BACKGROUND

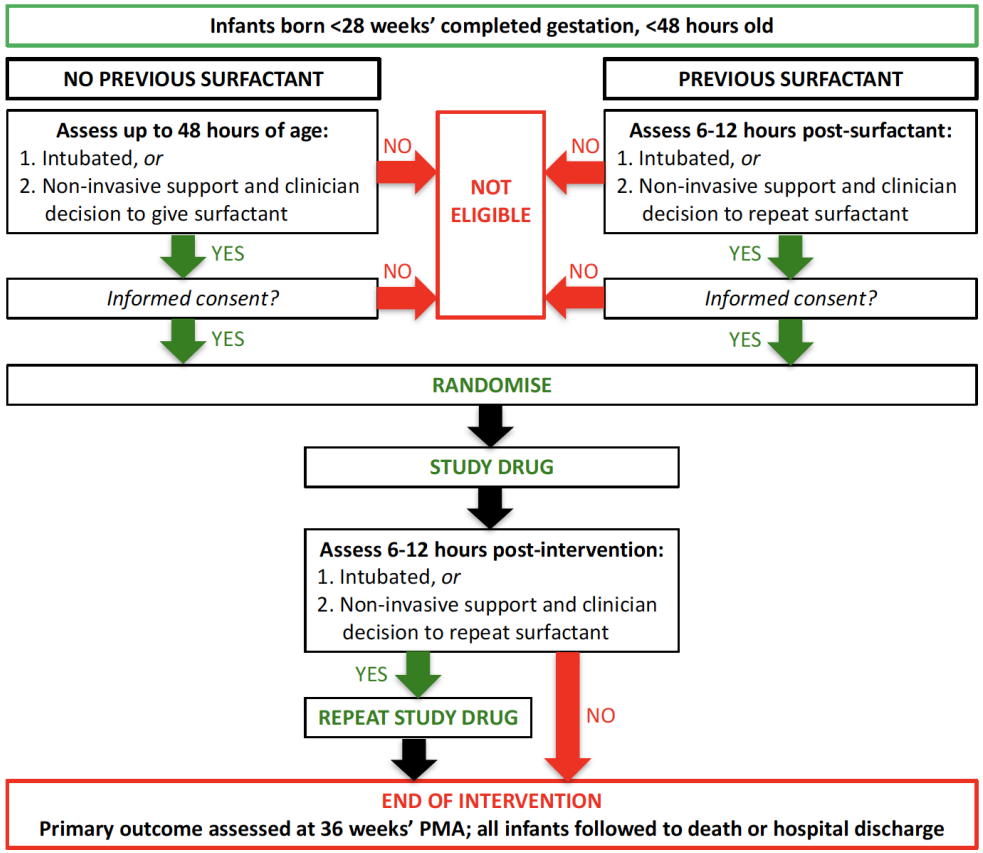
At least half of very preterm babies develop bronchopulmonary dysplasia (BPD) or neonatal chronic lung disease and require oxygen or respiratory support at 36 weeks' postmenstrual age. BPD is associated with increased infant mortality and adverse neurodevelopmental outcomes.[1] Despite many recent advances in neonatal care, BPD rates remain static with evidence of worsening lung function in surviving children.[2] Preventative therapies are urgently required.[3]

Systemic (enteral/intravenous) glucocorticoids are effective at preventing BPD due to their anti-inflammatory effects, but are not suitable for routine use because of significant short- and long-term harm, such as cerebral palsy.[4] The PREMILOC trial suggested that hydrocortisone may have less side effects, but there are concerns about the external validity of this trial due to the respiratory management practices used (nearly 50% on controls remained ventilated at 10 days).[5,6]

Intratracheal instillation of budesonide mixed with surfactant is a promising new preventative therapy for BPD.[7] It maximises glucocorticoid effect in the lung while minimising systemic uptake and adverse effects. Surfactant is an ideal vehicle as it distributes steroid throughout the distal airway. Budesonide is unique in that it is taken up and retained in epithelial cells by conjugation.[8] This creates an intracellular depot, resulting in prolonged local corticosteroid action even after one dose.[9] Only 4% of total dose is taken up systemically[10] and does not appear to enter the neonatal brain.[11] There is emerging evidence that budesonide not only suppresses pulmonary inflammation but may also promote lung maturation in a manner similar to antenatal glucocorticoids.

Inhalers have been proposed as alternative method for delivering glucocorticoid to the lung but are inefficient as much of the dose is swallowed. Prolonged treatment is required with high cumulative dose, and this may increase neonatal mortality.[12,13]

PLUS+S will be the first large trial of budesonide and surfactant and include not only ventilated infants but those on non-invasive respiratory support.



PURPOSE OF THE TRIAL

To determine whether intratracheal budesonide mixed with surfactant will increase survival free of BPD in extremely preterm babies.

ENTRY CRITERIA

Inclusion Criteria:

1. Inborn or outborn infants <28 weeks' (23^0 - 27^6 days) gestation, <48 hours of age
2. Receiving a) mechanical ventilation via an endotracheal tube, or b) non-invasive respiratory support (any type) *and* there is a clinical decision to treat with surfactant (1^{st} or 2^{nd} dose)
3. Prospective, written, informed consent obtained

Infants are still eligible after previous surfactant.

Exclusion Criteria:

1. Prior treatment with corticosteroids for lung disease
2. Infant is considered non-viable, not for NICU admission
3. Known or suspected major congenital anomaly that is likely to affect respiratory status
4. Infant likely to be transferred to a non-participating NICU within 24 hours of birth

STUDY GROUPS

Eligible infants will be randomly allocated to either **budesonide plus surfactant** or **surfactant alone**.

Budesonide plus surfactant group: Budesonide (Pulmicort™) 0.25 mg/kg (0.5 ml/kg of 1 mg / 2 ml solution). The surfactant (Curosurf) dose is 200 mg/kg (2.5 ml/kg) for the 1^{st} study treatment, and 100 mg/kg (1.25 ml/kg) for the 2^{nd} (if applicable).

Surfactant only group (control): Surfactant alone, dosing as above.

Enrolled infants will receive at least one, and no more than two, study treatments.

OUTCOMES

Primary:
Survival free of physiological BPD at 36 weeks' PMA

Secondary:

- BPD severity
- Death before discharge
- Respiratory support and/or oxygen at 40 weeks
- Duration of mechanical ventilation, respiratory support, supplemental oxygen, and hospitalisation
- Neonatal morbidities, including intraventricular haemorrhage, retinopathy of prematurity, necrotising enterocolitis, intestinal perforation, and patent ductus arteriosus
- Hyperglycaemia, hypertension, late-onset sepsis, oral candidiasis, and growth

Funding will be sought for long-term follow.

SAMPLE SIZE

A sample size of 1,060 will have 90% power to detect a reduction in survival free of BPD at 36 weeks' gestation from 50% to 40% (relative risk reduction 20%, absolute risk reduction 10%), allowing for 2% withdrawal.

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PLUS+S

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Preventing Lung Disease Using Surfactant and Steroid

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HEALTH PROFESSIONAL INFORMATION SHEET

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