OPTIMIST-A TRIAL PROTOCOL

MULTICENTRE RANDOMISED CONTROLLED TRIAL
OF MINIMALLY-INVASIVE SURFACTANT THERAPY IN
PRETERM INFANTS 25-28 WEEKS GESTATION
ON CONTINUOUS POSITIVE AIRWAY PRESSURE

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Table of contents

1. OPTIMIST-A TRIAL SUMMARY

2. BACKGROUND
   2.1 INTRODUCTION
   2.2 CPAP FAILURE AND ADVERSE OUTCOME
   2.3 INTUBATION FOR SURFACTANT ADMINISTRATION
   2.4 MINIMALLY-INVASIVE SURFACTANT THERAPY
   2.5 THE “HOBART METHOD” OF MIST
   2.6 CLINICAL EXPERIENCE WITH THE HOBART METHOD OF MIST
   2.7 THE NEED FOR FURTHER RANDOMISED CONTROLLED TRIALS OF MIST
   2.8 IMPORTANT CONSIDERATIONS IN TRIAL PROTOCOL DEVELOPMENT
      2.8.1 Entry criteria
      2.8.2 Surfactant dosage
      2.8.3 The surfactant delivery catheter
      2.8.4 Method of laryngoscopy
      2.8.5 Premedication
      2.8.6 Intubation criteria
      2.8.7 Primary outcomes and sample size

3. OPTIMIST-A TRIAL PROTOCOL
   3.1 TRIAL AIM
   3.2 HYPOTHESIS
   3.3 STUDY DESIGN
   3.4 STUDY POPULATION
   3.5 RECRUITMENT
      3.5.1 Entry criteria
      3.5.2 Exclusion criteria
   3.6 CONSENT
   3.7 RANDOMISATION
   3.8 MASKING
   3.9 INTERVENTION
      3.9.1 Setting
      3.9.2 Preparation of the infant by the treating clinicians
      3.9.3 Preparation of the infant by the OPTIMIST treatment team
      3.9.4 Intervention – surfactant administration via MIST
      3.9.5 Intervention – standard care (sham MIST procedure)
      3.9.6 Management immediately after MIST
      3.9.7 Post-MIST investigations
      3.9.8 Safety assessment
   3.10 POST-INTERVENTION MANAGEMENT
      3.10.1 Standard management
      3.10.2 Criteria for intubation
      3.10.3 Assessment of BPD at 36 weeks corrected gestational age
   3.11 DATA COLLECTION AND MANAGEMENT
      3.11.1 Data collection in hospital
      3.11.2 Follow up
   3.12 OUTCOME VARIABLES
      3.12.1 Primary outcome
      3.12.2 Secondary outcomes
   3.13 STATISTICAL ANALYSIS AND REPORTING
      3.13.1 Statistical analysis
      3.13.2 Data reporting and manuscript preparation
   3.14 SAMPLE SIZE
   3.15 TRIAL PLAN
   3.16 FEASIBILITY
   3.17 DATA AND SAFETY MONITORING COMMITTEE
      3.17.1 Interim analyses
      3.17.2 Adverse events
   3.18 FUNDING
   3.19 OUTCOMES AND SIGNIFICANCE

4. REFERENCES
1. OPTIMIST-A TRIAL SUMMARY

RESEARCH QUESTION
Does administration of exogenous surfactant using a minimally-invasive technique improve outcome in preterm infants 25-28 weeks gestation treated with continuous positive airway pressure (CPAP)?

BACKGROUND
Nasal CPAP is often very effective in preterm infants as the initial means of respiratory support, but a sub-group of infants, most with features of respiratory distress syndrome, fail on CPAP and require intubation and ventilation in the first 72 hours. When compared to those in whom CPAP is successful, infants failing CPAP have a substantially longer duration of respiratory support, and a higher risk of adverse outcomes. Decreasing the risk of CPAP failure would thus seem advantageous, and may be achievable with minimally invasive surfactant therapy (MIST), in which surfactant is administered to a spontaneously breathing infant who then remains on CPAP. A technique of MIST (the “Hobart method”) using a semi-rigid surfactant instillation catheter has been shown to be feasible in preterm infants on CPAP, and appears to have the potential to alter respiratory course and outcome. This method of MIST now requires evaluation in randomised controlled trials.

RESEARCH DESIGN
Multicentre, randomised, masked, controlled trial.

RECRUITMENT
Entry criteria
Inborn preterm infants 25-28 weeks gestation, aged less than 6 hours, who were not intubated at birth but require CPAP or NIPPV because of respiratory distress, with a CPAP pressure of 5-8 cm H₂O and FiO₂ ≥0.30.

Exclusion criteria
Infants will be excluded if in imminent need of intubation, or if there is a congenital anomaly or alternative cause for respiratory distress.

RANDOMISATION
With parental consent, eligible infants will be randomly allocated using a web-based randomisation server, with stratification by study centre, to receive exogenous surfactant via the Hobart MIST technique, or to continue on CPAP.
INTERVENTION
Infants randomised to surfactant treatment will receive a dose of poractant alfa (Curosurf) administered under direct laryngoscopy using a surfactant instillation catheter, at a dosage of 200 mg/kg. CPAP will thereafter be reinstituted. Controls will continue on CPAP. The intervention will be masked from the clinical team.

POST-INTERVENTION MANAGEMENT
Other than the requirement to adhere to intubation criteria in the first week, and in some cases perform a room air trial at 36 weeks corrected gestation, management after intervention will be at the discretion of the clinical team. Titration of CPAP pressure is encouraged, with a permitted maximum of 8 cm H₂O. Nasal IPPV (bi-level CPAP) is allowable. Early caffeine therapy is expected.

Criteria for intubation:
Enrolled infants on CPAP will be intubated if FiO₂ ≥0.45, or if there is unremitting apnoea or persistent acidosis. These criteria apply during the first week of life, and to the first episode of intubation only.

OUTCOMES
Primary outcome: Incidence of composite outcome of death or physiological bronchopulmonary dysplasia (BPD).
Secondary outcomes: Incidence of death, major neonatal morbidities (BPD, intraventricular haemorrhage, periventricular leukomalacia, retinopathy of prematurity, necrotising enterocolitis), pneumothorax and patent ductus arteriosus; need for intubation and surfactant therapy; durations of mechanical respiratory support, intubation, CPAP, intubation and CPAP, high flow nasal cannula (HFNC), oxygen therapy, intensive care stay and hospitalisation; hospitalisation cost; applicability and safety of the MIST procedure; and outcome at 2 years.

SAMPLE SIZE
606 infants (303 per group), giving 90% power to detect a 33% reduction in death or BPD from the anticipated rate of 38% in the control arm, α = 0.05.

TRIAL PLAN
The OPTIMIST trials will commence at RHH Hobart and RWH Melbourne during 2011. All Australasian neonatal units, and selected international centres including those in the Vermont-Oxford Network, will be invited to join the trials. A full complement of participating centres is expected by early 2014. Recruitment will thereafter proceed at full rate until completion, which is estimated to take up to 4 years.
2. BACKGROUND

2.1 INTRODUCTION
In the past two decades, exogenous surfactant therapy has been a cornerstone of therapy for preterm infants, and is known to be effective when given prophylactically in the delivery room, or as a rescue therapy to infants with established respiratory distress syndrome (RDS). Its introduction into neonatal practice in the early 1990s was followed by a considerable decrease in overall neonatal mortality rate. With the evolution and refinement of intensive care for preterm infants, the place of exogenous surfactant therapy is changing. The more widespread use of nasal continuous positive airway pressure (CPAP) as a primary means of respiratory support means many preterm infants with respiratory distress now avoid intubation in the delivery room or in early post-natal life. This approach also means delaying or avoiding administration of surfactant.

In preterm infants ≤29 weeks, the potential advantages of early CPAP have been highlighted in large randomised controlled trials in which treatment with CPAP from birth, without administration of surfactant, resulted in less ventilator days and a trend towards lower risk of bronchopulmonary dysplasia (BPD) compared to intubated controls. In these trials, however, a large number of infants starting on CPAP ultimately required intubation at some time. In the COIN trial, 46% of infants commenced on CPAP went on to be intubated in the first 5 days (at a median age of 6.6 hrs), with increasing oxygen requirement and/or respiratory acidosis being the most prominent reasons for intubation. A further 13% of CPAP-treated infants required intubation beyond 5 days. In the SUPPORT study more than 75% of infants randomised to the CPAP group were intubated at some time, and 67% received surfactant. In the VON study, 52% of infants commencing on CPAP without prior surfactant therapy ultimately required intubation, and 44% received surfactant. These findings appear to confirm those of earlier observational studies demonstrating that the most usual cause of early CPAP failure in preterm infants is unremitting RDS. Widespread application of CPAP for initial respiratory support in preterm infants provides benefit for many, but is to the detriment of a significant minority of infants destined to go on to fail CPAP because of surfactant deficiency.

2.2 CPAP FAILURE AND ADVERSE OUTCOME
The group of preterm infants failing CPAP has been incompletely characterised to date. Our research team has therefore examined the respiratory course and outcome for a large cohort of preterm infants initially managed on CPAP at RHH, Hobart and RWH Melbourne. We found that CPAP failure, defined as need for intubation before 72 hrs, was associated with a high risk of adverse outcome. Infants who failed CPAP and required intubation in the first 72 hours had a substantially longer duration of respiratory support than those in whom CPAP was successful (Table 1). At 25-28 weeks, infants failing CPAP had a higher risk of mortality, BPD, death or BPD, and necrotising enterocolitis (NEC).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>25-28 weeks</th>
<th>29-32 weeks</th>
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<tbody>
<tr>
<td></td>
<td>CPAP failure</td>
<td>CPAP success</td>
</tr>
<tr>
<td>Resp support days</td>
<td>50 (11-60)</td>
<td>10 (3.6-32)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>6 (20%)</td>
<td>2 (5.6%)</td>
</tr>
<tr>
<td>BPD</td>
<td>12 (40%)</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>Died</td>
<td>4 (13%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Died or BPD</td>
<td>16 (53%)</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>NEC</td>
<td>5 (17%)</td>
<td>0 (0%)</td>
</tr>
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</table>

Table 1. Comparison of outcomes in preterm infants failing and succeeding on CPAP
Median (interquartile range) or n (%). *P value from Mann-Whitney, X² or Fisher’s exact tests, as appropriate
As noted by other investigators, CPAP failure in the RHH-RWH preterm cohort most usually occurred in the context of unremitting RDS, with the median FiO₂ at intubation being 0.50 in the 25-28 week infants failing CPAP, and 0.44 in the 29-32 week group. In 23% of cases a pneumothorax was present at the time of intubation. Hypoventilation (PCO₂ > 60 mmHg) was a contributing factor in only 15% of cases overall.

2.3 INTUBATION FOR SURFACTANT ADMINISTRATION

Given the above, it is conceivable that outcomes for preterm infants managed initially with CPAP could be further improved if the subgroup of infants showing signs of surfactant deficiency were to receive exogenous surfactant. Recognizing the merits of surfactant, especially when given early, some clinicians choose to intubate infants on CPAP solely for the purpose of administering surfactant, followed by immediate extubation and return to CPAP. Several clinical trials of this technique have pointed to reductions in the need for subsequent mechanical ventilation and further surfactant therapy, and the risk of pneumothorax. A more recent study in infants 25-28 weeks gestation did not find a difference in the primary outcome of need for mechanical ventilation during the first 5 days, but 10% of those intubated solely for surfactant administration could not be extubated within 1 hour and were thus deemed to have reached the primary outcome. A larger proportion (17%) were not able to be extubated in the recent Vermont-Oxford Network trial.

Intubation solely for administration of surfactant is a common practice in many Scandinavian units, but is less popular elsewhere. Many clinicians consider the potential benefits of surfactant are outweighed by the risks of intubation. In the delivery room, intubation can be complicated by multiple intubation attempts and episodes of hypoxia. Beyond the delivery room, intubation in preterm infants is now rarely performed without pre-medicating with narcotics ± muscle relaxants, meaning that there may be a delay in extubation once surfactant has been administered. Such a delay has been observed in at least one clinical trial of intubation for surfactant therapy in infants on CPAP. The use of sedating premedication also means that where surfactant is given immediately after intubation, as it most usually is, the consequent suppression of respiratory effort may impair surfactant distribution. Experimental data suggest that surfactant administration in a spontaneously breathing subject results in more effective dispersion and greater tissue incorporation of phospholipid.

2.4 MINIMALLY-INVASIVE SURFACTANT THERAPY

In view of the difficulties associated with intubation for surfactant delivery, less invasive means of delivering surfactant have been pursued. Several techniques of “minimally-invasive surfactant therapy” (MIST) have been described in which surfactant is delivered without tracheal intubation, including nasopharyngeal instillation, laryngeal mask placement and aerosolisation. None of these methods appears ready for clinical application on a wider scale at present. Another method of MIST in which the trachea is catheterised with a feeding tube has been reported. The technique involves insertion of a 5 FG feeding tube into the trachea with Magill’s forceps. Surfactant is then administered over 1-5 minutes, and the catheter thereafter removed. A randomised controlled trial of MIST using this technique (the AMV trial) has recently been conducted in infants 26-28 weeks gestation having an FiO₂ >0.30 in the first 12 hours. Compared to controls, surfactant-treated infants had a lower rate of subsequent mechanical ventilation (28% vs 45%); no difference in the rate of pneumothorax or other adverse events was noted. A further trial comparing this method of MIST with standard intubation in very preterm infants (23-26 weeks gestation) is now underway (NINSAPP Study, NCT00751959, multicentre study comparing MIST with standard intubation, primary outcome: survival without chronic lung disease).
2.5 THE “HOBART METHOD” OF MIST
The method of surfactant instillation by flexible feeding tube has several technical difficulties that may limit its widespread application. Clinicians who solely practice oral intubation will be unfamiliar with Magill’s forceps, and may find them cumbersome and hard to use. Additionally, the highly flexible feeding tube may on occasions be difficult to insert through the vocal cords, and also difficult to maintain in position once inserted. For these reasons, and with the recognition of the potential benefits of MIST, our research group has developed an alternative and novel MIST technique using a narrow bore vascular catheter (16 gauge Angiocath, Product No. 382259, Becton Dickinson, Sandy, UT, USA).35 This catheter has an external diameter of 1.7 mm, and a length of 135 mm, and is made from fluorinated ethylene propylene polymer (Figure 1). It has the dual properties of sufficient stiffness to allow guidance towards and beyond the vocal cords, and sufficient elasticity and softness to avoid damage to the vocal cords and other vital structures. A curvature in the catheter can be fashioned if desired to facilitate intubation. This catheter can be advanced through the vocal cords under direct vision using a laryngoscope, without the need for Magill’s forceps. Surfactant can then be administered in one or several boluses, and respiratory support continued with nasal CPAP. A video of the technique can be accessed at the OPTIMIST trial website.

![Figure 1 MIST catheter (above) compared with standard 2.5 mm endotracheal tube, which has an external diameter of 3.5 mm](image)

2.6 CLINICAL EXPERIENCE WITH THE HOBART METHOD OF MIST
A preliminary evaluation of the Hobart method of MIST was conducted at the Royal Hobart Hospital (RHH), Hobart, Australia,35 and further feasibility studies have been undertaken at RHH and the Royal Women’s Hospital, Melbourne (RWH).36 In the initial study at RHH, MIST was performed in 25 infants, of gestational age range 25-34 weeks and birth weight range 500-3000 g.35 The MIST procedure was performed in the delivery room in 2 cases, and after arrival in the NICU in 23. No pre-medication was used. Surfactant (Curosurf, Chiesi Farmaceutici, Parma, Italy) was delivered at a dosage of approximately 100 mg/kg, given in 1 or 2 boluses. The surfactant was successfully administered in every infant, with two attempts at catheterisation needed in 9 (35%). Brief bradycardia (heart rate <100 beats per minute) was noted in 11 infants (44%), usually contemporaneous with insertion of the laryngoscope blade, and in all cases self-resolving within 10 seconds. Positive pressure inflations were required after surfactant administration in 11 infants (44%).

As at May 2011, the combined feasibility studies of the Hobart method of MIST had enrolled 61 infants of 25-32 weeks gestation.36 Eligibility for MIST was based on the need for CPAP pressure ≥7 cm H₂O and FiO₂ ≥0.3 (25-28 weeks) or ≥0.35 (29-32 weeks). At RHH, 3 infants in the 25-28 week gestation group were treated with FiO₂ <0.3; each had a CPAP pressure of 8 cm H₂O and signs of respiratory distress. Overall, the 25-28 week group received MIST at a mean age of 3.5±3.5 hrs (mean±SD), and the 29-32 week infants at 10.8±7.5 hrs. Surfactant was successfully administered in all cases, with two catheterisation attempts required in 20%. Positive pressure inflations by mask were used in 39% of infants prior to reinstition of CPAP.
Respiratory course and outcomes in infants treated with MIST have been compared with like-gestation historical controls achieving the same CPAP and FiO\textsubscript{2} thresholds (data from the RHH-RWH preterm CPAP cohort). Within each gestation range, the control infants were comparable to those treated with MIST in terms of median gestation, birth weight, exposure to antenatal corticosteroids, mode of delivery and Apgar score at 5 minutes. Several potential benefits of MIST were identified. FiO\textsubscript{2} was more rapidly weaned in surfactant-treated infants than controls in the first 72 hrs. Need for intubation <72 hrs was diminished after MIST (Table 2), most notably for infants at 25-28 weeks gestation (OR 0.21, 95% CI 0.083-0.55), but with a strong trend in the same direction in the 29-32 week group (odds ratio 0.34, 95% CI 0.11-1.06). Duration of oxygen therapy was reduced in infants treated with MIST at all gestations.

<table>
<thead>
<tr>
<th></th>
<th>25-28 weeks</th>
<th>29-32 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIST</td>
<td>Controls</td>
</tr>
<tr>
<td>N</td>
<td>38</td>
<td>41</td>
</tr>
<tr>
<td>Intubated at &lt;72 hrs</td>
<td>12 (32%)</td>
<td>28 (68%)</td>
</tr>
<tr>
<td>Intubated at any time</td>
<td>20 (53%)</td>
<td>30 (73%)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>3 (8.3%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Resp support days</td>
<td>32 (12-41)</td>
<td>38 (11-55)</td>
</tr>
<tr>
<td>Oxygen days</td>
<td>13 (2.8-41)</td>
<td>40 (16-75)</td>
</tr>
</tbody>
</table>

Table 2 Outcomes for infants treated with MIST, and like-gestation historical controls achieving the same CPAP and FiO\textsubscript{2} thresholds. n (%) or median (interquartile range). *P value from Mann-Whitney, \( \chi^2 \) or Fisher’s exact tests, as appropriate

2.7 THE NEED FOR FURTHER RANDOMISED CONTROLLED TRIALS OF MIST

The findings of the evaluation of MIST using the Hobart method, coupled with the clear evidence that CPAP failure occurs largely because of unremitting RDS and is associated with adverse outcomes, have been the genesis of the OPTIMIST-A trial. There is considerable scientific justification for this trial, with strong data in support of: a) the poor outcome for those failing CPAP, b) the capacity to identify such infants early (see section 2.8.1 below), c) the potential for MIST to alter the outcome in such infants, and d) the potential benefits of surfactant delivery in the spontaneously breathing infant. It is thus appropriate to subject MIST to the highest level of scientific scrutiny in the form of a randomised controlled trial. The OPTIMIST-A trial is opportune, given the increasing uptake of CPAP as initial therapy in the wake of the COIN and SUPPORT studies, and the state of equipoise that currently exists amongst clinicians in relation to MIST. OPTIMIST-A is timely, representing the logical next step in the effort towards minimisation of intervention in providing respiratory support to preterm infants 25-28 weeks gestation. Most importantly, the trial is feasible, employing a technique of surfactant delivery that is easy to accomplish, being directed by an experienced investigative team with a strong history of performing randomised trials and involving networks of NICUs with a strong history of being participation in such trials.

2.8 IMPORTANT CONSIDERATIONS IN TRIAL PROTOCOL DEVELOPMENT

2.8.1 Enrolment criteria

Not all preterm infants 25-28 weeks gestation managed on CPAP from the outset stand to benefit from surfactant administration with a minimally-invasive technique. Some have minimal or mild RDS, and are well supported by CPAP alone. For MIST to be of value, it must be coupled with early and accurate selection of infants at greatest risk of failing CPAP. In this regard, several indicators previously put forward have been rejected: a) radiological scores, which are confounded by variability of X-ray technique and subjectivity of interpretation, b) functional surfactant assays, which require specialised equipment and training, c) indices of oxygenation based on arterial pO\textsubscript{2}, which are impractical because so few infants on CPAP have arterial lines in situ, and d) Silverman clinical scores, which will vary considerably depending on the CPAP pressure level.
Using data from the RHH-RWH preterm CPAP cohort, we have sought a bedside predictor of early CPAP failure in the early post-natal period in infants 25-28 weeks gestation. In a logistic regression model incorporating demographic variables, FiO₂ and CPAP pressures, by far the strongest predictor of later need for intubation was the highest FiO₂ in the first 2 hours. Addition of CPAP pressure improved the goodness of fit only slightly ($R^2$ 0.5 vs 0.45). A similar regression analysis by De Jaegere et al in infants <30 weeks gestation found FiO₂ by 2 hours to be the most influential variable in prediction of later intubation. On this basis, and in recognition of the need for simplicity in framing the entry criteria, highest appropriate FiO₂ has been chosen as an entry criterion for the OPTIMIST-A trial. The FiO₂ threshold of ≥0.30 is the same as that used in the AMV trial, and in our preterm CPAP cohort predicted intubation <72 hrs with a sensitivity of 83% and positive predictive value of 60%. Infants achieving this threshold in the first 2 hrs had a relatively high likelihood of later intubation (OR 5.6, 95% CI 1.7-18). Area under the receiver operating characteristic curve for prediction of CPAP failure using FiO₂ was 0.83 in the RHH-RWH preterm CPAP cohort (Figure 2) and 0.84 in the study of De Jaegere et al.

Figure 2. Prediction of CPAP failure with highest FiO₂ in the first 2 hours
Receiver operating characteristic curve plotting true positive rate (sensitivity) against false positive rate (1-specificity) for prediction of CPAP failure at various FiO₂ thresholds in the first 2 hrs. The threshold FiO₂ is indicated in bold, and area under the curve (AUC) is indicated in italics.

2.8.2 Surfactant dosage
Standard surfactant dosage for preterm infants with RDS ranges from 100 to 200 mg/kg. At least when using Curosurf, there is some evidence that a dose of 200 mg/kg reduces the need for re-treatment. This dose has been used in several studies of surfactant administration by brief intubation in infants <30 weeks gestation. In the feasibility studies of the Hobart method of MIST, 7 infants 25-28 weeks gestation have thus far received a surfactant dosage of 200 mg/kg. No treatment complications have been noted in those receiving the larger dose, their oxygenation response was more pronounced and prolonged, and none required intubation <72 hrs. These observations, coupled with the wider experience, provide the basis for the 200 mg/kg surfactant dosage stipulated in the OPTIMIST-A trial.

2.8.3 The surfactant delivery catheter
The surfactant delivery catheter used in both feasibility studies of the Hobart MIST method has been the 16G Angiocath (Becton Dickinson, Sandy, UT, USA). These studies revealed no major deficiencies with the catheter for the purpose of surfactant instillation, other than the need to mark the depth of insertion with a marker pen. The 16G Angiocath will thus be used in the OPTIMIST-A trial until a purpose-built surfactant delivery catheter with very similar design features becomes available.

2.8.4 Method of laryngoscopy
In the initial feasibility studies at RHH and RWH, direct laryngoscopy for tracheal catheterisation has been performed using a standard laryngoscope with a Miller 0 or 00 blade. During further evaluation, tracheal catheterisation has been successfully undertaken using a Glidescope Cobalt AVL video laryngoscope (Verathon Medical, Burnaby, Canada) with a size 0 blade. This approach
may assist in guiding the catheter through the vocal cords. The use of this video laryngoscope will be permitted in the OPTIMIST-A trial once modifications of the laryngoscope blade (known as a “stat”) have been pursued, validated and CE-marked.

2.8.5 Premedication
Experience from the RHH-RWH feasibility studies suggests that the MIST procedure is generally well-tolerated without any premedication. Initial evaluation of the Cologne method reported the use of atropine at a dose of 25 μg/kg,\textsuperscript{31} although this has since become optional.\textsuperscript{33} In the OPTIMIST-A trial premedication with atropine will be at the discretion of the OPTIMIST Treatment Teams. Use of narcotic analgesics or other sedating medications will not be permitted.

2.8.6 Intubation criteria
Criteria for intubation of infants on CPAP have been stipulated in the OPTIMIST-A trial, based on experience from previous studies, examination of the RHH-RWH data, and knowledge of local practices. All enrolled infants will be intubated if persistently requiring an FiO\textsubscript{2} of 0.45. As with previous trials,\textsuperscript{7,8} other intubation criteria apply in the event of apnoea, persistent acidosis or need for an intervention.

2.8.7 Primary outcomes and sample size
An initial randomised controlled trial of MIST had as its primary outcome the need for intubation and mechanical ventilation, and found a reduction in this outcome after MIST.\textsuperscript{34} Whilst avoidance of mechanical ventilation is a worthy goal, it would seem that if infants are to undergo direct laryngoscopy and tracheal surfactant administration, it should be with the aim of producing a more tangible benefit than simply reducing the intubation rate. The choice of primary outcome in the OPTIMIST-A trial reflects this. The primary outcome is the composite of death or BPD, which according to our experience in 25-28 week infants (RHH-RWH data) currently occurs in 53% of those failing CPAP and 38% of those reaching the enrolment threshold. The OPTIMIST A trial has been powered to detect a reduction by one-third in this outcome (from 38% to 25%). Such a reduction appears to be a realistic target given that the rate of death or BPD in those succeeding on CPAP (not intubated in the first 72 hours) is 14%. It would also represent a major improvement in outcome for the 25-28 week group overall.

With the publication of feasibility studies and small clinical trials, there is a possibility that surfactant administration via MIST could become popular in the neonatal community before being adequately scrutinised. The OPTIMIST-A trial offers timely and rigorous evaluation of MIST, and we believe it will be a definitive trial in shaping the future approach to this therapy. For this reason we have calculated the sample sizes for the OPTIMIST-A trial based on 90% power.
3. OPTIMIST-A TRIAL PROTOCOL

3.1 TRIAL AIM
To evaluate in a randomised controlled trial the efficacy of surfactant delivery via a minimally-invasive technique in preterm infants 25-28 weeks gestation with RDS treated with CPAP.

3.2 HYPOTHESIS
That early surfactant administration via a minimally-invasive technique to preterm infants on CPAP will result in a lesser duration of mechanical respiratory support, and a higher incidence of survival without bronchopulmonary dysplasia.

3.3 STUDY DESIGN
Multicentre, randomised, masked, controlled trial.

3.4 STUDY POPULATION
Preterm infants of gestation 25 weeks 0 days to 28 weeks 6 days who are inborn and admitted to the NICU of a participating study centre, and who fulfill the entry criteria detailed below.

3.5 RECRUITMENT

3.5.1 Entry criteria
1. Requiring CPAP or nasal IPPV because of respiratory distress.
2. CPAP pressure of 5-8 cm H2O and FiO2 ≥0.30.
3. Less than 6 hours of age.
4. Agreement of the Treating Physician in charge of the infant’s care.
5. Signed parental consent.

3.5.2 Exclusion criteria
1. Previously intubated, or in imminent need of intubation because of respiratory distress, apnoea or persistent acidosis.
2. Congenital anomaly or condition that might adversely affect breathing.
3. Identifiable alternative cause for respiratory distress (e.g. congenital pneumonia or pulmonary hypoplasia).
4. Lack of availability of an OPTIMIST treatment team.

3.6 CONSENT
Written parental consent will be obtained prior to randomisation by the treating clinicians. A plain language document outlining the rationale for the study will be given to the parents. Consent should be obtained prenatally where possible, in which case the infant would only be enrolled after birth if all inclusion and no exclusion criteria were fulfilled.

In all cases, written consent will be obtained using a specifically-designed consent form. Verbal consent may be secured initially as long as the Study Investigator is confident that there has been provision of adequate information, and an informed decision has been reached.

3.7 RANDOMISATION
Once consent has been obtained, the infant will be randomised by the OPTIMIST Treatment Team, after handover of care from the treating clinicians. Enrolled infants will be randomised into “surfactant via MIST” and “standard care” groups, with an allocation ratio of 1:1, using a web-based randomisation procedure that will require confirmation of eligibility criteria and consent before revealing the randomly determined allocation. The randomisation schedule and web-based
service will be provided by the Clinical Epidemiology and Biostatistics Unit at the Murdoch Childrens Research Institute. The randomisation will be in randomly permuted blocks of variable length, stratified by study centre, and by gestational age. For the OPTIMIST-A trial there will be two gestational age strata (25-26 weeks and 27-28 weeks). Twins and higher order multiples will be randomised independently. Infants who are unstable and in need of intubation should not be randomised, even if consent has been obtained; such infants will not be considered to have been enrolled.

3.8 MASKING
Whilst recognizing the inherent difficulties, we are confident that the intervention in the OPTIMIST-A trial can be effectively masked from the clinical team. Masking considerably strengthens the trial design, allowing both the clinicians and researchers to carry out their work in an unbiased manner. Our proposed method of masking draws on that used in early trials of surfactant therapy, and in a recent randomised controlled trial of brief intubation for surfactant administration, in which staff were successfully masked during an intervention that was considerably more complex and long-lasting than proposed here (A/Prof. Carl d’Angio, personal communication Oct 2010).

In order to mask the group allocation from the treating clinicians, an OPTIMIST Treatment Team will be mobilized to perform the randomisation and intervention. This team will consist of a neonatologist, senior neonatal trainee or neonatal nurse practitioner, and a neonatal nurse, neither of whom will be currently involved in the infant’s care. Their role will be to screen the infant as effectively as possible from the treating clinicians, to obtain the randomisation, and then, within 1 hour of randomisation, to administer the intervention in accordance with the randomised allocation. Their activities, including removal of surfactant from the medication refrigerator, movement and speech within the screened space, and manipulation of the infant, will be such that the treating clinicians cannot discern which intervention is received. All treating clinicians will be made aware that the OPTIMIST Treatment Team will be concealing treatment allocation by performing a sham procedure on those infants randomised to standard care. The time taken to perform the intervention should be the same regardless of treatment allocation, and the infant will be returned to the pre-intervention CPAP settings prior to removing the screens. A survey of clinical staff will be conducted after each OPTIMIST intervention in order to assess the success of masking.

Members of OPTIMIST Treatment Teams at all institutions will undertake not to reveal the allocation group of randomised infants.

3.9 INTERVENTION
Given the experimental nature of MIST, it is the expectation of the Chief Investigators that participating centres would only offer MIST to 25-28 week infants within the context of the OPTIMIST-A trial.

3.9.1 Setting
The intervention will be performed in the NICU of participating centres.

3.9.2 Preparation of the infant by the treating clinicians
Prior to intervention, all neonates must be stable on CPAP delivered by prongs or mask. An intravenous cannula should be in situ. It is desirable that a blood gas analysis (arterial or capillary) will have been performed before intervention, although this is not mandatory. A chest X-ray is recommended to confirm the diagnosis of RDS, and to exclude other causes of respiratory distress.
3.9.3 Preparation of the infant by the OPTIMIST treatment team
Having been briefed on the current condition of the infant, the OPTIMIST Treatment Team will screen the infant from treating clinicians as completely as possible. The infant will then be randomised, and the allocated intervention carried out as soon as possible (maximum 1 hr). Pre-intervention observations will be recorded. The Treatment Team will take a labeled box containing full or empty surfactant vials from the OPTIMIST canister in the medication refrigerator. This canister will not be accessed by any other person other than the NICU pharmacist responsible for replenishing the stock of surfactant, which will be supplied specifically for the study.

3.9.4 Intervention – surfactant administration via MIST
The following protocol will be used for performing MIST:

**Preparation**
- Prepare the 16G Angiocath by marking a point indicating the desired depth of insertion beyond the vocal cords with a marker pen. The required depth is as follows: 25-26 weeks: 1.5 cm; 27-28 weeks 2.0 cm.
- Some investigators may find that tracheal catheterisation is facilitated by fashioning a slight anterior curve in the catheter.
- Draw up the surfactant (Curosurf™, Chiesi Farmaceutici, Parma, Italy) in a 3 or 5 mL syringe.
- Surfactant dosage:
  - The surfactant dose is 200 mg/kg (2.5 mL/kg)
- Draw up an additional 0.5 mL of air into the syringe, taking account of the dead volume of the instillation catheter (~0.3 mL).
- Optional: administer atropine 20 μg/kg intravenously.

**Performing MIST**
- Position the infant as for a standard intubation procedure.
- If possible, the laryngoscopy and tracheal cannulation should be performed with the CPAP prongs remaining in situ. An alternative which may improve the view of the vocal cords is to remove the CPAP prongs and apply CPAP by mask until the laryngoscopy commences.
- Perform direct laryngoscopy using a standard laryngoscope and blade. Alternatively, if approved, validated and CE-marked, the Glidescope Cobalt AVL video laryngoscope and modified size 0 stat may be used.
- Insert the surfactant instillation catheter through the vocal cords to the desired depth, and hold it in position at the lips. The laryngoscope should then be removed.
- Connect the surfactant syringe to the catheter hub, and instill the surfactant in 2-4 boluses over 15-30 seconds.
- Once the surfactant is instilled, immediately remove the instillation catheter and apply CPAP by prongs or facemask.
- If on the first attempt catheterisation of the trachea is not possible within 20-30 seconds, remove the laryngoscope, allow recovery on CPAP as required, and then attempt tracheal catheterisation once again. The maximum number of catheterisation attempts should be 3, after which the procedure should be abandoned.

**After MIST**
- Once heart rate, SpO₂ and respiratory effort are close to baseline values, restore the infant to their previous position, and re-establish CPAP with the same device and settings as prior to surfactant instillation.
- Details of the procedure will be recorded on a data form specifically related to the intervention. This form will be removed from the bedside by the Treatment Team, and sent
to the OPTIMIST Data Management Centre in a reply paid envelope. A copy of the form should be placed in locked cabinet away from the clinical area.

- Once the procedure is completed, clear all rubbish and consumables, and discard the surfactant instillation catheter in a sharps container (along with the trochar). All items that could reveal the treatment allocation to the treating clinicians should be cleared from the bedside.

Given the novelty of the MIST technique, OPTIMIST Investigators will be given the opportunity to practise the technique on an intubation mannequin during an OPTIMIST training workshop. Experience from the feasibility studies at RHH Hobart and RWH Melbourne indicates that neonatologists and neonatal fellows are highly likely to succeed in tracheal catheterisation from the outset, although two attempts at catheterisation may be required until familiarity with the technique is gained.

3.9.5 Intervention – standard care (sham MIST procedure)

The following protocol will be used in the standard care group:

**Sham procedure**

- Position the infant as for a standard intubation procedure. This will be the only actual intervention for babies randomised to standard care. CPAP will not be interrupted at any time in this group.
- Simulate the MIST procedure in terms of time taken and movement and communication within the screened area.

**After the sham procedure**

- Restore the infant to their previous position, and ensure the CPAP settings are the same as prior to the sham procedure.
- Record the time of the sham intervention on the OPTIMIST Intervention Form, remove the form from the bedside, and send to the Study Coordinator, retaining a copy, exactly as described for the MIST procedure above.

3.9.6 Management immediately after MIST

Once the MIST procedure or sham procedure is completed, the screens around the infant will be removed, and care of the infant returned to the treating clinicians. For all infants, attention will be drawn to the possible need to reduce the FiO2 so as to keep SpO2 in the target range. An entry will be made on the drug chart to indicate the timing of the OPTIMIST study intervention. A card will be placed at the bedside indicating that the infant has been enrolled in the trial, and displaying the intubation criteria. Post-intervention observations will be recorded by the treating clinicians at 4 hours.

3.9.7 Post-MIST investigations

A blood gas analysis (arterial or capillary) should be performed at 4 hours post-intervention, or earlier if clinically indicated.

3.9.8 Safety assessment

Data will be collected by the Treatment Team regarding the safety of the MIST procedure in infants randomised to receive MIST. These data will include the number of attempts at tracheal catheterisation, the duration of bradycardia (HR <100 bpm) and desaturation (SpO2 <80%), and the requirement for, and duration of, positive pressure inflations. These results may be communicated by the Treatment Team to the treating clinicians as necessary to aid in further care of the infant. Clinical observations will also be made at 5 minutes post-intervention and at 4 hrs post-intervention in both randomisation groups (CPAP pressure, FiO2, heart rate and SpO2). The results of the blood
gas analysis closest to 4 hours post-intervention will be recorded, and compared with a pre-
intervention value. These blood gas analyses are to be performed as part of routine care.

3.10 POST-INTERVENTION MANAGEMENT

3.10.1 Standard management

Other than the requirement to adhere to intubation criteria in the first week, and in some cases
perform a room air trial at 36 weeks corrected gestation, management of enrolled infants after
intervention will be at the discretion of the clinical team. Titration of CPAP pressure according to
work of breathing and oxygen requirement is encouraged. Maximum acceptable CPAP pressure is 8
cm H2O. Nasal IPPV (bi-level CPAP) is allowable. Adjustment of FiO2 should be so as to target an
SpO2 range appropriate for gestation and post-natal age.43 Prophylactic caffeine therapy would be
expected in all infants.37

3.10.2 Criteria for intubation

Infants should be intubated and ventilated if, and only if, they fulfill any of the following criteria:

- FiO2 ≥0.45. To qualify for intubation, the FiO2 must be sustained at intubation level for at least 15
  minutes, and all other aspects of CPAP management must have been optimised (including prong
  size and position, and minimisation of CPAP pressure leak).
- Apnoea unresponsive to caffeine therapy and stimulation, which is either frequent (6
  episodes in 6 hours requiring vigorous stimulation), or severe (more than one episode
  requiring positive pressure ventilation)
- Persistent respiratory acidosis with pH < 7.20 and PCO2 > 65 mm Hg on two blood gas
  samples at least 30 minutes apart, or metabolic acidosis refractory to treatment
- Need for an anaesthetic or an intervention requiring intubation

Note that these criteria apply only during the first week of life, and only for the first episode of
intubation.

Once intubated, surfactant therapy can be given, at the discretion of the treating clinicians. There is
no likelihood of harm if a further dose of surfactant is given less than 6 hours after surfactant
administration via MIST. Thus the treating clinicians will not be unmasked in this circumstance.

If treating clinicians judge that an enrolled infant should receive surfactant even though intubation
criteria are not met, they may exercise discretion and proceed to intubate and administer surfactant.
This will be logged as a protocol violation. The treating clinician may alternatively choose to
withdraw the infant from the study.

3.10.3 Assessment of BPD at 36 weeks corrected gestational age

Incidence of BPD based on oxygen requirement at 36 weeks corrected gestational age is variable
within units in the ANZNN, certainly in part due to variability in approach to oxygen therapy
amongst units. Given the primacy of BPD as an outcome in the OPTIMIST trials, a standardised
approach to its recognition has been incorporated into the trial design, based around the NICHD
consensus panel definition of “physiological BPD”.44 On or shortly after 36 weeks 0 days corrected
gestation, infants not requiring respiratory support (intubation / CPAP / HFNC ≥ 2 L/min) but
receiving oxygen therapy with an FiO2 of less than 0.3 will have a trial of room air. For infants on
nasal cannula oxygen the “effective FiO2” will be determined using the Benaron-Benitz formula,45
currently available as on online calculator (http://pub.emmes.com/study/rop/stop-js.html). Those
with an FiO2 <0.3 will have stepwise FiO2 reductions 5 minutes apart until either room air is being
administered or SpO2 is no longer within the target range. Based on current evidence, the SpO2
target range for this trial will be 91-95%.43 A successful room air trial will be defined as SpO2
readings in the target range for 30 minutes in room air with nasal prongs removed.44 Oxygen therapy
can thereafter be re instituted if deemed necessary by the treating clinicians.
Infants receiving HFNC therapy with FiO2 0.21 and flow < 2 L/min will also have a room air trial as above with the nasal prongs removed.

Infants requiring respiratory support, and those failing the room air trial, will be deemed to have physiological BPD. BPD using the standard (clinical) definition will be diagnosed if oxygen and/or respiratory support (intubation / CPAP / HFNC ≥2 L/min) is being administered for any portion of the day at 36 weeks and 0 days corrected gestational age.

Severity of BPD will be categorised according to the NIH consensus definitions:44

- **Mild BPD**: need for oxygen at 28 days but not at 36 weeks corrected gestation.
- **Moderate BPD**: need for oxygen at 28 days and continued oxygen requirement at 36 weeks (confirmed by room air trial), with FiO2 <0.3
- **Severe BPD**: need for oxygen at 28 days, and at 36 weeks an oxygen requirement with FiO2 ≥0.3 and/or need for positive pressure support (intubation, CPAP, HFNC ≥2 L/min).

3.11 DATA COLLECTION AND MANAGEMENT

Within the OPTIMIST Investigator Team at each site, nominated personnel (e.g. Unit Data Collectors, Unit Research Nurses) will collect data and enter it onto hard copy and/or electronic forms, as available. Data management will be coordinated from the Clinical Epidemiology and Biostatistics Unit (CEBU) at MCRI, using a web-based database management system.

3.11.1 Data collection in hospital

- Basic demographic, perinatal, and clinical data, as well as in-hospital outcomes, will be collected prospectively for each patient, starting at enrolment. The data will be entered on a hard copy clinical report form.
- Data pertaining to the MIST procedure will be collected by the OPTIMIST Treatment Team, on a separate randomisation and intervention form. This form will not be viewed by other clinical or research staff. Once filled in, it will be sent by reply paid post to CEBU at MCRI. Information recorded will include the number of attempts required to catheterise the trachea, the total time taken, the lowest heart rate noted during the MIST procedure and time for restoration of heart rate above 100 beats per minute, the lowest SpO2 noted and time for restoration of SpO2 above 80%, and the need for and duration of positive pressure inflations by mask.
- Data on heart rate, CPAP pressure, FiO2, and SpO2 prior to, and at four hours after intervention will be collected, along with the results of pre- and post-intervention blood gas analysis.
- Provision will be made to follow-up infants after discharge from hospital by recording contact details of parents and grandparents, and seeking parental consent to track address changes through the Medicare database.

3.11.2 Follow up

Each infant will have a full clinical and neurological assessment performed at 2 years by a developmental paediatrician blinded to the initial randomisation. Psychometric testing will be performed by a trained practitioner using the Bayley III scales of infant development (or equivalent). Hospitalisation history in the first two years will be documented at this visit.

3.12 OUTCOME VARIABLES

3.12.1 Primary outcome

Incidence of composite outcome of death by 36 weeks corrected gestation or physiological BPD44

3.12.2 Secondary outcomes

- Physiological BPD44
• Clinical BPD (requirement for oxygen or any form of positive pressure support at 36 weeks corrected gestation).\textsuperscript{46}
• Mild/moderate/severe BPD\textsuperscript{46}
• Death by 36 weeks corrected gestation, and throughout hospitalisation
• Death by 36 weeks corrected gestation or BPD (clinical definition)
• Intraventricular haemorrhage (IVH) (all grades)
• IVH grades III and IV\textsuperscript{47}
• Periventricular leukomalacia
• Retinopathy of prematurity > stage II
• Major morbidity (any of IVH grade III or IV, periventricular leukomalacia, ROP > stage II, physiological BPD)\textsuperscript{48}
• Death by 36 weeks corrected gestation or major morbidity
• NEC (Modified Bell stage 2 or greater)\textsuperscript{49}
• NEC or spontaneous intestinal perforation requiring surgery
• Requirement for intubation in the first 72 hours of life
• Requirement for intubation at any time
• Need for additional surfactant therapy
• Overall number of surfactant doses (including that given by MIST)
• Duration of intubation (all episodes)
• Duration of CPAP/NIPPV (all episodes)
• Duration of intubation and CPAP

Duration of high flow nasal cannula (HFNC), minimum flow rate 2 L/min
Duration of respiratory support
Duration of oxygen therapy
Requirement for oxygen at home
Length of stay in intensive care
Length of hospital stay
Total hospital billings
Calculated cost of hospitalisation
Pneumothorax requiring drainage
Pulmonary haemorrhage
Patent ductus arteriosus (PDA) requiring anti-prostaglandin therapy
PDA requiring ligation
Late onset sepsis (positive bacterial or fungal culture from a normally sterile site)
Time to regain birth weight

**Applicability/safety of the MIST procedure:**
• Incidence of successful surfactant administration via MIST
• Number of catheterisation attempts
• Duration of bradycardia and hypoxaemia
• Requirement for, and duration of, positive pressure ventilation by mask
• Incidence of apparent discomfort

**Longer term outcomes**
• Number of hospitalisations in the first 2 years
• Number of hospitalisations with respiratory illness in the first 2 years
• Major disability at 2 years
• Death or major disability at 2 years

**3.13 STATISTICAL ANALYSIS AND REPORTING**

**3.13.1 Statistical analysis**

Data handling, verification and analysis for the OPTIMIST-A trial will be performed by CEBU at MCRI. A trial statistician will be appointed for the trial, supervised by Prof. John Carlin. Statistical analysis will follow standard methods for randomised trials and the primary analysis will be by intention to treat. For dichotomous outcomes, including the primary outcome in OPTIMIST-A, proportions will be compared using the odds ratio with 95% CI, obtained from a logistic regression analysis with adjustment for the strata (defined by centre and gestational age category) used in the randomisation. Continuous outcomes, will be compared using differences between mean values, estimated from normal linear regression models with the same stratification adjustments. Secondary analyses will use expanded regression models to explore potential confounding effects of chance imbalances between arms in birth weight, gender, antenatal steroids, or mode of delivery. In further
secondary analysis, we will explore evidence for heterogeneity of effects between the two gestational age strata in the trial, using interaction tests and subgroup analyses.

3.13.2 Data reporting and manuscript preparation
A clinical study report will be generated from the Data Management Centre. This document will, after approval by the Trial Steering Committee, form the basis of conference presentations and manuscripts for publication. Responsibility for manuscript preparation will rest with the Trial Steering Committee. Authorship will be in the form of: Author A, Author B, Author C,… for the OPTIMIST Investigators.

3.14 SAMPLE SIZE
In the RHH-RWH CPAP study, amongst infants of 25-28 weeks gestation the proportion positive for the outcome of death or BPD was 53% in those failing CPAP and 38% in those reaching the OPTIMIST A enrolment threshold in the first 2 hours. A reduction by one-third in the proportion of infants with this outcome (i.e. from 38% to 25%) would be a major advance in care for this patient group, relieving the burden at both individual and NICU levels. Detection of a reduction of this magnitude with 90% power and $\alpha = 0.05$ (two-sided) would require 297 subjects per arm. An allowance will be made for withdrawal of 2% of subjects post-recruitment. The number of subjects to be randomised in each arm will thus be 303, for an overall total of 606. If large scale funding is not obtained by the end of 2012, the trial protocol allows for an analysis based on the outcome of requirement for intubation <72 hours, i.e. the same outcome as for the trial of Göpel et al. This comparison in its own right would give important additional information about the place of MIST. For this analysis, a sample size of 88 infants would allow detection of a reduction in the rate of intubation from 60% to 30% with 80% power, $\alpha=0.05$.

3.15 TRIAL PLAN
Year 1 (2012)
The OPTIMIST-A trial commenced at RHH in December 2011, and will commence at RWH Melbourne in early 2012. All Australasian neonatal units, and selected international centres, including those in the Vermont-Oxford network, will be invited to join the trials, and local information sessions held in each centre as required. The Trial Coordinating Centre Team will assist units joining the study with ethics submissions and organisational matters.

At the time of study commencement at each site, a trial workshop will be conducted by a team from the Trial Coordinating Centre. These workshops will consist of 1) a formal outline of the trial, 2) a hands-on demonstration of the MIST technique using an intubation mannequin, 3) a bedside simulation of the MIST procedure and of the sham intervention by an OPTIMIST Treatment Team, and 4) in-depth discussion of the practicalities of screening, randomisation and data collection.

Years 2-5 (2013-2016)
A full complement of participating centres is expected for the OPTIMIST-A trial by early 2014. Recruitment will thereafter proceed at full rate until completion, which is estimated to take 4 years for each trial.

3.16 FEASIBILITY
Each year, approximately 1000 infants of gestational age 25-28 weeks are inborn in tertiary level neonatal units in Australia and New Zealand without congenital anomalies or PPROM, of whom approximately 550 are treated in the first instance with CPAP. Indicative figures from RHH Hobart and RWH Melbourne would suggest that approximately 56% of those on CPAP would be eligible for entry into the OPTIMIST trial, i.e. around 300 infants per year. Over a 4 year period (2013-2016) it will necessary to enroll around 50% of these infants to complete the study in the 25-28
week gestation group.

In view of the numbers of infants required, selected international centres will be invited to join the study, in part dependent upon participation and recruitment rates in Australasian centres.

3.17 DATA AND SAFETY MONITORING COMMITTEE
An independent Data and Safety Monitoring Committee (DSMC) has been established for the OPTIMIST-A trial. The terms of reference for this committee will include performance of interim data analysis, periodic examination of emerging external evidence in relation to MIST, and monitoring of adverse events, compliance with the trial protocol, and progress of recruitment. The DSMC will develop their own charter for the conduct of these and other activities.

3.17.1 Interim analyses
The Trial Steering Committee expects that there will be a maximum of three interim analyses for the OPTIMIST-A trial. Relevant event rates in enrolled infants will be compared to the background rates in data from the RHH-RWH preterm CPAP study, and recommendations for change in sample size made if a substantial disparity is noted. The odds ratios for major outcomes will be examined in the two randomisation groups. For this comparison the statistical approach will be conservative, with a recommendation to cease the trial on efficacy grounds only to be made in the presence of very strong interim evidence. Later analyses will also include consideration of whether there is an unequivocal lack of efficacy. At each meeting of the DSMC the ethical position in relation to further randomisation will be considered based on results of other randomised controlled trials comparing MIST with standard care (continuation of CPAP).

3.17.2 Adverse events
Serious adverse events (SAEs), including those leading to death, prolonged hospitalisation or persistent disability, are relatively common in preterm infants 25-28 weeks gestation. Serious adverse events which are in the opinion of the local investigator unexpected will be reported within 24 hours to the Sponsor. The SAE will then be reported to the local Ethics Committee, the Tasmania Health and Medical Ethics Committee, the Trial Steering Committee, the DSMC, and, as appropriate, the Therapeutic Goods Administration and/or other federal regulatory bodies. The data pertaining to the SAE will be examined by the DSMC, and any recommendations made will be disseminated to local investigators.

3.18 FUNDING
Funding has been obtained for commencement of the OPTIMIST-A trial from the RHH Research Foundation (for 2011 and 2012), and from the Australian NH&MRC for 2013 and beyond. Chiesi Farmaceutici, Parma, Italy has agreed to supply the surfactant at significantly reduced cost. The trial sponsor will be the Menzies Research Institute Tasmania, and the trial insurer will be Unimutual Limited.

3.19 OUTCOMES AND SIGNIFICANCE
This proposed trial is the next logical step in refining the care we provide to preterm infants 25-28 weeks gestation. It will be by far the largest randomised controlled trial investigating MIST conducted to date, and in its own right will have sufficient power to give definitive information about the place of this therapy. The concept of MIST is exciting because of the possibility that giving surfactant in this way to preterm infants may improve respiratory outcomes including duration of respiratory support and risk of BPD. A reduction in the incidence of BPD in the 25-28 week infants would represent a significant advance for this group, in which the risk of BPD remains high, and leads in many cases to chronic respiratory ill health in infancy.
4. REFERENCES


