1. SYNOPSIS

1.1 Study Summary

Table 1: Study Summary

Section	Information
Background	Without adequate ambient humidity, extremely preterm (EPT) babies lose water through their skin, causing dehydration and hypernatraemia, which is associated with death, intraventricular haemorrhage (IVH) and disability. Between 2007–19, 11.4% of 32,841 Japanese infants of <30 weeks gestation died or had severe (Grade 3 or 4) IVH, the lowest rate in the world. The rate in 24,850 Australian infants for this gestation was 13.1%, so that of every 1,000 EPT infants, 17 more Australian infants died or had severe IVH. One of the main differences in management of these high-risk infants between the two countries, is that Japan usually starts with incubator humidity of 95%, compared with starting humidity of 80% in Australia. Despite this, there are no RCTs of incubator humidity assessing these outcomes in EPT babies
Aims and Objectives	The aim of the HUM-TE trial is to assess the clinical effect and explore implementation contexts of starting incubator humidity at 95% compared with 80% on EPT infants during the first three days of life. The overall objective of the HUM-TE trial is to test the hypothesis that 95% vs 80% initial incubator humidity for 3 days after randomisation in infants born <27 weeks' gestation reduces hypernatraemia, skin injury, sepsis and brain damage, before a future prospective meta-analysis of trials powered to find moderate reductions in mortality.
Primary Objective	To assess the clinical effect of starting incubator humidity at 95% compared with 80% humidity in EPT infants born less than 27 weeks' gestation, as assessed by the primary outcomes of: (1) any episode of hypernatremia (serum sodium ≥150 mmol/L) and/or (2) Mean of all serum sodium concentration (mmol/L) in the first 3 days after randomisation
Secondary Objectives	To compare the following between study arms: (1) Number of postpartum skin injuries during the first 14 days after birth (2) Late onset sepsis (LOS) in the first 21 days after birth (3) Any brain injury (all grades of intraventricular haemorrhage or cerebellar haemorrhage or periventricular leukomalacia) before hospital discharge (4) Survival until hospital discharge

Safety Objectives	Safety of the intervention, defined as rates of Suspected Unexpected Serious Adverse Reaction (SUSAR) attributed to 95% incubator humidity versus 80% humidity
Process Evaluation Objectives	(1) Context, uptake, acceptability of starting incubator humidity at 95% (2) Parent experience measure (Parent Stress Scale on day 4 and at 1 month after birth)
Tertiary and Exploratory, Hypothesis-Generating Objectives	To assess differences in infants exposed to 95% incubator humidity versus 80% incubator humidity, in: (1) Any hypernatraemia >145 mmol/L in the first 7 days after birth (2) Mean of all sodium concentration (mmol/L) for the first 7 days after birth (3) Highest sodium level in the first 7 days after birth (4) Maximum daily total fluid intake (ml/kg/day) for the first 3 and 7 days after birth (5) Mean of daily total fluid intake (ml/kg/day) for the first 3 and 7 days after birth (6) Bronchopulmonary dysplasia (BPD) if occurred or not and its grade (7) Necrotising enterocolitis (NEC) if occurred or not and its grade (8) Patent ductus arteriosus (PDA) requiring surgical closure (9) Advanced retinopathy of prematurity (ROP) treated with laser surgery and/or intravitreal injection of anti-vascular endothelial growth factor (10) Accidental dislodgement of essential monitoring or treatment interface (e.g.: dislodgment of intra-vascular catheters or endotracheal tubes from wet tapes) (11) Maximum body weight loss (percent) from birth weight (12) Change in body weight on days 3, 7 and 14 after randomisation (13) Skin integrity assessment using standardised digital images on days 3, 7, 14 and 28 after randomisation – a sub-study at up to 10 study sites (14) Skin integrity assessment using an evaporimeter to measure transepidermal water loss (TEWL) + skin surface hydration using a corneometer on days 3, 7, 14 and 28 after randomisation – a sub-study at up to 3 study sites (15) Non-invasive measure of skin health around kangaroo care (KC) in the first 28 days after randomisation using an evaporimeter to measure TEWL, a measure of skin barrier integrity – a sub-study at up to 3 study sites (16) To assess whether the number of postpartum skin injuries during the first 14 days is associated with risk of death (17) To explore the characteristics of skin injury in the first 14 days after birth with risk of death

	(18) To explore the association between the cumulative burden of hypernatraemia >145 mmol/L and ≥ 150 mmol/L in the first 3 and 7 days after birth and the risk of death, any IVH, sepsis and skin injury.
Design	This study is a multi-centre, 2-arm, parallel, open-label, phase II, randomised, comparative effectiveness trial with a mixed method process evaluation.
Population	All inborn preterm infants born less than 27 weeks' gestation (includes infants born at 22 weeks') **and** less than or equal to 6 hours of age
Assessments	Assessments are scheduled at regular intervals from enrolment until hospital discharge (Table 1). Routine assessments will be collected at baseline and at discharge to home. (1) First week after birth: serum sodium levels (mmol/L) and total fluid intake (ml/kg/day)– assessed daily. (2) First two weeks after birth: skin injury - assessed daily; body weight – assessed every two or three days. (3) Before hospital discharge: any brain injury (any grade of intraventricular haemorrhage or cerebellar haemorrhage or periventricular leukomalacia), BPD, LOS (first 21 days after randomisation), PDA, ROP, NEC and survival will be assessed before hospital discharge. In addition, in a subgroup of infants: (4) Skin integrity assessment by obtaining standardised serial images of the skin from two body sites – shoulder and 1 cm below the xiphoid assessed on days 3, 7, 14 and 28 after randomisation, (5) Skin integrity assessment by measuring the transepidermal water loss (TEWL) using an evaporimeter + skin surface hydration using a corneometer from three body sites – skin over the shoulder, 1 cm below the xiphoid process and the mid-lateral thigh area on days 3, 7, 14 and 28 after randomisation. (6) Measuring skin water loss ($g/m^{2/}/hr$) up to 30 minutes before starting kangaroo care (KC), during (30 minutes after commencing KC) and up to 30 minutes after finishing KC in the first 28 days after randomisation
Study Intervention	Inborn infants will be randomly allocated to (A) 95% initial incubator humidity OR to (B) 80% initial incubator humidity as soon as possible upon admission to the neonatal intensive care unit (NICU) and within 6 hours after birth and continued for 72 hours from randomisation. Incubator humidity weaning is requested as per schedule on Table 5.

	The intervention (95% initial incubator humidity) may be reduced within 72 hours of randomisation for the following reasons: (1) persistent incubator rainout (2) consistently low blood sodium level (<135 mmol/L on successive tests) or (3) other potential for a harm (e.g., essential patient monitoring/treatment device adhesion issues).
Sample Size and Statistical Considerations	A sample size of 308 infants (154 infants in each arm) will have 90% power to detect a difference in the proportion of infants experiencing hypernatraemia in the first 3 days after randomisation assuming a rate of 42% at 80% humidity and a reduction to 21% at 95% humidity (50% relative reduction). This allows for 2% for non-compliance, 16% of babies being twins and correlation of 0.1 between twins. Sample sizes are calculated with two-sided alpha of 0.01 to allow for multiple primary outcomes. This sample size (N=308) has 95% power to detect a difference of 2.5 mmol/L in mean blood sodium concentration assuming a standard deviation of 5 mmol/L. Randomisation will be stratified by gestational age (<25^{+0} and 25^{+0}–$26^{+6/7}$ weeks), hospital site and incubator type with 1:1 allocation, with all babies of multiple births being allocated to the same treatment.