PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Study protocol for the POPART study – Prophylactic Oropharyngeal surfactant for Preterm infants: A Randomised Trial
AUTHORS	murphy, madeleine; Galligan, Marie; Molloy, Brenda; Hussain, Rabia; Doran, Peter; ODonnell, Colm

VERSION 1 - REVIEW

REVIEWER	Jann Foster Western Sydney University
REVIEW RETURNED	21-Dec-2019

GENERAL COMMENTS	Thank you for the opportunity to review the protocol submitted by Dr Madeleine Murphy and colleagues where they outline their funded multicentre study comparing oropharyngeal surfactant and CPAP or CPAP alone at birth in infants <29 weeks gestation. The primary outcome is the incidence of endotracheal intubation for respiratory failure within 120 hours of birth. This is a novel, very well-designed and clinically important study that may have future application in infants of other gestations with RDS. The study is being conducted by a experienced research team with an excellent track record in performing high quality clinical trials. My questions were answered as I read the protocol (thank you) and I look forward to the results.

REVIEWER	Peter Dargaville Royal Hobart Hospital & University of Tasmania I am the Chief Investigator of the OPTIMIST-A trial, examining the question of whether administration of surfactant via thin catheter has advantages over continuation of CPAP in preterm infants at 25-28 weeks gestation. This trial has support from Chiesi Farmaceutici (provision of surfactant).
REVIEW RETURNED	27-Dec-2019

GENERAL COMMENTS	Murphy et al present the protocol for the POPART study investigating prophylactic oropharyngeal surfactant administration for preterm infants <29 weeks gestation at risk of respiratory failure due to RDS. The protocol is well-written and easy to read. The study has considerable merit and will provide important information (although see Major Comment 2 below regarding thin catheter surfactant

	delivery). MAJOR COMMENTS 1. The trial makes no mention of, and no allowance for, administration of surfactant by thin catheter as an alternative to intubation for surfactant therapy. The protocol authors appear to be dismissive of the thin catheter delivery techniques, stating they "appear more difficult than intubation" (page 9, line 30), and not citing any of the numerous meta-analyses of RCTs suggesting that administration of surfactant via thin catheter is more effective than via ETT (e.g. Isayama et al JAMA 2016), nor the publications of the German Neonatal Network reporting a favourable experience (short and long term) based on unrandomised data from thousands of infants. 2. Further, there is no statement in the protocol indicating whether administration of surfactant via thin catheter is allowable in infants that have been enrolled in the study. This is highly relevant information given that the trial primary outcome is intubation <120 hours, which in most cases (especially the controls) will be because the infant has RDS and needs a dose of surfactant. If thin catheter surfactant delivery is allowed, infants reaching treatment failure (i.e. intubation criteria) may not be intubated, fundamentally altering the interpretation of the primary outcome measure. If thin catheter surfactant delivery is not allowed, then this will make the result of POPART less relevant to the many NICUs, especially across Europe, that now appear to be adopting this approach as part of their practice. Preclusion of thin catheter delivery (if this is the case) also begs the question of how this can be mandated and overseen in the different participating centres. I strongly urge the authors to make clear how they have handled the question of thin catheter surfactant in trial participants (in the section headed "Primary Outcome" – page 12) and other relevant sections, and also to mention and justify their approach in the Background (page 9, para 2). 3. The definition of the primary outcome measure (page 12, para 1) includes for intubation in the NICU a number of commonly used indicators of respiratory insufficiency. But there are some combinations of two of them (e.g. worsening tachypnoea plus PCO2 >9.0 kPa) that might not compel clinicians to proceed to intubate. So as with many trials using intubation as an outcome measure, there is the need to also measure "treatment failure", i.e. the achievement of the intubation threshold, whether or not the infant is intubated. It is later mentioned (Page 17, line 46) that a per protocol analysis will be performed in relation to the primary endpoint. One presumes this means collecting data on all the indicators of respiratory insufficiency over the first 5 days. This isn't explicitly stated anywhere, and in some cases begs the question of how the data will be collected (e.g. for "increasing tachypnoea", recessions etc). At the very least I would suggest an acknowledgement that perhaps not all infants achieving 2 of the intubation indicators will be intubated, and a statement that there will be an attempt to collect data on those achieving "treatment failure". MINOR COMMENTS Abstract 4. Page 5, line 17-18: Should state the gestation at which preterm infants have a 50% intubation rate after starting on CPAP (<29 weeks).

	5. Page 5, line 41-42: For clarity, suggest "…are randomised at birth…" and remove "at birth" from the end of the sentence. 6. Page 5, line 42: Definitely should mention drug, approach to dosing and how given. Strengths and limitations 7. Page 7, line 12: Given that in the ten centre study the infants were randomised to receive their first dose of surfactant or placebo intra-pharyngeally at birth, the first dot point of this section claiming to be the first randomised study is not correct. Suggest to state "…first randomised study to specifically examine…" Background 8. Page 8, para 1: The first two sentences of the opening paragraph, concerning lung fluid and its clearance, seem to be quite a distraction, and could easily be removed without loss of message or continuity. 9. Page 8, line 12: Suggest "…is a lung condition of the preterm infant…" 10. Page 9, line 3: As for comment 3 above. 11. Page 10, para 2: Should mention the Ten Centre study. Inclusion and exclusion criteria 12. Page 11, lines 34-44. The sentence regarding exclusion based on the presence of a congenital anomaly is a bit confusing, largely because it includes conditions that would be expected to be diagnosed prenatally (and hence preclude an approach for consent), as well as conditions not apparent until post-natal life, e.g. "major dysmorphic features" that would then require a different form of exclusion of an infant already randomised. This should be clarified. 13. Page 12, line 7-8: It should be stated that the decisions regarding intubation in the DR should follow ILCOR guidelines. Secondary outcomes 14. Page 12, line 46: Suggest "Number of doses, and total dose" 15. Page 12, line 55: Clinical and radiological evidence of RDS – are these dichotomous outcomes or will some score be applied? If the latter, please clarify. 16. Page 12, line 60: Suggest to include pneumothorax requiring drainage 17. Page 13, line 19: Suggest "Mild BPD – requirement for O2 at 28 days of life" 18. Page 13, line 21: Should state that the diagnosis of BPD at 36 weeks includes those still on respiratory support at that time (and should also address the situation of nasal high flow plus room air at 36 weeks). Fact is that only about 20% of all infants in the study will require the oxygen reduction test. 19. Page 13, line 50: Survival without BPD at hospital discharge – does this mean survival to discharge without a diagnosis of BPD made at 36 weeks CGA? 20. Page 13, line 53: Please define CLD 21. Page 13, line 55: Duration of hospitalisation – should perhaps state that it's the first hospitalisation, and in any hospital (assuming that is the case). Intervention arm 22. Page 14, line 23: Suggest replace "This will be done…" with "Surfactant will be administered…" Control group: CPAP

	23. Page 14, line 50: Is it "routine practice" to stabilise infants at 23 and 24 weeks on CPAP in the participating centres? Investigational medical product Page 15, line 41: I believe the license for poractant alfa now extends to thin catheter delivery. Safety monitoring and interim analysis Page 20, line 54-57: Should state whether the DSMB are going to receive the data blinded to the intervention groups (i.e. as treatment A / treatment B), or with the intervention group revealed. Table 2. It does seem a pity that the 25 week infants, perhaps the lowest gestation really likely to gain a benefit from pharyngeal surfactant (by way of potentially avoiding intubation in DR and beyond), are receiving the lowest average dose. PROTOCOL LAYOUT It would be usual to see the section on Screening and Consent much further up in the protocol under the major heading of Participants, instead of after Sample Size Calculation etc. The sections on Randomisation and Blinding also would fit in further up. LANGUAGE AND GRAMMAR 1. It is always difficult to know how to present a protocol of a study already underway – in present or future tense. There are some inconsistencies with this in the manuscript. Given the fact that the trial is well underway, one can strongly argue that the present tense should be used. 2. Should use drug name “poractant alfa” rather than “poractant alpha”, throughout. 3. Page 22, line 32: “…track record of enlisting…”

REVIEWER	Louise Owen Royal Women's Hospital, Melbourne, Australia
REVIEW RETURNED	29-Jan-2020

GENERAL COMMENTS	This paper describes the methodology for a modest sized multicentre RCT that is examining the efficacy of prophylactic pharyngeal surfactant delivery versus standard expectant intubation with endotracheal surfactant therapy. The background is well written and explanatory. There are a few sections of the methodology that could benefit from a little further expansion and detail. The issue of immediate or deferred cord clamping is interesting, is this mandated at study sites? How is CPAP routinely given at study sotes? Is this mandated? Is this by t-piece and face mask or other interfaces? Beyond the delivery room, is surfactant treatment by MIST-type procedures prohibited? If so, this should be clearly stated. What do the authors mean by ‘surfactant tubing’ on line 26, page 14? There are some abbreviations not fully explained in the text e.g. PPV, PedCRIN, IMP withdrawal The authors point out that it is not possible to blind the intervention

	for this study. It is therefore very important that careful, objective criteria are used to determine outcomes. The primary outcome ie intubation within 5 days ,but the authors state that infants will be 'watched closely to see if they need extra treatment for their RDS at any stage, including surfactant given endotracheally'. It should be clarified, if it is the case, that the criteria outlined n p12, lines 10-19 are what will be used to determine this need. This study describes off label use for a licenced product , presumably this is clearly stated to eligible families? The dosing schedule is practical but interesting given that some infants will receive doses well above the recommended 200mg/kg , meaning that 26 week infants will receive almost double dose of 25 week infants. This is worthy of some discussion. Will the primary outcome also be analysed by GA strata? If so, this should be stated. This is an international multicentre trial at nine study sites, there is potential for large scale recruitment. Is there a reason that 80% power was chosen given that within these centres there is potential for more precision through more comprehensive recruitment? The authors describe that the sample size is adjusted for an anticipated death rate of 10% 'from local data'. Are these data derived from local death rates of all infants of eligible GAs, or from the subset of those GA infants who could have been eligible for this study that requires prospective consent? These two things are quite different given that death rates are likely to be considerably higher in the whole population compared with those who have a period of inpatient time prior to delivery. Might this impact on the required sample size? The SAEs not fully outlined. Is this study funded? The authors state that when families do not speak the local language interpreters will be provided, how will this be supported financially? Some more detail is required regarding the enrolment rate, how many potentially eligible infants are born at the 9 study sites, what is the anticipated recruitment rate, the sentence stating that 'we belive that with their help we can enrol these infants' needs substantiating.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Jann Foster
Institution and Country: Western Sydney University
Please state any competing interests or state 'None declared': None declared

Thank you for the opportunity to review the protocol submitted by Dr Madeleine Murphy and colleagues where they outline their funded multicentre study comparing oropharyngeal surfactant and CPAP or CPAP alone at birth in infants <29 weeks' gestation. The primary outcome is the incidence of endotracheal intubation for respiratory failure within 120 hours of birth.

This is a novel, very well-designed and clinically important study that may have future application in infants of other gestations with RDS. The study is being conducted by an experienced research team

with an excellent track record in performing high quality clinical trials. My questions were answered as I read the protocol (thank you) and I look forward to the results.

Reviewer: 2

Reviewer Name: Peter Dargaville
Institution and Country: Royal Hobart Hospital & University of Tasmania
Please state any competing interests or state 'None declared':
I am the Chief Investigator of the OPTIMIST-A trial, examining the question of whether administration of surfactant via thin catheter has advantages over continuation of CPAP in preterm infants at 25-28 weeks' gestation. This trial has support from Chiesi Farmaceutici (provision of surfactant).

Murphy et al present the protocol for the POPART study investigating prophylactic oropharyngeal surfactant administration for preterm infants <29 weeks' gestation at risk of respiratory failure due to RDS.

The protocol is well-written and easy to read. The study has considerable merit and will provide important information (although see Major Comment 2 below regarding thin catheter surfactant delivery).

MAJOR COMMENTS

1. The trial makes no mention of, and no allowance for, administration of surfactant by thin catheter as an alternative to intubation for surfactant therapy. The protocol authors appear to be dismissive of the thin catheter delivery techniques, stating they "appear more difficult than intubation" (page 9, line 30), and not citing any of the numerous meta-analyses of RCTs suggesting that administration of surfactant via thin catheter is more effective than via ETT (e.g. Isayama et al JAMA 2016), nor the publications of the German Neonatal Network reporting a favourable experience (short and long term) based on unrandomised data from thousands of infants.

Apologies for not making this clear in the protocol. We had reduced this section to ensure our manuscript was in keeping with the word count. Thank you for highlighting this to us. We have revised the manuscript and added this section to the background.

Less invasive surfactant administration (LISA) techniques involve introducing either a feeding tube or vascular catheter into the trachea of a spontaneously breathing infant at laryngoscopy.1-4 LISA is associated with lower rates of mechanical ventilation among preterm infants in randomised1 4 observational studies.5 Two year follow up outcomes for infants enrolled in the randomised trial Avoid Mechanical Ventilation,1 where infants were randomised to surfactant via LISA or to standard care with CPAP and ET instillation of surfactant if necessary, are similar between groups.6 However, the technique appears more difficult than intubation and the short-term adverse effects of laryngoscopy are not avoided. The procedure is becoming more widely used, but rates vary between countries.7-10 Concerns regarding the validity and risk of bias within studies, a lack of familiarity with the technique, and patient discomfort have been reported as reasons for not using LISA.9 Use of sedation and analgesia prior to laryngoscopy is not standard for the LISA procedure.1 While meta-analyses report that the LISA technique is associated with less death or BPD,11-13 further RCTs are needed. The Optimist-A trial,14 evaluating minimally invasive surfactant therapy in preterm infants born between 25 – 28 weeks' gestation is ongoing.

2. Further, there is no statement in the protocol indicating whether administration of surfactant via thin catheter is allowable in infants that have been enrolled in the study. This is highly relevant

information given that the trial primary outcome is intubation <120 hours, which in most cases (especially the controls) will be because the infant has RDS and needs a dose of surfactant. If thin catheter surfactant delivery is allowed, infants reaching treatment failure (i.e. intubation criteria) may not be intubated, fundamentally altering the interpretation of the primary outcome measure. If thin catheter surfactant delivery is not allowed, then this will make the result of POPART less relevant to the many NICUs, especially across Europe, that now appear to be adopting this approach as part of their practice. Preclusion of thin catheter delivery (if this is the case) also begs the question of how this can be mandated and overseen in the different participating centres. I strongly urge the authors to make clear how they have handled the question of thin catheter surfactant in trial participants (in the section headed "Primary Outcome" – page 12) and other relevant sections, and also to mention and justify their approach in the Background (page 9, para 2).

Apologies for not making this clear in the protocol, and thank you for highlighting this to us. Yes, administration of surfactant via a thin catheter is allowed for infants who meet the primary outcome criteria. We have added this to the methods under primary outcome heading.

The primary outcome is intubation within 120 hours of birth. We define any instrumentation of the trachea, i.e. with an ETT or thin catheter, for the purpose of giving surfactant as intubation and reaching the primary outcome. 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

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.

3. The definition of the primary outcome measure (page 12, para 1) includes for intubation in the NICU a number of commonly used indicators of respiratory insufficiency. But there are some combinations of two of them (e.g. worsening tachypnoea plus PCO2 >9.0 kPa) that might not compel clinicians to proceed to intubate. So as with many trials using intubation as an outcome measure, there is the need to also measure "treatment failure", i.e. the achievement of the intubation threshold, whether or not the infant is intubated. It is later mentioned (Page 17, line 46) that a per protocol analysis will be performed in relation to the primary endpoint. One presumes this means collecting data on all the indicators of respiratory insufficiency over the first 5 days. This isn't explicitly stated anywhere, and in some cases begs the question of how the data will be collected (e.g. for "increasing tachypnoea", recessions etc). At the very least I would suggest an acknowledgement that perhaps not all infants achieving 2 of the intubation indicators will be intubated, and a statement that there will be an attempt to collect data on those achieving "treatment failure".

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

MINOR COMMENTS

Abstract

4. Page 5, line 17-18: Should state the gestation at which preterm infants have a 50% intubation rate after starting on CPAP (<29 weeks).

This has been updated in the manuscript.

5. Page 5, line 41-42: For clarity, suggest “…are randomised at birth…” and remove “at birth" from the end of the sentence.

This has been updated in the manuscript.

6. Page 5, line 42: Definitely should mention drug, approach to dosing and how given.

This has been updated in the manuscript.

Strengths and limitations

7. Page 7, line 12: Given that in the ten centre study the infants were randomised to receive their first dose of surfactant or placebo intra-pharyngeally at birth, the first dot point of this section claiming to be the first randomised study is not correct. Suggest to state “…first randomised study to specifically examine…”

This has been updated in the manuscript.

Background

8. Page 8, para 1: The first two sentences of the opening paragraph, concerning lung fluid and its clearance, seem to be quite a distraction, and could easily be removed without loss of message or continuity.

This has been updated in the manuscript.

9. Page 8, line 12: Suggest “…is a lung condition of the preterm infant…”

This has been updated in the manuscript.

10. Page 9, line 3: As for comment 3 above.

This has been updated in the manuscript.

11. Page 10, para 2: Should mention the Ten Centre study.

While the Ten Centre Study was already cited in the manuscript, we have expanded this section in the manuscript. We have added this to the background.

A Cochrane review of pharyngeal surfactant15 did not identify any eligible trials to assess whether pharyngeal installation of surfactant before the first breath prevented morbidity and mortality in infants at risk of RDS. The Ten Centre Study randomised 328 infants born between 25 – 29 weeks’ gestation to artificial surfactant therapy or saline. For those randomised to surfactant therapy, the first dose was given via the oropharynx, with subsequent doses given via an ETT if the infant was intubated, however the outcomes of infants who received pharyngeal surfactant alone were not reported. Large well conducted RCTs are needed, due to the evidence from animal16 17 and observational human studies18 19 suggesting that pharyngeal surfactant administration is potentially safe, feasible, and may be effective.

Inclusion and exclusion criteria

12. Page 11, lines 34-44. The sentence regarding exclusion based on the presence of a congenital anomaly is a bit confusing, largely because it includes conditions that would be expected to be diagnosed prenatally (and hence preclude an approach for consent), as well as conditions not apparent until post-natal life, e.g. “major dysmorphic features” that would then require a different form of exclusion of an infant already randomised. This should be clarified.

Infants will be excluded if they have major congenital anomalies (including neural tube defects, major structural cardiac anomalies (excluding patent ductus arteriosus, ventricular septal defect, atrioventricular septal defect), abdominal wall defects, congenital diaphragmatic hernia and major dysmorphic features with an abnormal karyotype) and if the treating physician does not plan to offer intensive care.

If there is a known anomaly prenatally, families are not approached for consent. In the event of a postnatal diagnosis of the aforementioned conditions, these infants meet criteria for post-randomisation exclusion.

13. Page 12, line 7-8: It should be stated that the decisions regarding intubation in the DR should follow ILCOR guidelines.

This is stated on page 15, line 12.

Secondary outcomes

14. Page 12, line 46: Suggest “Number of doses, and total dose”

This has been updated in the manuscript.

15. Page 12, line 55: Clinical and radiological evidence of RDS – are these dichotomous outcomes or will some score be applied? If the latter, please clarify.

We record whether there is radiological evidence of respiratory distress syndrome at the time of first intubation.

16. Page 12, line 60: Suggest to include pneumothorax requiring drainage

We are recording the incidence of pneumothorax; and whether these infants have a drain inserted, have needle aspirated performed, or are not treated.

We have updated this in the manuscript.

17. Page 13, line 19: Suggest “Mild BPD – requirement for O2 at 28 days of life”

We are recording BPD as oxygen treatment at 28 days of life.

18. Page 13, line 21: Should state that the diagnosis of BPD at 36 weeks includes those still on respiratory support at that time (and should also address the situation of nasal high flow plus room air at 36 weeks). Fact is that only about 20% of all infants in the study will require the oxygen reduction test.

We are recording chronic lung disease as oxygen treatment at 36 weeks corrected gestational age. We are recording the FiO2 at that time, which will allow us to evaluate infants who remain on respiratory support on trivial or no supplemental oxygen.

19. Page 13, line 50: Survival without BPD at hospital discharge – does this mean survival to discharge without a diagnosis of BPD made at 36 weeks CGA?

This means survival to discharge without a diagnosis of BPD made at day of life 28.

20. Page 13, line 53: Please define CLD

We are recording chronic lung disease as oxygen treatment at 36 weeks corrected gestational age.

21. Page 13, line 55: Duration of hospitalisation – should perhaps state that it's the first hospitalisation, and in any hospital (assuming that is the case).

This is duration of hospitalisation prior to discharge home. This has been updated in the manuscript.

Intervention arm

22. Page 14, line 23: Suggest replace "This will be done…" with "Surfactant will be administered…"

We have updated this in the manuscript.

Control group: CPAP

23. Page 14, line 50: Is it "routine practice" to stabilise infants at 23 and 24 weeks on CPAP in the participating centres?

Yes, we stabilise infants on CPAP regardless of their gestational age.

Investigational medical product

24. Page 15, line 41: I believe the license for poractant alfa now extends to thin catheter delivery.

We have updated this in the manuscript.

Safety monitoring and interim analysis

25. Page 20, line 54-57: Should state whether the DSMB are going to receive the data blinded to the intervention groups (i.e. as treatment A / treatment B), or with the intervention group revealed.

The DSMB will not be blinded to the intervention groups. We have updated this in the manuscript.

Table 2.

26. It does seem a pity that the 25 week infants, perhaps the lowest gestation really likely to gain a benefit from pharyngeal surfactant (by way of potentially avoiding intubation in DR and beyond), are receiving the lowest average dose.

While it is possible that infants born at 25 weeks' gestation may receive a lower average dose of surfactant, it is in the recommended therapeutic range for prophylaxis of RDS. This will form part of our discussion upon completion of the study.

Protocol layout

27. It would be usual to see the section on Screening and Consent much further up in the protocol under the major heading of Participants, instead of after Sample Size Calculation etc. The sections on Randomisation and Blinding also would fit in further up.

We have rearranged this in the manuscript.

Language and grammar

28. It is always difficult to know how to present a protocol of a study already underway – in present or future tense. There are some inconsistencies with this in the manuscript. Given the fact that the trial is well underway, one can strongly argue that the present tense should be used.

We have updated this in the manuscript

29. Should use drug name “poractant alfa” rather than “poractant alpha”, throughout.

We have updated this in the manuscript

30. Page 22, line 32: “…track record of enlisting…”

We have updated this in the manuscript.

Reviewer: 3

Reviewer Name: Louise Owen
Institution and Country: Royal Women's Hospital, Melbourne, Australia
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

This paper describes the methodology for a modest sized multicentre RCT that is examining the efficacy of prophylactic pharyngeal surfactant delivery versus standard expectant intubation with endotracheal surfactant therapy.

The background is well written and explanatory. There are a few sections of the methodology that could benefit from a little further expansion and detail.

1. The issue of immediate or deferred cord clamping is interesting, is this mandated at study sites?

While we do not mandate that deferred cord clamping is performed, we suggest that the cord is clamped and cut at 60 seconds, as this is what we recommend at our hospital. We are recording the time at which the cord is clamped and cut for each patient, which we expect may differ from site to site.

2. How is CPAP routinely given at study sites? Is this mandated? Is this by t-piece and face mask or other interfaces?

We do not mandate how it is given across the different sites, hence we did not include this in the protocol. Respiratory support is given with a T-piece via a round face mask (Fisher & Paykel Healthcare, Auckland, New Zealand).

3. Beyond the delivery room, is surfactant treatment by MIST-type procedures prohibited? If so, this should be clearly stated.

Surfactant treatment via MIST-type procedures is permitted. Apologies for not making this clear in the protocol, and thank you for highlighting this to us. We have added this to the methods section, under primary outcome.

The primary outcome is intubation within 120 hours of birth. 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.

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.

4. What do the authors mean by 'surfactant tubing' on line 26, page 14?

We administer surfactant to the oropharynx via a thin flexible catheter e.g. a catheter used to administer surfactant via endotracheal tube (chosen as it easily connects to a regular syringe), or a feeding catheter. Either may be used.

We have updated this in the manuscript.

5. There are some abbreviations not fully explained in the text e.g. PPV, PedCRIN, IMP withdrawal

The text has been updated.

6. The authors point out that it is not possible to blind the intervention for this study. It is therefore very important that careful, objective criteria are used to determine outcomes. The primary outcome i.e. intubation within 5 days ,but the authors state that infants will be 'watched closely to see if they need extra treatment for their RDS at any stage, including surfactant given endotracheally'. It should be clarified, if it is the case, that the criteria outlined n p12, lines 10-19 are what will be used to determine this need.

Infants are intubated should they meet the primary outcome using the criteria as outlined in the protocol. We have removed the sentence that 'infants will be watched closely to see if they need extra treatment for RDS at any stage' to improve clarity for the reader.

7. This study describes off label use for a licenced product , presumably this is clearly stated to eligible families?

This is not stated in the parent information leaflet and consent form.

8. The dosing schedule is practical but interesting given that some infants will receive doses well above the recommended 200mg/kg , meaning that 26 week infants will receive almost double dose of 25 week infants. This is worthy of some discussion.

While it is possible that infants born at 25 weeks' gestation may receive a lower average dose of surfactant, it is in the recommended therapeutic range for prophylaxis of RDS. This will form part of our discussion upon completion of the study.

9. Will the primary outcome also be analysed by GA strata? If so, this should be stated.

Subgroups of interest include infants of different gestational age strata (e.g. less than 26 weeks, and 26-28 weeks' gestation at birth), and infants from different participating centres.

We have added this to the manuscript.

10. This is an international multicentre trial at nine study sites, there is potential for large scale recruitment. Is there a reason that 80% power was chosen given that within these centres there is potential for more precision through more comprehensive recruitment?

At the time at which the trial commenced, we had not secured funding for expansion to European sites.

11. The authors describe that the sample size is adjusted for an anticipated death rate of 10% 'from local data'. Are these data derived from local death rates of all infants of eligible GAs, or from the subset of those GA infants who could have been eligible for this study that requires prospective consent? These two things are quite different given that death rates are likely to be considerably higher in the whole population compared with those who have a period of inpatient time prior to delivery. Might this impact on the required sample size?

Our primary outcome is determined within the first 5 days. It is likely that all enrolled infants who do not survive to discharge and die within the first 5 days will have met the primary outcome criteria and therefore will have no impact on the sample size.

12. The SAEs not fully outlined.

The defined SAEs for the study are important medical events, and death before discharge.

13. Is this study funded? The authors state that when families do not speak the local language interpreters will be provided, how will this be supported financially?

The study is funded and described in the section 'Funding' at the start of the manuscript. The neonatal team provide antenatal counselling to women at risk of preterm delivery. At our hospital, if the local language is not their first language, they are offered the opportunity to have an interpreter present to discuss their care and to discuss research in general. This is not within the remit of the trial.

14. Some more detail is required regarding the enrolment rate, how many potentially eligible infants are born at the 9 study sites, what is the anticipated recruitment rate, the sentence stating that 'we believe that with their help we can enrol these infants' needs substantiating.

The National Maternity Hospital is a stand-alone university maternity hospital with a tertiary NICU to which >150 infants <1500g are admitted annually. Approximately 60 babies <29 weeks' gestation are admitted annually. Though the enrolment rates to our studies amongst eligible infants are consistently excellent (> 80%), we believe it is necessary to enrol infants at multiple sites in order to enrol our planned target sample of 250 infants in a timely fashion. We have a track record enlisting the help of collaborators nationally17 and internationally19 20 to perform our studies. We believe that with their help, we can enrol these infants in 3 years.

We have updated this in the manuscript.

1. Gopel W, Kribs A, Ziegler A, et al. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. Lancet (London, England) 2011;378(9803):1627-34. doi: 10.1016/s0140-6736(11)60986-0 [published Online First: 2011/10/04]
2. Dargaville PA, Aiyappan A, De Paoli AG, et al. Minimally-invasive surfactant therapy in preterm infants on continuous positive airway pressure. Archives of disease in childhood Fetal and neonatal edition 2013;98(2):F122-6. doi: 10.1136/archdischild-2011-301314 [published Online First: 2012/06/12]
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VERSION 2 – REVIEW

REVIEWER	Peter Dargaville Royal Hobart Hospital, Hobart, Australia Chief Investigator, OPTIMIST-A trial
REVIEW RETURNED	30-Mar-2020

GENERAL COMMENTS	Murphy et al have responded adequately to the comments of the reviewers, including my comments. One criticism remains. 1. As mentioned in my earlier review, I feel the comment that thin catheter delivery techniques “appear more difficult than intubation” (page 9, line 30) is quite dismissive of a method that is now well-entrenched in clinical practice, and without a firm basis. I can find no clear published evidence to indicate that this is the case. My recommendation would be to remove this statement. Typo: Page two of introduction Current: …in randomised observational studies Change to: …in randomised and observational studies.

REVIEWER	Louise Owen Royal Women's Hospital, Melbourne, Australia
REVIEW RETURNED	25-Mar-2020

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript again. The authors have made considerable changes. Many of my queries have been addressed, however there remain some unanswered questions and areas that warrant clarification. 1. Is it explicitly stated to families during the consent process that this product is being used off licence? 2. Although there has been clarification over whether the use of surfactant via LISA/INSURE within the primary outcome period is considered achievement of the primary outcome, the wording of this is somewhat opaque. It may be clearer to simply state that "The primary outcome is achieved if a baby is treated with surfactant, by any method (ETT/LISA/INSURE) with 5 days of birth.' 3. Once the primary outcome is reached, are subsequent surfactant treatments limited to one dose? Will clinicians know whether the infant has already received surfactant within the trial? If more than one additional dose is allowed, will the maximum total dose be limited to 400mg/kg as stated? These points need clarification. 4. The details of the intervention arm should explicitly state that after receipt of pharyngeal surfactant CPAP will be commenced as per routine practice, and as is stated in the control group. 5. Sample size calculation: The authors note that local death rates in this GA group is 10%, although the authors should note that death rates amongst eligible enrolled infants may be lower as prospective antenatal consent is required, meaning that enrolled infants will be selected from a subgroup of the preterm population who have a better outcome, as they are more likely to have received antenatal steroids during a period of inpatient care prior to birth than those who are unable to be approached and deliver soon after presentation to hospital. 6. Defined SAEs are not listed – just explained as "important medical events", what are these? 7. Recruitment: The authors state that approximately 60 babies are born in the study GA range annually at the lead centre. They also state that recruitment is typically high (80%) - does this include recruitment when antenatal consent is required? Many women may not be able to be approached prior to birth in this GA range. Regardless, 80% of 3-years worth of 60 infants is approx. 145 (of the planned 250) infants. Details of birth rates at all the participating centres should also be included to support the expected recruitment rate. 8. The discussion section is very short – either here, or in the section regarding the pragmatic decision regarding DR surfactant dosing, there should be some acknowledgement of the discrepancies of surfactant dosing across the GA range.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer Name: Louise Owen
Institution and Country: Royal Women's Hospital, Melbourne, Australia
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
Thank you for the opportunity to review this manuscript again. The authors have made considerable changes. Many of my queries have been addressed, however there remain some unanswered questions and areas that warrant clarification.

1. Is it explicitly stated to families during the consent process that this product is being used off licence?

Response:

Poractant alfa (Curosurf, Chiesi Farmaceutici, Parma, Italy) is licensed for endotracheal use and administration via thin catheter for the prevention and treatment of RDS in preterm infants. It is currently not licensed for oropharyngeal administration, and therefore this study is examining the off-label use of a licensed product. The study was approved initially by the Research Ethics Committee at National Maternity Hospital Dublin, and the Health Products Regulatory Authority of Ireland. Approval was also obtained at the research ethics committees at each participating site and at the relevant competent authority for each participating country.

The use of unlicensed and off-label drugs prescribed in neonatal intensive care units (NICU) is widespread. Studies from Irish1 and Australian2 NICUs report that nearly all extremely preterm extremely low birth weight infants received either an unlicensed or an off-label prescription or both during their neonatal course. We don't explicitly being use the term "off-label" during the consent process, as we doubt that this term would be meaningful to the general public. However, we do explain that it is being used off-label, in that we explain that surfactant is an effective drug that has been used for the treatment and prevention of RDS in premature babies for many years; that it is usually given directly by tube into the windpipe; and that while it isn't usually used in this fashion, we are studying whether or not it is effective when it is given into the throat. We wished to ensure our parent information leaflet (PIL) and consent form was readable to parent(s)/guardian(s) and made efforts to describe the process whilst avoiding medical language.

2. Although there has been clarification over whether the use of surfactant via LISA/INSURE within the primary outcome period is considered achievement of the primary outcome, the wording of this is somewhat opaque. It may be clearer to simply state that "The primary outcome is achieved if a baby is treated with surfactant, by any method (ETT/LISA/INSURE) with 5 days of birth.'

Response:

While we appreciate your comment, the primary outcome is the incidence of intubation rather than surfactant replacement therapy. We have separated the paragraph describing how the primary outcome is achieved for clarity to the reader.

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.

3. Once the primary outcome is reached, are subsequent surfactant treatments limited to one dose? Will clinicians know whether the infant has already received surfactant within the trial? If more than one additional dose is allowed, will the maximum total dose be limited to 400mg/kg as stated? These points need clarification.

Response:

The dosing recommendations for treatment with Curosurf when given by endotracheal tube are 200mg/kg for established RDS and 100 – 200mg/kg for prophylaxis. Further doses of 100mg/kg Curosurf may be given to infants who have persistent respiratory distress despite treatment with surfactant (maximum recommended dose 400mg/kg).

In the trial, if an infant is felt to need endotracheal surfactant following initial oropharyngeal administration, then it is recommended that they receive the standard initial dose via endotracheal tube, e.g. 200mg/kg initial recommended dose. Subsequent doses are allowed and are at the discretion of the treating clinician. While the maximum recommended dose is 400mg/kg, we do not limit the maximum total dose within the context of the trial and this is at the discretion of the treating clinician. As this study is not blinded, the clinicians will know whether the infant has already received surfactant within the trial. We are recording the number of doses and total dose of surfactant for each patient.

We have added the sentence that “Additional doses are given at the discretion of the attending physician.”

4. The details of the intervention arm should explicitly state that after receipt of pharyngeal surfactant CPAP will be commenced as per routine practice, and as is stated in the control group.

Many thanks for this observation. We have updated this in the manuscript.

5. Sample size calculation: The authors note that local death rates in this GA group is 10%, although the authors should note that death rates amongst eligible enrolled infants may be lower as prospective antenatal consent is required, meaning that enrolled infants will be selected from a subgroup of the preterm population who have a better outcome, as they are more likely to have received antenatal steroids during a period of inpatient care prior to birth than those who are unable to be approached and deliver soon after presentation to hospital.

Response:

It is well-described that prospective antenatal consent may restrict the sample of the enrolled population, leading to selection bias in that enrolled infants are healthier than those not enrolled, which may as a result limit the generalisability of the results. Rich et al3 reported that there was evidence from randomised trials that patients randomised to the control arm have better outcomes than those that were eligible but not randomised due to a lack of consent.

To date, we have recruited > 85% of all eligible infants to the POPART trial at our centre. We acknowledge that should a large proportion of eligible infants not be enrolled to the study that that would have an impact on the sample of population studied, and would acknowledge this in the discussion of the published manuscript on completion of our results.

The death rate of 10% was stated in relation to the sample size estimation, and our sample size was inflated as a result. Should the death rate be lower than anticipated, this would have no impact on the power of the study.

6. Defined SAEs are not listed – just explained as “important medical events”, what are these?

Response:

The SAEs are death before hospital discharge and important medical events. The rationale for this is that infants meeting eligibility criteria in this study are born prematurely and thus require prolonged hospitalisation. Complications of prematurity are recorded in the CRF and reported as secondary outcomes. Important medical events are reported at the discretion of the attending physician. This has been approved by the regulatory authorities and research ethics committees, and all members of the DSMB are in agreement.

7. Recruitment: The authors state that approximately 60 babies are born in the study GA range annually at the lead centre. They also state that recruitment is typically high (80%) - does this include recruitment when antenatal consent is required? Many women may not be able to be approached prior to birth in this GA range. Regardless, 80% of 3-years' worth of 60 infants is approx. 145 (of the planned 250) infants. Details of birth rates at all the participating centres should also be included to support the expected recruitment rate.

Response:

We have enrolled 80% of our sample size to date and are on target to complete recruitment within 3 years.

We have recruited > 85% of all eligible infants to the POPART trial at our centre. This includes data for those infants who delivered soon after arrival to hospital and there was no time to discuss the study prior to delivery; those where the study was discussed with parents but infant delivered before a decision was made; those who had given consent for participation into the study but delivered quickly and no time to randomise the infant; and those who declined consent.

The birth rates between the additional participating sites vary. In addition, participating sites did not start recruiting to the study at the same time. We do not expect recruitment as high as 80% at all sites, and our expected recruitment rate was adjusted to accommodate for this.

8. The discussion section is very short – either here, or in the section regarding the pragmatic decision regarding DR surfactant dosing, there should be some acknowledgement of the discrepancies of surfactant dosing across the GA range.

Response:

The length of our discussion is limited by the recommended word count as laid out in the guidelines for authors on the BMJ Open website, which we are already in excess of. We plan to discuss the pragmatic decision regarding surfactant dosing, along with acknowledgement of the discrepancies of surfactant dosing across gestational age ranges in the published manuscript upon completion of the study.

Reviewer: 2

Reviewer Name: Peter Dargaville
Institution and Country: Royal Hobart Hospital, Hobart, Australia
Please state any competing interests or state 'None declared': Chief Investigator, OPTIMIST-A trial

Please leave your comments for the authors below
Murphy et al have responded adequately to the comments of the reviewers, including my comments.

One criticism remains.

1. As mentioned in my earlier review, I feel the comment that thin catheter delivery techniques "appear more difficult than intubation" (page 9, line 30) is quite dismissive of a method that is now well-entrenched in clinical practice, and without a firm basis. I can find no clear published evidence to indicate that this is the case. My recommendation would be to remove this statement.

Response:

We have removed this sentence from the manuscript.

Typo:
Page two of introduction
Current: …in randomised observational studies
Change to: …in randomised and observational studies.

Many thanks for this observation. We have updated this in the manuscript.

1. Kieran EA, O'Callaghan N, O'Donnell CP. Unlicensed and off-label drug use in an Irish neonatal intensive care unit: a prospective cohort study. Acta paediatrica (Oslo, Norway : 1992) 2014;103(4):e139-42. doi: 10.1111/apa.12541 [published Online First: 2014/01/09]
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3. Rich W, Finer NN, Gantz MG, et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. Pediatrics 2012;129(3):480-4. doi: 10.1542/peds.2011-2121 [published Online First: 2012/03/01]

VERSION 3 - REVIEW

REVIEWER	Peter Dargaville Royal Hobart Hospital, Australia Chief Investigator, OPTIMIST-A trial
REVIEW RETURNED	09-Apr-2020

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.