35 16 time should they so wish; and that a decision not to consent to their infants' participation in the
36
37 17 study or to withdraw their infant from the study once enrolled does not affect their infant's access
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39 18 to the best available treatment and care.
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45 20 Outcome measures

46 21 47 22 Primary outcome

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54 24 The primary outcome is the incidence of endotracheal intubation for respiratory failure within 120
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56 25 hours of birth. Enrolled infants are intubated for persistent apnoea and/or bradycardia (HR
57
58 26 <100bpm) in the delivery room (DR), or for respiratory failure in the NICU defined as ≥ 2 of:
59
60

- 1 - Clinical signs – worsening tachypnoea; grunting; subcostal, intercostal and/or sternal recession
- 2 - Acidosis – pH < 7.2 on 2 blood gases (arterial or capillary) \geq 30 minutes apart
- 3 - Hypoxaemia – FiO₂ > 0.4 to keep oxygen saturation (SpO₂) \geq 90% for > 30 minutes
- 4 - Hypercarbia – PCO₂ > 9.0 kPa on 2 blood gases (arterial or capillary) \geq 30 minutes apart
- 5 - 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 \geq 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

- 1
- 2
- 3 1 4. Adrenaline administration in the DR
- 4
- 5 2 5. Rectal temperature on admission to the NICU
- 6
- 7 3 6. NICU intubation
- 8
- 9
- 10 4 7. Surfactant use before death or hospital discharge
- 11
- 12 5 a. Number of doses, and total dose
- 13
- 14 6 b. Intra-tracheal surfactant received post-intervention
- 15
- 16 7 c. Doses of post-intervention surfactant
- 17
- 18
- 19 8 8. Respiratory distress syndrome
- 20
- 21 9 a. Clinical evidence and radiological evidence of respiratory distress at the time of first
- 22
- 23 10 intubation
- 24
- 25 11 9. Incidence of pneumothorax
- 26
- 27 12 a. Incidence of pneumothorax on chest x-ray
- 28
- 29 13 b. Pneumothorax treated with needle aspiration or chest drain insertion
- 30
- 31
- 32 14 10. Incidence of pulmonary haemorrhage
- 33
- 34 15 a. Clinical evidence of pulmonary haemorrhage
- 35
- 36
- 37 16 11. Mechanical ventilation
- 38
- 39 17 12. Days of mechanical ventilation
- 40
- 41 18 13. Use of postnatal corticosteroids for ventilator dependence
- 42
- 43 19 14. Days of duration of respiratory support (endotracheal ventilation, high-frequency oscillatory
- 44
- 45 ventilation, CPAP, heated humidified high-flow nasal cannula O₂, low flow nasal cannula O₂)
- 46
- 47 20
- 48 21 15. BPD – supplemental O₂ at 28 days of life
- 49
- 50 22 16. Chronic lung disease of prematurity (CLD) –O₂ treatment at 36 weeks corrected GA; we are
- 51
- 52 23 also recording physiological BPD as determined by physiological oxygen reduction test
- 53
- 54 24 17. Medical treatment for a patent ductus arteriosus (PDA)
- 55
- 56 25 a. Administration of ibuprofen or paracetamol for PDA
- 57
- 58
- 59 26 18. Surgical treatment for a PDA
- 60

- 1
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- 3 1 19. Proven necrotising enterocolitis (\geq Bell's stage 2)
- 4
- 5 2 20. Incidence of Intraventricular haemorrhage (IVH) (any and severe: IVH grade \geq 3)
- 6
- 7 a. Evidence on surveillance cranial ultrasounds performed as standard of care
- 8 3
- 9
- 10 4 21. Incidence of cystic periventricular leukomalacia
- 11
- 12 a. Evidence on surveillance cranial ultrasounds performed as standard of care
- 13 5
- 14 6 22. Retinopathy of prematurity treated with laser photocoagulation or intravitreal injections
- 15
- 16 a. Evidence on surveillance ophthalmology review performed as standard of care
- 17 7
- 18
- 19 8 23. Death before hospital discharge
- 20
- 21 9 24. Survival without BPD at hospital discharge
- 22
- 23 10 25. Survival without CLD at hospital discharge
- 24
- 25 11 26. Duration of first hospitalisation
- 26
- 27 12 27. Use of home oxygen therapy
- 28
- 29 a. Discharged home on oxygen therapy
- 30 13
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- 32 14
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- 34 15 Investigational medicinal product (IMP)
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- 36 16
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- 38
- 39 17 Poractant alfa (Curosurf, Chiesi Farmaceutici, Parma, Italy) is a natural surfactant prepared from
- 40
- 41 18 porcine lungs. It is licensed for ET use and administration via thin catheter for the prevention and
- 42
- 43 19 treatment of RDS in preterm infants. The dosing recommendations for treatment with Curosurf
- 44
- 45 20 when given by ETT are 200mg/kg for established RDS and 100 – 200mg/kg for prophylaxis. Further
- 46
- 47 21 doses of 100mg/kg Curosurf may be given to infants who have persistent respiratory distress despite
- 48
- 49 22 treatment with surfactant (maximum recommended dose 400mg/kg). It is currently not licensed for
- 50
- 51 23 oropharyngeal administration, and therefore this study is examining the off-label use of a licensed
- 52
- 53 24 product. The timing or dosage of ET surfactant is not be affected by oropharyngeal surfactant. If an
- 54
- 55 25 infant is felt to need ET surfactant following initial oropharyngeal administration, then they receive
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3 1 the standard initial dose via ETT. Additional doses are given at the discretion of the attending
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5 2 physician.
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10 4 Randomisation

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13 6 Infants are randomised (1:1) to receive oropharyngeal surfactant in addition to CPAP or CPAP alone
14
15 7 using variable block randomisation, with block sizes of 4, 6 and 8. Randomisation is stratified by
16
17 8 participating centre and GA (<26 weeks and 26-28⁺⁶ weeks inclusive). Infants of multiple gestations
18
19 9 are randomised as individuals.
20
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23 10

24
25 11 A computer-generated randomisation schedule using sequential 6-digit randomisation codes was
26
27 12 prepared by an independent statistician who was not be involved with subsequent data analysis or
28
29 13 interpretation and stored securely on a password-protected computer. Each participating centre is
30
31 14 provided with two separate boxes for the two GA strata with consecutively numbered, sealed
32
33 15 opaque randomisation envelopes containing the assigned treatment allocation. The boxes
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35 16 containing the envelopes are stored securely in the NICU. An envelope from the appropriate box is
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37 17 opened immediately before birth.
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41 18

42 19 Blinding

43 20

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46
47 21 This is an open-label study. The study is not blinded to investigators, subjects, or medical or nursing
48
49 22 staff. We are not using a placebo, and in the event of the infant being randomised to the 'CONTROL'
50
51 23 arm, then they will be commenced on CPAP immediately after birth. The trial statistician will be
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53 24 blinded for data analysis and will be kept unaware of treatment group assignments. We defined
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55 25 objective criteria for the primary outcome to minimise potential bias.
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3 1 Intervention arm: Oropharyngeal surfactant
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7 3 Infants randomised to oropharyngeal surfactant receive a dose of poractant alfa (Curosurf, Chiesi
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9 4 Farmaceutici, Parma, Italy) immediately after birth, ideally before the cord is clamped e.g. 60
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11 5 seconds, and are then commenced on CPAP as per routine practice. If it is given after the cord is
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13 6 clamped, it is given once the infant is placed on the resuscitaire. It is given within 5 minutes of birth
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15 7 in all cases. We are recording the timing of cord clamping for all patients.
16

17 8
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19 9 The surfactant is warmed prior to being drawn up in a sterile syringe as per manufacturer's
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21 10 recommendation. Surfactant is administered by opening the mouth gently and giving the surfactant
22

23 11 as a single bolus into the oropharynx using a thin flexible catheter attached to the syringe.
24

25 12
26

27 13 Infants are not weighed prior to enrolment. The 50th centile for birth weight (BW) for boys and girls
28

29 14 according to GA is shown in table 1. In our study, infants < 26 weeks receive a full 120mg vial of
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31 15 Curosurf. We estimate that this provides dosing in the range as indicated in table 2. In our study,
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33 16 infants 26 – 28 weeks receive a full 240mg vial of Curosurf, and we estimate that this provides
34

35 17 dosing in the range as indicated in table 3.
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39 19 Control group: CPAP
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43 21 Infants randomised to the control group do not have anything injected into their oropharynx and are
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45 22 stabilised on CPAP in the DR as per routine practice.
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49 24 Clinical management
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3 1 After the initial intervention, infants then receive standard care with CPAP, regardless of their group
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5 2 assignment. DR care is carried out by the neonatal team who are trained in neonatal resuscitation as
6
7 3 per the recommendations of the International Liaison Committee on Resuscitation (ILCOR). Infants
8
9 4 in both groups are intubated in the DR for persistent apnoea and/or bradycardia despite PPV by
10
11 5 mask as per ILCOR recommendations. Infants are not intubated in the DR solely for surfactant
12
13 6 administration. All other aspects of neonatal intensive care is at the discretion of the treating
14
15 7 physicians. Infants in both groups are treated equally. The frequency of blood gas monitoring is
16
17 8 based on the decision of the treating physician. Enrolled infants are intubated if they reach the pre-
18
19 9 determined criteria for respiratory failure. After giving endotracheal surfactant for the treatment of
20
21 10 RDS, attending clinicians may attempt to extubate the babies immediately or they may elect to
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23 11 ventilate the babies for a longer period at their discretion.
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32 14 Data management

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38 16 Data is collected by the on-site investigators from the patient's clinical notes. This is recorded on a
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40 17 data worksheet and transferred to an electronic Case Report Form (CRF) to be stored in a secure,
41
42 18 dedicated, password-protected electronic database. The clinical study monitor and representative of
43
44 19 the regulatory authority can directly access source documents for comparison of such data with the
45
46 20 data in the electronic CRFs and can verify that the study is carried out in compliance with the
47
48 21 protocol and local regulatory requirements.
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52 22 The investigators adheres to national and hospital protocols on data use and storage. Data is coded.
53
54 23 It is stored in a locked filing cabinet then uploaded onto a password-protected computer in a locked
55
56 24 office. Documents are stored safely in confidential conditions. On all study-specific documents other
57
58 25 than the signed consent, the subject is referred to by the study subject identification code.
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3 1
45 2 Description of statistical methods
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7 3
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910 4 Trial results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT).
11

12 5 The flow of patients through the trial will be represented on a CONSORT flow diagram, and the
13
14 6 number included in the primary and secondary analyses as well as all reasons for exclusions will be
15
16 7 reported per trial arm. Analysis of efficacy endpoints will be carried-out following the Intention-To-
17
18 8 Treat principle. A Per-Protocol analysis will also be carried out on the primary endpoint, excluding
19
20 9 infants with incomplete data on the primary outcome and infants with any major protocol
21
22 10 deviations.
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26 11

27 12 Demographic and baseline data will be summarised by treatment group to evaluate comparability.
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29 13

30 14 Primary outcome analysis
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35
36 16 The primary outcome will be summarised per group. Ratios of relative risk will be
37
38 17 reported with 95% confidence intervals. A two-sided, two-proportion Z test will be
39
40 18 carried out to investigate whether the rate of endotracheal intubation differs between
41
42 19 intervention and standard-of-care. This analysis will be carried out both on the
43
44 20 intention-to-treat set and on the per protocol set.
45
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47 21

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49 22 A competing risks model will be fitted to investigate the effect of the intervention on
50
51 23 the primary endpoint, adjusting for competing outcomes (e.g. mortality) that may
52
53 24 impact on observation of the primary endpoint.
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3 1 The sensitivity of the estimated intervention effect to measured covariates of interest,
4
5 2 including centre, GA, birth weight, gender, mode of delivery and antenatal
6
7 3 corticosteroid treatment, will be evaluated with regression analysis.
8
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10 4

11 5 Secondary outcome analysis

12 6 Categorical outcomes will be summarised per treatment group, with between-group differences
13
14 7 expressed as a relative risk with 95% confidence intervals. A two-sided, two-proportion Z test will be
15
16 8 carried out for each categorical outcome to investigate whether the proportion differs between
17
18 9 intervention and standard of care. For the important secondary endpoint of death before hospital
19
20 10 discharge, regression analysis will be employed to determine sensitivity of the estimated
21
22 11 intervention effect to potentially relevant covariates (as specified above for the primary outcome).
23
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30 13 Numeric secondary outcomes will be summarised by treatment group and between-group
31
32 14 differences will be presented with a 95% confidence interval. A superiority hypothesis test will be
33
34 15 carried out to test for a difference in the outcome between control and intervention, using a t-test
35
36 16 or a Mann-Whitney U test where relevant.
37
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41 18 Subgroup analyses

42
43 19 Subgroups of interest include infants of different gestational age strata (e.g. less than 26 weeks, and
44
45 20 26-28 weeks' gestation at birth), and infants from different participating centres. Subgroup analysis
46
47 21 of the primary outcome and the important secondary outcome of death before hospital discharge
48
49 22 will be carried out by regression modelling to determine differences in the intervention effect for
50
51 23 infants of different GA strata, and infants from different participating centres.
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57 25 Missing data

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3 1 Any missing data or data anomalies will be communicated to the study site(s) for prompt
4
5 2 clarification and resolution. For outcomes missing more than 5% of data in either treatment group,
6
7 3 missing data methods will be employed in analysis. For categorical outcomes with censored data,
8
9 4 Kaplan-Meier analyses will be used to estimate treatment effect. For other missing data, a suitable
10
11 5 imputation method will be selected during blind review of the data.
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14 6

16 7 Sample size and power

18 8
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20 9 The sample size calculation assumed a rate of endotracheal intubation of 46% for infants treated
21
22 10 with CPAP alone, and a rate of 28% for infants receiving oropharyngeal surfactant and CPAP. The
23
24 11 former was informed by published RCTs showing a rate of mechanical ventilation in the days after
25
26 12 birth among preterm infants treated with CPAP alone from 40– 60%¹⁰⁻¹² and rates of CPAP failure of
27
28 13 43% reported in a cohort of preterm infants 25 – 28 weeks' gestation initially commenced on
29
30 14 CPAP.¹⁴ The latter was informed by a cohort of infants born 26 – 28 weeks' gestation reporting that
31
32 15 minimally invasive surfactant techniques reduced the rate of mechanical ventilation to from 46% to
33
34 16 28%.²⁸ Sample size was calculated in G*power based on a two-sided, two-proportion Z test. A
35
36 17 sample size of 125 infants per arm will be required to give a statistical power of 80% at a significance
37
38 18 level of 5%, adjusted for an anticipated death rate of 10% (estimated from local data (NMH,
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40 19 Neonatal Clinical Report, 2015).
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52 21 Safety analyses

53 22
54 23 Adverse events following administration of oropharyngeal surfactant will be documented. Safety
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56 24 analyses will be carried out on the Safety Set, defined as patients in the intervention arm who
57
58 25 received oropharyngeal surfactant and patients who received CPAP only. The frequency of adverse
59
60 26 events and the number and percentage of infants reported as having at least one emergent adverse

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

6 Safety monitoring and interim analysis

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

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

19 The DSMB will conduct interim analysis to determine whether the data provide overwhelming
20 evidence of efficacy or futility, defined as a highly statistically significant difference in the primary
21 outcome or a highly statistically significant difference in the important secondary outcome of death
22 before hospital discharge. The type I error rate for interim analysis will be set to 0.001 in accordance
23 with the Haybittle-Peto stopping boundary. For final analysis, the type I error rate will remain at
24 0.05. Interim analysis will be carried out after approximately 50% of participants (n=126) have
25 completed the study. The DSMB may recommend early termination of the trial due to efficacy or
26 futility; or for unanticipated concerns for the safety of enrolled infants. Standard procedures for

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2
3 1 reporting AEs will be used in accordance with Good Clinical Practice guidelines.
4
5

6 2 Ethics and dissemination
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8
9

10 3 The study was initially approved by the Research Ethics Committee at NMH, Dublin, and the Health
11
12 4 Products Regulatory Authority of Ireland. Approval was also obtained at the research ethics
13
14 5 committees at each participating site and at the relevant competent authority for each participating
15
16 6 country. All bodies are informed in writing of any substantial changes to the protocol, prior to any
17
18 7 such changes being implemented. University College Dublin, Ireland is the sponsor for this study.
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22 8
23

24 9 Patient and public involvement (PPI)
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28 10

29 11 We liaised with the Irish Neonatal Health Alliance for assistance when designing the parent
30
31 12 information leaflet and consent form. Parent focus groups were held via Pediatric Clinical Research
32
33 13 Infrastructure Network (PedCRIN) prior to expansion of the study to European sites.
34
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36 14

37 15 Recruitment
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41 16

42 17 The National Maternity Hospital is a stand-alone university maternity hospital with a tertiary NICU to
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44 18 which >150 infants <1500g are admitted annually. Approximately 60 babies <29 weeks' gestation are
45
46 19 admitted annually. Though the enrolment rates to our studies amongst eligible infants are
47
48 20 consistently excellent (> 80%), we believe it is necessary to enrol infants at multiple sites in order to
49
50 21 enrol our planned target sample of 250 infants in a timely fashion. We have a track record enlisting
51
52 22 the help of collaborators nationally⁵³ and internationally^{54 55} to perform our studies. We believe that
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54 23 with their help, we can enrol these infants in 3 years.
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58 24

59 25 Current status
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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.

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Publication of results

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

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Discussion

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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.

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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

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<u>Procedures</u>	<u>Screening</u>	<u>Allocation</u>	<u>Post-allocation</u>	<u>Close-out</u>
	Screening	Day of Birth	120 hours after birth	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 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title <i>Page 1</i>	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration <i>P1, line 12</i>	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 <i>P1 line 15</i>	3	Date and version identifier
Funding <i>Pg 2 line 7</i>	4	Sources and types of financial, material, and other support
Roles and responsibilities <i>Page 1 Line 17</i> <i>Page 2 + 3</i>	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 <i>Page 7</i>	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 <i>Page 9 line 22</i>	7	Specific objectives or hypotheses
Trial design <i>Page 10 line 6</i>	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

1
2
3
4 Study setting 9 Description of study settings (eg, community clinic, academic hospital)
5 *Page 10 line 12* and list of countries where data will be collected. Reference to where
6 list of study sites can be obtained
7

8
9 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility
10 *Page 10 line 23* criteria for study centres and individuals who will perform the
11 interventions (eg, surgeons, psychotherapists)
12

13 Interventions 11a Interventions for each group with sufficient detail to allow replication,
14 *Page 15* including how and when they will be administered
15 *Line 1*

16 11b Criteria for discontinuing or modifying allocated interventions for a
17 given trial participant (eg, drug dose change in response to harms,
18 participant request, or improving/worsening disease)
19

20 11c Strategies to improve adherence to intervention protocols, and any
21 procedures for monitoring adherence (eg, drug tablet return,
22 laboratory tests)
23
24

25 11d Relevant concomitant care and interventions that are permitted or
26 prohibited during the trial
27

28 Outcomes 12 Primary, secondary, and other outcomes, including the specific
29 *Page 11 line 24* measurement variable (eg, systolic blood pressure), analysis metric
30 (eg, change from baseline, final value, time to event), method of
31 aggregation (eg, median, proportion), and time point for each
32 outcome. Explanation of the clinical relevance of chosen efficacy and
33 harm outcomes is strongly recommended
34
35

36 Participant 13 Time schedule of enrolment, interventions (including any run-ins and
37 *Page 10 line 10* washouts), assessments, and visits for participants. A schematic
38 *(Page 22 line 15)* diagram is highly recommended (see Figure)
39
40

41 Sample size 14 Estimated number of participants needed to achieve study objectives
42 *Page 10* and how it was determined, including clinical and statistical
43 *Line 7* assumptions supporting any sample size calculations
44

45 Recruitment 15 Strategies for achieving adequate participant enrolment to reach
46 target sample size
47 *Page 12 line 15*
48

Methods: Assignment of interventions (for controlled trials)

49 Allocation:
50

51
52 Sequence 16a Method of generating the allocation sequence (eg, computer-
53 generation generated random numbers), and list of any factors for stratification.
54 To reduce predictability of a random sequence, details of any planned
55 *Page 15 line 4* restriction (eg, blocking) should be provided in a separate document
56 that is unavailable to those who enrol participants or assign
57 interventions
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- 1
2 Allocation 16b Mechanism of implementing the allocation sequence (eg, central
3 concealment telephone; sequentially numbered, opaque, sealed envelopes),
4 mechanism describing any steps to conceal the sequence until interventions are
5 assigned
6 *Page 15 Line 15*
- 7 Implementation 16c Who will generate the allocation sequence, who will enrol participants,
8 and who will assign participants to interventions
9 *Page 15 Line 14*
- 10
11 Blinding 17a Who will be blinded after assignment to interventions (eg, trial
12 (masking) participants, care providers, outcome assessors, data analysts), and
13 how
14 *Page 15*
15 *Line 19*
- 16 17b If blinded, circumstances under which unblinding is permissible, and
17 procedure for revealing a participant's allocated intervention during
18 the trial
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20 **Methods: Data collection, management, and analysis**

- 21
22 Data collection 18a Plans for assessment and collection of outcome, baseline, and other
23 methods trial data, including any related processes to promote data quality (eg,
24 *P17 Line 16* duplicate measurements, training of assessors) and a description of
25 study instruments (eg, questionnaires, laboratory tests) along with
26 their reliability and validity, if known. Reference to where data
27 collection forms can be found, if not in the protocol
- 28
29
30 *P19 Line 25* 18b Plans to promote participant retention and complete follow-up,
31 including list of any outcome data to be collected for participants who
32 discontinue or deviate from intervention protocols
- 33
34 Data 19 Plans for data entry, coding, security, and storage, including any
35 management related processes to promote data quality (eg, double data entry;
36 *Page 17 Line 22* range checks for data values). Reference to where details of data
37 management procedures can be found, if not in the protocol
- 38
39
40 Statistical 20a Statistical methods for analysing primary and secondary outcomes.
41 methods Reference to where other details of the statistical analysis plan can be
42 *P18 Line 2* found, if not in the protocol
- 43
44 20b Methods for any additional analyses (eg, subgroup and adjusted
45 analyses)
- 46
47 20c Definition of analysis population relating to protocol non-adherence
48 (eg, as randomised analysis), and any statistical methods to handle
49 missing data (eg, multiple imputation)
50
51

52 **Methods: Monitoring**

- 53
54 Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role
55 and reporting structure; statement of whether it is independent from
56 *Page 21* the sponsor and competing interests; and reference to where further
57 *Line 6* details about its charter can be found, if not in the protocol.
58 Alternatively, an explanation of why a DMC is not needed
59
60

1			
2		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
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7	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
8	<i>Page 20</i>		
9	<i>Line 23</i>		
10			
11	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
12	<i>Page 17</i>		
13	<i>Line 18</i>		
14			
15			
16	Ethics and dissemination		
17			
18	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
19	<i>Page 22 line 2</i>	<i>and Page 2 line 10</i>	
20	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
21	<i>Page 22</i>		
22	<i>Line 6</i>		
23			
24			
25			
26	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
27	<i>Page 11</i>		
28	<i>Line 10</i>		
29			
30		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
31			
32			
33	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
34	<i>Page 17</i>		
35	<i>Line 24</i>		
36			
37	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
38	<i>Page 2 line 7</i>		
39	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
40	<i>Page 3 line 16</i>		
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45	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
46	<i>with</i>		
47			
48	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
49	<i>Page 21 line 2</i>		
50	<i>Page 18 line 6</i>		
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54		31b	Authorship eligibility guidelines and any intended use of professional writers
55			
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57		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
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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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.