Randomised trial comparing CPAP machines with reusable vs disposable circuits

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TRIAL SUMMARY

1. **Aim & Hypothesis:**

   The study aims to assess the basic functionality of a newly designed CPAP machine with reusable circuits to existing machines with disposable circuits, for treatment of newborn infants diagnosed with respiratory distress syndrome. The assessment will compare a comprehensive list of physiological parameters over the first 72 hours of treatment, and will also monitor rates of side effects and adverse events. The null hypothesis is that infants treated on the two categories of machine (reusable vs disposable) will not differ in relation to key physiological parameters by more than 0.63 standard deviations.

2. Background:

2.1. Plain language summary

One of the commonest sources of serious newborn morbidity and mortality is difficulty with breathing. When this occurs, three main types of supportive therapy are available to increase the provision of oxygen to cells: a) passive provision of oxygen-enriched gases (i.e., higher than the 21% O_2 found in the earth's atmosphere) through tubes in the nostrils, or by putting a hood over the baby's head and enriching the gases under that hood; b) provision of room air or oxygen-enriched gasses under pressure, frequently performed using a method called continuous positive airway pressure [CPAP] therapy; and/or c) by using a machine that is able to breath on behalf of the baby, most commonly referred to as mechanical ventilation [MV].

Passive therapy is the least invasive method but is also of limited benefit, particularly for infants born preterm. CPAP is more effective than passive methods because continuous distending pressure to the lungs allows better oxygen exchange; however, the distending pressure increases the risk of damage to the lung. MV is the only method that can be used on babies without a neurological impulse to breath, but the mechanical breathing action can damage the lungs, and MV is usually provided through a tube inserted into the lungs which increases the risk of lung infection; MV machines are also significantly more expensive than CPAP machines.

In high resource settings, CPAP is now the preferred method of providing oxygen for infants where passive therapy is insufficient, because of the lower infection risk, lower risk of lung damage, and relative ease of clinical care. CPAP is increasingly recommended for low resource settings, but the CPAP machines used in high resource settings are too expensive for low resource settings due to high-priced consumables ($US50-200/baby), and are usually unusable in low resource settings because they require 'medical air' (clean air in a cylinder, or through a piped wall system) with which to blend 100% oxygen. Low cost 'indigenous' machines ('jury-rigged' by hospital staff) have also been developed, but these do not provide the heated, humidified and blended gasses, that are recommended for CPAP.

This study seeks to evaluate a novel CPAP machine that provides heated, humidified, blended gasses, in line with recommendations for high-resource settings, while massively reducing costs by including re-usable tube sets and humidifiers that can be autoclaved, and with an on-board air-compressor to allow use in a broader range of clinical settings. By reducing the cost per CPAP treatment, such a machine can dramatically increase the number of hospitals in low resource settings that can provide high quality CPAP treatment.

2.2. Literature review

Neonatal deaths (0-27 days of age) were estimated to account for 40% of all deaths under five years of age in 2010.[1] Preterm birth complications are the largest single cause of neonatal mortality, accounting for three in every eight neonatal deaths in 2010.[2] As other causes of child mortality such as tetanus, diarrhoea and pneumonia are addressed, it becomes increasingly urgent that prevention and treatment programs address complications of preterm birth, if we are to continue to reduce child mortality in low resource settings.

The basic bilateral structure of the lungs develops through the embryonic stage (4-7 weeks of gestation) and then proceeds with the formation of the basic vascular structure, ending at around 24 weeks of gestation. From 24-36 weeks' gestation, basic alveoli are formed for gas exchange, increasing the surface area over time, and related cells commence producing surfactant. At around 36 weeks' gestation the final stage of lung development commences, with rapid growth in the number of alveoli; this stage continues in the postnatal period. [3]
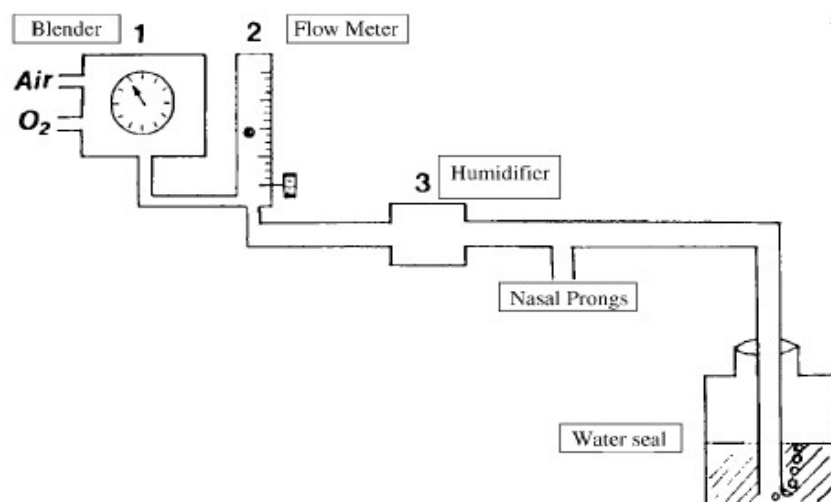
Preterm birth disrupts this process and often leads to poor lung development with permanently impaired lung function. Surfactant, which is detectable by 24 weeks of intrauterine life,[4] reduces surface tension in the lung, preventing lung collapse, and reducing the work of breathing and increasing lung compliance.[5] Neonatal Respiratory Distress Syndrome (RDS) is a direct result of pulmonary immaturity and surfactant deficiency:[5] the incidence of RDS increases sharply with *decreasing* gestational age,[6] such that the majority of liveborn babies <32 weeks gestation develop RDS.[7] The case fatality rate of infants with RDS also increases with decreasing gestation, indicating more severe disease at lower gestations.

RDS can be prevented and/or reduced in severity by accelerating fetal lung maturation through use of antenatal corticosteroids,[8] by permitting the onset of labour which stimulates surfactant production,[6] and by postnatal administration of exogenous surfactant.[9] Although use of antenatal corticosteroids is promoted in low resource settings, the evidence shows that its use is rare in these settings;[7] and exogenous surfactant is too expensive for routine use in low resource settings[10]. Even if all of these interventions could be implemented fully, however, there would still remain a group of infants with RDS who would need supportive therapy.

The use of CPAP to treat RDS was first reported in 1971.[11] While many different methods of providing CPAP are available, a common combination uses short binasal prongs as an interface to deliver heated and humidified gases, blending oxygen and air to achieve the desired amount of oxygen enrichment; a typical configuration is shown in Figure 1. Pressure can be delivered in a variety of ways, but is commonly delivered in the fashion shown in Figure 1, by submerging an expiratory tube in water to provide a distending pressure determined by the depth of insertion; this 'bubble CPAP' is increasingly popular as it is relatively easy to manage and because the bubbling of the water in the expiratory circuit results in high frequency oscillations in the lungs which may result in more efficient gas exchange.[12] The new and existing CPAP machines to be compared in the current study are bubble CPAP devices.

Cochrane reviews of randomised trials in high resource settings have demonstrated that CPAP can reduce the need for intubation[13] and reduce re-intubation of infants being weaned from MV.[14] More recently, separate meta-analyses have demonstrated that CPAP can be used in the delivery room[15] or at any stage prior to intubation[16] to reduce the use of MV and thereby prevent the chronic lung disease associated with MV.

Figure 1:   Schematic diagram of a 'bubble' CPAP circuit[17]

A recent review of changes in mortality over time in the USA found that the most rapid reduction in RDS mortality coincided with the introduction of CPAP and argues, on that basis, for the roll-out of CPAP to treat RDS in low-resource settings[18]. A separate review of studies of CPAP in low resource settings found consistent evidence of benefit in avoiding MV[19], and a related editorial proposes that CPAP should be promoted as the standard of care for RDS in low resource settings.[20]

The accumulated evidence of the value of CPAP is reflected in its inclusion in the list of Essential Interventions, Commodities and Guidelines for Reproductive, Maternal, Newborn and Child Health by the Partnership for Maternal, Newborn & Child Health[21], which includes the World Health Organization. Indian clinicians have recognised the value of CPAP for treating RDS for more than a decade[22, 23], and have more recently concluded that surfactant is prohibitively priced, relegating it to the status of a salvage therapy where CPAP fails[10].

The recent establishment of a nationwide infrastructure of Level II Special Care Newborn Units (SCNUs) funded by the National Rural Health Mission has created a structural opportunity to roll-out a high quality CPAP program. A recent estimate suggest that up to half a million Indian newborns will require CPAP each year[24] but, as with surfactant, the capacity to satisfy this demand will be dependent on price. If state of the art disposable tubes and humidifiers cost $US100 each, this would imply an annual consumable cost of over $US50 million, without taking into account the capital cost of acquisition.

The March of Dimes Global Action Report on Preterm Birth notes that there is a need for innovation to create robust low cost CPAP for use in low resource settings[7]. While bubble CPAP machines in high-resource settings routinely cost around $US6,000 to purchase, a recent project has built a simple bubble CPAP machine with an estimated cost of goods of $US350.[25] Unlike homemade bubble CPAP machines, this machine allows blending of air and oxygen, but does not allow humidification and heating of the inspired gases; the cost per treated patient on such a machine is not as yet known.

As the current standard of care includes use of humidified and heated gases during treatment with neonatal CPAP,[26] it is not envisaged that the Indian public health system or private health providers will adopt these minimal-function devices, and it is not clear if they provide superior outcomes to existing 'indigenous' CPAP machines. The current study seeks therefore to compare a fully-functional bubble CPAP system with a dramatically lower cost per CPAP-treated neonate, achieved by reducing the number and cost of consumables, with state of the art CPAP machines. The current study will seek to compare, by randomised controlled trial, physiological indices indicative of the quality of respiratory support provided to demonstrate the basic functionality of the new CPAP machine with re-usable tube sets and humidifiers in comparison to current state of the art machines using consumables. Similar methods[27, 28] and outcomes[27-29] have previously been used to compare alternative methods of providing CPAP.

3. **Design:**

3.1. Patient selection criteria

Inclusion criteria: The following groups of infants will be considered eligible:

a) Infants born at the hospital ('inborn infants') or born elsewhere, and admitted to Ramaiah hospital under 6 hours of age;

b) Infants with a gestational age at birth (weeks $^{+days}$) in the range $\geq 28^{+0}$ to $\leq 36^{+6}$;

c) Infants thought to have RDS (clinically diagnosed after onset of respiratory distress <6 hours of age, sometimes confirmed by X-ray showing homogenous bilateral opacity) who would routinely be provided CPAP; and

d) Infants <24 hours old at the time of fulfilling other inclusion criteria.

Exclusion criteria: The following groups of infants will be excluded to avoid any accidental imbalance in rare conditions between groups post-randomisation:

a) Infants with a 1-minute Apgar score <3 (as a marker of severe birth asphyxia);

b) Infants who received MV prior to randomisation;

c) Infants with suspected meconium aspiration syndrome will be excluded to avoid any imbalance in this condition across groups;

d) Infants clinically suspected to have another specified serious condition as their main disease process, ***diagnosed prior to randomisation***, specifically: cardiac anomaly, other congenital malformation with respiratory sequelae, septicaemia, pulmonary haemorrhage, pneumothorax, meningitis, poor respiratory effort or recurrent apnoea, or brain haemorrhage (IVH Grades III or IV);

e) Infants who have an airway abnormality precluding the use of the standard CPAP interface proposed for this study (e.g., Pierre-Robin sequence, cleft lip or cleft palate) or who have a neuromuscular condition that interferes with respiration;

f) Any infant whose treating clinician believes should not be randomised due to some other condition, or for any other reason (reason to be documented).

3.2. Primary outcome

The primary outcome will be a comparison of fraction of inspired oxygen (FiO_2), measured as a change from baseline at 6, 12, 24, 48 and 72 hours after treatment commencement.

3.3. Secondary outcomes

A range of secondary outcomes will be assessed:

- Oxygen saturation by pulse oximetry (SpO_2), measured as a change from baseline at 6, 12, 24, 48 and 72 hours after treatment commencement;

- Respiratory rate (breaths/minute), measured as a change from baseline at 6, 12, 24, 48 and 72 hours after treatment commencement;

- Arterial blood gas analyses, measured as a change from baseline at 6, 12, 24, 48 and 72 hours after treatment commencement, including:
  - pH;
  - Partial pressure of oxygen (PaO_2); and
  - Partial pressure of carbon dioxide ($PaCO_2$).

- CPAP failure (death or need for intubation and mechanical ventilation as demonstrated by an FiO_2 requirement $\geq 60\%$ for ≥ 1 hour to maintain SpO_2 at 90-95%);

- Surfactant provided when $FiO_2 > 40\%$ to maintain SpO_2 at 90-95% for $\geq$ 30 minutes, with RDS confirmed by chest X-Ray, in line with current Ramaiah standard practice;
- An omnibus indicator comprising CPAP failure or surfactant provision;
- Duration of CPAP treatment (hours) in infants that do not fail CPAP;
- Selected complications of treatment will be evaluated as sentinel outcomes. These, include:
    - Damage to the nasal septum;
    - Damage to the nares;
    - Pneumothorax as diagnosed by X-ray;
    - Intra-ventricular haemorrhage (IVH), intra-cranial haemorrhage (ICH), or periventricular leukomalacia (PVL) as diagnosed by cranial ultrasound scan;
    - $FiO_2 \geq 60\%$ to maintain SpO_2 at 90-95% for one hour or more, during CPAP treatment;
    - Intubation and mechanical ventilation;
    - For infants born at 28^{+0} to 33^{+6} weeks' gestation, oxygen dependent at 36 weeks' gestation; and
    - Death prior to hospital discharge.
- A Serious adverse Event (SAEs) is any untoward medial occurrence that:
    - Results in death;
    - Is life-threatening;
    NOTE: the term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
    - Requires inpatient hospitalisation or prolongation of existing hospitalisation;
    - Results in persistent or significant disability/incapacity, or
    - Is a congenital anomaly/birth defect

4. **Procedures**:

4.1. Recruitment

Inborn infants: If preterm delivery is imminent, obstetric staff and/or their pediatric counterparts will inform parents that their baby may be eligible for the study, and will provide an information sheet pre-approved by the Ramaiah Medical College and Hospitals Ethics Committee, to give them additional time to consider whether they wish to consent. Pre-consent can be provided at this time, with randomisation to follow only if the infant meets all the inclusion criteria and none of the exclusion criteria. If pre-consent has not been sought, once a baby is born and deemed to meet all inclusion criteria, and does not meet any exclusion criterion, trained pediatric staff will approach the parents to seek informed consent.

Outborn infants admitted to Ramaiah <6 hours of age: The parents of outborn infants likely to be eligible can be approached by the Ramaiah transfer team to seek pre-consent at the referring hospital, with randomisation to follow only if the infant meets all inclusion criteria and none of the exclusion criteria. If pre-consent has not been gained and a parent is available at the time an infant meets all inclusion criteria, and none of the exclusion criteria, trained pediatric staff will approach the parent(s) to seek informed consent.

Information sheets and consent forms: An information sheet and consent forms approved by the Ramaiah Medical College and Hospitals Ethics Committee will be used during the recruitment process.

4.2. Randomisation

Block randomisation with variable block sizes will be used within each of two gestational age strata: 28^{+0}-33^{+6} weeks' gestation and 34^{+0}-36^{+6} weeks' gestation. These gestational age strata are chosen to reduce the possibility of a chance imbalance in gestational ages between the intervention and controls groups, post-randomisation, as the severity of RDS is inversely related to gestation. Infants of multiple births, of which more than one infant are eligible, will be randomised individually.

The order of the block sizes (4, 6, or 8) will be randomly selected and the assignment of will be random within each block, until the selection is forced. Random numbers will be generated by SAS 9.4 using randomly selected seed numbers; the seed will be selected by opening a large book and choosing left or right page by coin toss (heads=right).

Ramaiah hospitals will be provided with consecutively numbered, sealed opaque randomisation envelopes containing the assigned treatments: the two gestational strata will be differentiated using different colours. The envelope will be opened after written consent has been obtained and the infant has become eligible for the trial, and the assigned treatment will be immediately applied to the infant.

The randomisation procedure is as follows:

a) Ensure that one machine of each type (FP/Dolphin) is available for use within 10 minutes;
b) Confirm that the infant meets ALL inclusion criteria;
c) Confirm that infant does NOT meet ANY exclusion criterion; and
d) Confirm that inform consent has been received.

If all of the steps are confirmed, the infant's gestational group is identified, to determine the correct stratum, and the next randomisation envelope for that infant will be opened.

4.3. Blinding

Blinding of intervention is not possible, as the machines are visibly different. Some blinding of outcomes assessment will be performed – see item 4.5 Measurement of Outcomes.

4.4. Data collection

Infants meeting all of the inclusion criteria will have *de-identified* information collected on selected characteristics of mother, delivery and infant. This information will allow a comparison of randomised and non-randomised infants to determine the impact on generalizability of exclusions, infants where consent was not sought for some reason, and infants where consent was refused. Infants that are randomised will also have their randomisation number recorded on the form, allowing linkage to data collected in the study. Annex A lists the variables on which data will be collected on infants meeting all inclusion criteria.

Infants that are randomised will have additional detailed information collected on the course of treatment, and on all key primary and secondary outcomes. Annex B lists the variables on which data will be collected on randomised infants.

Information from the data collections forms will be entered into a password protected online database operated by the Australian Pediatric Trials Network ('WebSpirit') which will be accessed through the Ramaiah Hospital computer network, accessible to study administrators; the database includes an FDA-compliant audit mechanism which tracks all data queries and modifications after initial entry. The database will not contain any names or addresses, only Study ID numbers and Medical Record Numbers (MRNs). A listing of Study ID numbers will be linked to names, addresses and contact numbers in paper records kept in a locked filing cabinet in the Medical Records Department of Ramaiah Medical College, until results are published.

4.5. Measurement of outcomes

As blinding to exposure is not possible, it is important that steps are taken to prevent differential measurement error. Thus, the following steps will be taken to ensure consistency of measurement in the two treatment arms:

Primary outcome:
FiO_2 is measured on the CPAP machines themselves, which creates a possibility of differential error. The oxygen readings for the study will be algorithmically or arithmetically calibrated prior to analysis, based on measurement of FiO_2 as the gas exits the patient interface, to identify if there are any systematic differences in the reported FiO_2 being provided and the actual FiO_2 delivered to the patient interface; this will be done prior to study commencement and at the end of the first, third, fifth and seventh months after commencement. The AAI model PSR-11-917-MH oxygen analyser will measure the FiO_2 delivered against that reported by each CPAP machine across the full range of FiO_2 (21%, 25%, 30%, 35%, and every 10% from 40%-99%).

Secondary outcomes:
- SpO_2: SpO_2 will be measured using the same stand-alone pulse oximeters in both the intervention and control arms (i.e., ignoring the built-in pulse oximeter on the new CPAP to prevent differential measurement error) – both groups will be monitored using the Mindray multichannel monitor (MEC 3000), placed on the right hand/arm (i.e., pre-ductal) in line with a standardised SpO_2 measurement protocol developed for the study, which will apply to both treatment groups;
- Respiratory rate: A standard measurement protocol will be developed and introduced which requires measurement of respiratory rate over 30 seconds at 0, 6, 24, 48 and 72 hours, doubling this number to achieve a rate per minute. The protocol will outline the conditions under which measurement is to take place, and the extent to which measurement can be deferred if an infant has a temporarily elevated respiratory rate due, for example, to crying;
- Arterial blood gases: A standard measurement protocol will be introduced which governs the process for taking arterial blood samples at 0, 6, 24, 48 and 72 hours. If blood samples

are not required for clinical management, they will be ceased, so not all readings will be performed for all babies.

- Damage to septum: A standard measurement protocol will be introduced which governs the process for diagnosing damaged septum;
- Damage to nares: A standard measurement protocol will be introduced which governs the process for diagnosing damaged nares;
- Pneumothorax: The treating clinician will order and interpret the X-ray for clinical purposes, but the X-rays will be provided to the radiologist for independent verification, blinded to treatment arm;
- IVH/ICH/PVL: The consultant radiologist will undertake the scans for IVH/ICH/PVL, but it is not possible to blind to study allocation.
- $FiO_2 \geq 60\%$: This is made objective by having the same saturation targeting protocol for both treatment groups (90-95% by SpO_2), and by requiring that the oxygen requirement is maintained for one hour or more;
- Intubation & ventilation: This may be subjective and will therefore be interpreted alongside the objective indicator of a high oxygen requirement ($\geq 60\%$ for ≥ 1 hour);
- Surfactant: This may be subjective and will therefore be interpreted alongside the objective indicator of a high oxygen requirement and chest X-Ray result ($FiO2 > 40\%$ to achieve 90-95% SpO_2, with chest X-Ray suggestive of RDS); and
- Death prior to hospital discharge: This is an objective indicator unless infants are routinely discharged home moribund, which occurs in some low resource settings (to avoid mortuary costs), but which is not practised at Ramaiah Medical College.

4.6. *Safety and significant adverse events*

A subset of the sentinel events being evaluated as secondary outcomes will also be monitored as adverse events during the course of the study. These, include:

- Damage to the nasal septum;
- Damage to the nares;
- Pneumothorax as diagnosed by X-Ray;
- IVH/ICH/PVL as diagnosed by cranial ultrasound;
- Intubation and mechanical ventilation; and
- Death prior to hospital discharge.

Adverse events will be referred to the Chief Investigator as they occur to allow ongoing monitoring, and corrective action if required. A Data Safety Monitoring Board (DSMB) is not proposed, as the small number of randomised infants in the trial (40 per arm) mean that the anticipated number of adverse events are expected to be too small for meaningful analysis. If an unusual group of events is noted, the Chief Investigator can choose to suspend randomisation and convene a DSMB.

4.7. *Trial funding*

Funding is being provided through Thrive Networks, which is in receipt of funding from the Wellcome Trust under the R&D for Affordable Healthcare in India scheme. The purpose of this project, entitled "Continuous Positive Airway Pressure (CPAP) machine to promote rational oxygen use for neonates and to reduce the incidence of retinopathy of prematurity (ROP)" is to develop and commercialise a low-cost CPAP machine for the Indian marketplace.

5. **Sample size and statistical analysis:**

5.1. ***Sample size calculation***

Sample size calculations are based on the primary outcomes. All the outcomes are selected to be continuously distributed. A sample size of 40 infants per group has been selected as something that is achievable at the anticipated recruitment rate at Ramaiah Hospital in the time available (10 months, including 8 months for recruitment at 10 randomised infants/month). The trial will cease when 40 infants have been randomised to each arm (i.e., at this point the other arm must have 40 or more randomised infants). With this sample size, a difference of 0.63 standard deviations is detectable, with 80% power (1-β) and a 5% false-positive rate (α). We lack data, within the study population, on the anticipated outcomes in the primary and secondary endpoints.

Feasibility: An assessment of eligible infants meeting the inclusion criteria (and none of the exclusion criteria) in February and March 2016 (two complete months) identified:
- 24 inborn neonates eligible for randomisation (i.e., 12/month); and
- 11 outborn neonates admitted to Ramaiah <6 hours of age (i.e., 5.5 /month).

This give a total of 17.5 eligible infants per month. Previous experience at Ramaiah is reported to be a 70% recruitment rate which, if maintained in the current study, would yield an average of 12.2 randomised infants/month. This is above the required randomisation rate of 10 infants per month, and suggests that the project would be feasible with a 60% recruitment rate.

5.2. ***Statistical analysis***

Primary and selected secondary outcomes - descriptive: The raw values of the primary outcome (FiO_2) and five secondary outcomes (SpO_2, respiratory rate, pH, PaO_2, $PaCO_2$) will be graphed to allow visual comparison of differences at baseline and over time.

Primary outcome: With longitudinal measurement, the interpretation of later results can be impacted by differential losses before 72 hours (death or intubation and ventilation). Analysis will therefore commence with a Kaplan-Meier curve comparing 'loss' (death or intubation and ventilation), and an associated Cox regression model to compare the rate of loss in the two treatment arms. The results of this survival analysis will provide the context within which the longitudinal results will be interpreted. If there are differential losses over time, the least affected time point will be 6 hours after treatment commencement, and this time point will be promoted to being the primary outcome. If losses over time are not differential, the planned analysis is described below.

The preferred omnibus analysis is a longitudinal mixed effects model (using PROC MIXED in SAS 9.4), controlling for baseline through a random 'intercept', in line with international recommendations for controls on baseline.[30] Individual analyses at each time point (6, 12, 24, 48, and 72 hours) will be by multiple regression, again adjusting for baseline as a covariate.[30] If multiple regression model requirements for normality and homoscedasticity are not met, analysis will be by t-test which is known to be robust to violations of the normality assumption, and will be based on the change in variable from baseline value, providing some control for different baselines, but without the additional control offered by multivariate analysis.

Where performed, multivariate analysis will control for stratification; if univariate analysis is used, separate stratum-specific sub-analysis will be undertaken, and a stratified t-test will be performed. Additional covariates will be adjusted for in multivariate analysis, if the baseline comparison shows substantial group difference in significant prognostic factors (e.g., onset of labour is associated with the stimulation of surfactant production, so analysis will control for mode of delivery if there is a clinically relevant mal-distribution).

Secondary outcomes: Five of the secondary outcomes (SpO_2, respiratory rate, pH, PaO_2, $PaCO_2$) will be analysed using the same procedures as for the primary outcome. It is anticipated that the three arterial blood gases (pH, PaO_2, $PaCO_2$) will not be performed on all infants, particularly infants that recover rapidly; if so, this analysis will be restricted to change from baseline at the 6-hour reading.

Duration of CPAP (hours), for those not failing CPAP treatment, is the only continuous secondary outcome this is expected to be non-normally distributed and will therefore be assessed using Wilcoxon's rank sum test, with stratum-specific contributions aggregated using van Elteren's extension to the Wilcoxon test.[31]

The remaining secondary outcomes are dichotomous and will be tabulated and compared using stratum-specific relative risks (RRs); the homogeneity of stratum-specific RRs will be assessed using Cochran's Q and the I^2 tests[32].

Software: All analysis will be conducted in SAS/STAT® 9.4, except for the calculation of stratum-specific and pooled relative risks, which will be performed in RevMan 5.3.[33]

Secondary outcomes: Five of the secondary outcomes (SpO_2, respiratory rate, pH, PaO_2, $PaCO_2$)

6. <u>**Clinical protocol:**</u>

6.1. Interventions

This study compares routine CPAP care on existing machines with CPAP care on a new machine that uses a re-usable humidifier and tube set.

Routine CPAP care will be on a Fisher & Paykel [FP] CPAP machine which includes separate oxygen and medical air intakes, a FP blender, and a disposable FP humidification chamber and tube set including a heater wire (Fisher & Paykel Healthcare Ltd, Auckland, New Zealand; hereafter referred to as FP CPAP). The new machine (hereafter referred to as the 'Dolphin CPAP') includes an oxygen intake, an on-board air compressor, built in Massimo pulse oximeter (not used in this study – see para 4.5 above), and an autoclavable humidifier and tube set.

6.2. Treatment protocol features that are common to both arms

The following systems will be common to both groups regardless of treatment allocation:

- Baby interface: An identical FP infant interface will be used for both groups of babies; this may require the creation of a special adaptor to permit use of the FP interface with the Dolphin CPAP tube set if the FP interfaces for non-FP connectors is not identical to the FP interface for FP tube sets;
- Pulse oximetry: The FP CPAP does not include built-in pulse oximetry, while the Dolphin CPAP does. To ensure consistency in measurement of pulse oximetry, Ramaiah Medical College will use a single pulse oximeter (built into the Mindray MEC 3000), for monitoring SpO_2 on all infants regardless of the treatment allocation. This ensures that any measurement error in SpO_2 will be non-differential.

A standard clinical protocol will be prepared for the study, based on existing clinical practice at Ramaiah Medical College, which will apply equally to both treatment groups. The clinical protocol will specify:

1. Standard prong sizes to be used, by infant weight;
2. The SpO_2 range to be targeted;
3. The timing of obligatory outcome measurements (baseline, 6, 12, 24, 48 and 72 hours) and how they should be conducted, and how measurement complications should be managed if they arise (e.g., how long to delay with scheduled measurement of respiratory rate if infant is crying; how to address missed measurement) – this includes:
   a. FiO_2;
   b. SpO_2;
   c. Respiratory rate; and
   d. Arterial blood gasses, including pH, PaO_2, and $PaCO_2$.
4. Procedures governing the diagnosis and treatment of all adverse events, specifically:
   a. Identification and confirmation of damage to the septum and nares;
   b. Determining the need for screening for pneumothorax, and the process for blinded verification; and
   c. Determining the need for cranial ultrasound, and the process for (unblended) diagnosis of IVH or ICH or PVL.
5. A clinical algorithm for managing all aspects of CPAP provision, including:
   a. FiO_2 and PEEP, including starting points and rules governing stepping up and stepping down of these (including order, and size of increment);
   b. Transfer to intubation and ventilation; and/or
   c. Weaning from CPAP; and/or
   d. Rules covering re-commencement of CPAP.

6.3. Treatment protocol differences between the two arms

The FP and Dolphin CPAP machines have the following features in common:

- Simple dial setting of desired FiO_2
- Simple dial setting of desired blended gas flow rate; and
- Simple connector to the end of the expiratory tube which submerges into the PEEP bottle, to create distending pressure which varies with the depth of insertion but, as discussed immediately below, the FP and Dolphin machines are operate differently in important ways.

While these features are designed to achieve the same ends, there are two major differences that need to be checked and corrected for:

1. PEEP: The FP CPAP machine is designed to be used with a standard FP tube set and interface; as a result, the setting at the PEEP bottle is designed to give the desired PEEP at the end of the interface on the assumption that the standard FP circuit is used. If the 'CPAP probe' above the lid of the PEEP bottle is set to a number (the available range is 3-10), this achieves a PEEP approximately equivalent to that number at the end of the patient interface, at a flow rate of 4 L/min. With higher flow rates, the PEEP increases by approximately 0.11-0.14 cm H_2O per additional 1 L/min (i.e., at a flow of rate of 9 L/min, the PEEP at the end of the interface will be approximately 0.6 cm H2O higher than at 4 L/min). If non-FP interfaces are used, the PEEP at the end of the interface may be different, to that shown on the FP circuit.

   The Dolphin CPAP, by contrast, is designed to be used with numerous interfaces, and thus the PEEP setting is set at the actual depth of insertion of the expiratory probe in water. Setting the depth to 6cm H_2O, for example, does not indicate that 6 cm H_2O is being achieved at the end of the interface.

   The Ramaiah CPAP treatment protocols are based on the FP settings, so laboratory assessment will be made of the PEEP settings required on the Dolphin CPAP to achieve the same PEEP at the end of the interface. After adjustment, the protocols will be identical in relation to PEEP delivered at the end of the interface.

2. FiO_2: As FiO_2 is a primary outcome, the FiO_2 of all machines will be independently verified using the AAI model PSR-11-917-MH oxygen analyser across the full range of deliverable FiO_2 – see relevant dot point of Section 4.5. If there are calibration differences, these will be taken into account in analysis of this outcome.

   As FiO_2 is also key to determining the need for other crucial interventions, differences (if found) will also be taken into account in setting Dolphin-specific treatment protocols, most importantly: oxygen requirement for surfactant (> 40% FiO_2 to maintain SpO_2 of 90-95% for ≥ 30 minutes); and for intubation and mechanical ventilation (FiO_2 ≥ 60% to maintain SpO_2 of 90-95% for ≥ 1 hour). As the FP CPAP is the basis of current Ramaiah protocols, we will determine the FiO_2 at the patient interface when the FP CPAP reads 40% and 60%, and ensure that the protocol for the Dolphin CPAP uses thresholds that are delivering the same FiO_2 as measured at the patient interface.

Other differences to the FP and Dolphin CPAP machines will not be calibrated, as they are intrinsic to the machines and thus relate directly to the treatment comparison.

Annex A: Data to be collected on all eligible infants

A limited number of pieces of information will be collected on all eligible infants, regardless of whether they are ultimately randomised.

This information will be used to explore the limits of generalizability of the study results, by showing how babies who were excluded, who were missed for some reason or whose guardians declined to participate in the trial, differ from the babies that were ultimately randomised. The form will indicate whether babies were:

- Excluded (no identifier);
- Missed (eligible, but consent not sought for some documented reason – no identifier);
- Declined consent (no identifier); or
- Randomised (these babies will have a unique identifier, enabling linkage to other infant information);

The information to be collected includes:

1. Specification of all three inclusion criteria. If answer to the questions is 'Yes' the form must be completed.
2. Babies not randomised, by reason (specifically, as indicated above: i) meets one or more exclusion criterion; ii) failed to seek consent; iii) consent sought but declined)
3. IF consented & randomised, record randomisation number to permit linkage; if not randomised create dummy ID number for administrative purposes in the PTNA system.
4. Maternal information:
   a. Age (completed years)
   b. Previous preterm birth (Y/N)
   c. Previous perinatal death (Y/N)
   d. Presenting antenatal problem (Unknown/PPROM/PTL/PIH/APH/IUGR/Fetal distress/Other/None/NS; If 'Other', describe)
   e. Onset of labour (Spontaneous/Induced/No labour)
   f. Hours from rupture of membranes to birth
   g. Anaesthetic (None / Spinal or epidural / General / NS)
   h. Chorioamnionitis as reason for delivery (Y/N)
   i. Corticosteroids (Unknown/None/<24 hrs/Complete/> 7 days)
   j. Delivery (NVD/Forceps/Vacuum/Vaginal Breech (forceps)/Vaginal Breech (no forceps) / CS/NS)
   k. Meconium (Y/N)
   l. Plurality (Singleton/Multiple/NS; if 'multiple', number and birth order of this infant)
5. Newborn information:
   a. Month and year of birth
   b. Gestation (weeks _____; days _____)
   c. Birthweight (g)
   d. Sex (M/F/Ambiguous/NS)
   e. Apgar1
   f. Apgar5
   g. Resuscitation [highest] (None/Minimal/CPAP/Bag & Mask or T-piece/Intubation/ECM/ NS)
   h. Indication for respiratory support (Clinical signs/Respiratory acidosis [gas]/O2 requirement/ Apnoea/Other/NS; If 'Other' describe)

---- ENDS ----

Annex B: Data which will be collected on all randomised infants

Detailed information will be collected on a set of related forms for all randomised infants. The forms to be used includes:

1. Listing of randomised infants (one register-style form)
   a. Randomisation number [Primary ID]
   b. Infant's MRN [Secondary ID]
   c. Infant's name
   d. Mother's MRN
   e. Mother's name
   f. Parent phone number
   g. Parent address
2. Adverse Event form (one per discrete AE)
   a. Randomisation number [Primary ID]
   b. Infant's MRN [Secondary ID]
   c. Type of AE (Nares/Septum/Pneumothorax/IVH/ICH/PVL/ $FiO_2 \geq 60\%$/Intubated & MV/Death/Other; If 'Other' describe; if IVH, give grading; must report separately even if the two are related, such as [$FiO_2 \geq 60\%$] AND [intubated & MV] AND [Death])
   d. Date and time AE diagnosed
   e. Severity (Mild / Moderate / Severe / Life-Threatening / Death)
   f. Outcome (Resolved – No sequelae / Resolved - Sequelae / Not resolved / Death)
   g. Link to CPAP therapy (Definite/Likely/Possible/Unlikely/Unrelated/Unclear)
   h. Respiratory therapy at time of event (None/Dolphin CPAP/FP CPAP/Passive/MV/Other/Unknown; if other, describe)
   i. Text field for details, including treatment
3. General form (one per baby)
   a. Dates and Times
      - Birth
      - Admission
      - Randomisation (allowing calculation of hours at randomisation, by subtracting date and time of birth)
      - Commencement of CPAP (allowing calculation of hours at age of CPAP commencement, by subtracting date and time of birth)
   b. Selected information prior to treatment commencement
      - Weight at admission (g)
      - Method of respiratory support prior to randomisation, with details (the usual Ramaiah practice is to provide hood oxygen with a flow rate of 5 L/min)
      - Any unexpected delay between eligibility and randomisation? (Y/N; if Yes, describe)
      - Any unexpected delay between randomisation and treatment commencement? (Y/N; if Yes, describe)
   c. Setting at treatment commencement
      - Prong size
      - Flow rate
      - PEEP
   d. Primary and secondary endpoints, as measured at baseline (just prior to CPAP commencement) and 6, 12, 24, 48 and 72 hours:
      - FiO_2;
      - SpO_2;

- Respiratory rate;
- Arterial blood gases: pH, PaO_2, and $PaCO_2$; and
- Date and times of each reading.

e. Adverse events:
- Total number of discrete events (one AE form per discrete event);

f. Respiratory treatment details
- Surfactant? (Y/N; if Yes, number of doses, and date and time of first dose; FiO2 at time surfactant ordered, and chest X-Ray diagnosis prior to surfactant)
- Number of apnoeic episodes during stay (0/1-4/5-9/≥ 10), as per existing Ramaiah protocol defining an apnoeic episode
- Any treatment for apnoea (No / Aminophylline / Theophylline / Caffeine / Other; if 'Other', describe);
- Date and time CPAP first ceased for 1 or more hours
- Any further CPAP provided and, if so, duration
- Hours of passive oxygen (low flow cannulae, mask or head box/hood)
- Hours of mechanical ventilation

g. Selected other treatments and diagnoses
- Treated with antibiotics (Y/N; if Yes, which antibiotics)
- Any positive blood cultures? (Y/N; If Yes, identify sample site and organism)
- Any congenital anomalies (Y/N; if Yes, describe)

h. Feeding
- Number of days of IV fluids
- Date on which infant first achieved 24 hours without IV fluids or naso- or oro-gastric feeds
- Full breastfeeding at hospital discharge (N/Y)
- Last weight prior to discharge (g), and date of this weight

i. Discharge
- First NICU discharge
- Duration of all other NICU admissions before hospital discharge
- Hospital discharge
- Final diagnosis of the early respiratory distress (RDS/TTN/Congenital pneumonia /Meconium aspiration/pneumothorax or air leak syndrome/Other/NS)
- Outcome at hospital discharge (Home/Transfer/Death/Abscond/Other)
    - If infant transferred, reason for transfer, place transferred to, and infant condition at time (Well / Uncertain / Moribund)
    - If Abscond, infant condition at time (Well / Uncertain / Moribund)
    - If Other, describe

---- ENDS ----

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