TITLE: Pragmatic **E**valuation of **T**herapies to **E**nhance **R**espiratory **M**anagement in Preterm Infants in **Africa**

Version 2

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Short title of the Research project (Not more than 5 words)

PRETERM AFRICA STUDY

Full title of the Research project

Pragmatic **E**valuation of **T**herapies to **E**nhance **R**espiratory **M**anagement in Preterm Infants in **Africa**

Key words

Preterm, CPAP, Africa

Duration of study (in months)

36 months

Proposed start date of the study

September 2024

Proposed completion date
August 2027

Funding for the study

Date when funding starts

01 July 2024

Date when funding ends

31st August 2027

Study location –

Mama Lucy Kibaki Hospital and Coast General Teaching and Referral Hospital

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Abbreviations

AOP	Apnea of prematurity
BPD	Bronchopulmonary dysplasia
CPAP	Continuous positive airway pressure
DSMB	Data safety monitoring board
DSMP	Data safety monitoring plan
HIC	High-income country
ICC	Intraclass correlation
IRB	Institutional review board
ITT	Intention to treat
IU	Indiana University
IVH	Intraventricular hemorrhage
LISA	Less invasive surfactant administration
LMIC	Low- and middle-income country
PI	Principal investigator
REDCap	Research electronic data capture
RDS	Respiratory distress syndrome
ROP	Retinopathy of prematurity
SAE	Severe adverse event
SSA	Sub Saharan Africa

1.0 Background & Rationale

Substantial progress in child survival has been achieved in the last two decades as childhood global mortality declined by 59% – from 93 to 38 deaths per 1000 live births – between 1990 and 2021.[1] While laudable, to meet the 2030 Sustainable Development Goal of ≤12 deaths per 1000 live births,[2] directed efforts at the period of life, region, and leading causes of childhood deaths are critical.[3] Of the 2.4 million annual childhood deaths, 47% occur in the neonatal period,[4] and sub-Saharan Africa (SSA) carries the highest global burden of 27 deaths per 1000 live births – accounting for 43% of all global newborn deaths.[5] The complications of prematurity and infections, including pneumonia, are the main drivers of neonatal mortality.[6,7] Globally, one million preterm babies die yearly, and survivors face significant lifelong disabilities and healthcare burdens.[6,8] Over 80% of the global preterm births and deaths burden occurs in low- and middle-income countries (LMICs).[9] The leading cause of preterm death in LMICs is respiratory distress syndrome (RDS) – accounting for 45% of all preterm deaths,[10] a figure dramatically different from the 2% death rate from RDS in high-income countries (HIC).[11]

The World Health Organization's Every Newborn Action Plan (ENAP) identifies the management of the complications of prematurity as a high-yield area for improvement critical to reducing neonatal deaths.[12,13] Specifically, the ENAP coverage target is for 80% of districts to access crucial treatment modalities for sick and small newborns, including continuous positive airway pressure (CPAP) for treating respiratory failure. Furthermore, WHO recommends using caffeine citrate for treating apnea of prematurity (AOP), and surfactant for treating respiratory distress syndrome (RDS).[12,13] Evidence from high-income countries shows that these therapies effectively reduce preterm mortality. However, ***knowledge gaps*** exist in translating these newborn respiratory therapies from high- to low-resource countries. Furthermore, there are no high-quality studies from SSA on the impact of these interventions, individually or in combination, on the survival of small and sick newborns.

Justification:

A) Respiratory failure in small and sick newborns involves the use of invasive (e.g., ventilator) and non-invasive (e.g., CPAP) positive pressure devices.[14] The use of invasive ventilators in SSA is limited due to the cost of procuring, maintaining, and using the devices.[14,15] Consequently, CPAP is often the highest level of support. Starkly different from high-income countries, in LMICs, CPAP failure invariably means death. The most commonly available CPAP devices in LMICs are the locally customized CPAP, which are untested, do not provide optimal pressure due to their interface, and do not blend oxygen, thus increasing the risk of oxygen toxicity and the development of retinopathy of prematurity – a leading cause of blindness.[16,17] Standardized low-cost CPAP devices with safety and potential effectiveness advantages over the locally customized CPAP now exist.[18,19] However, it is unknown if implementing standardized low-cost CPAP into

clinical practice can improve clinical indicators and outcomes compared to flow cannula or the locally customized device.[20] Studies from moderately resourced settings show promise.[20,21]

B) Caffeine citrate and aminophylline are the mainstay pharmacologic treatments for AOP. However, caffeine possesses proven therapeutic (short, intermediate, and long), safety, and dosing advantages, making it the preferred treatment.[22–24] The benefits of caffeine have not been tested in settings where CPAP is the primary and highest level of respiratory support.[25]

C) The ventilator-avoidant surfactant replacement technique involving administering surfactant while on CPAP using a thin catheter is now the standard of care in most high-income countries. There is strong evidence from high-income countries that this Less Invasive Surfactant Administration (LISA) technique significantly reduces CPAP failure, ventilator use, and RDS- and all-cause preterm mortality. These studies were conducted in well-resourced neonatal intensive care units with rescue ventilators.[26] It is, however, unknown what the benefit of LISA is in LMICs where there are no or a very limited number of rescue ventilators.

Research gaps: The clinical impact of a standardized low-cost CPAP, LISA, and caffeine is unknown in a low-resource setting. ***The long-term goal*** is to improve preterm survival in LMICs by normalizing safe and effective interventions for treating preterm infants with respiratory distress. The ***specific objectives*** of this proposal are 1) to determine the effect of implementing a standardized low-cost CPAP, caffeine, and LISA on preterm survival in SSA and 2) to characterize the process of implementing Vayu bCPAP, caffeine, and LISA in clinical settings of SSA. The ***central hypothesis*** is that when combined and successfully implemented, a standardized low-cost CPAP with Caffeine and LISA will improve preterm survival. The specific aims of this proposal are:

2.0 Study Aims: In newborns with birth weight between 750 to 2000 grams or between ≥24 and 35 weeks gestation with respiratory distress.

2.1 **Primary aims:**

2.1.1 Determine the effect of Vayu bCPAP + Caffeine + LISA **vs.** Vayu bCPAP + Caffeine on hospital survival.

2.1.1.1 Sub aim 1: Determine the 72-hour of life survival

2.2 **Secondary aims**: The incidence of major neonatal complications, including.

2.2.1 Neonatal sepsis: Incidence of a positive blood culture during hospitalization.

2.2.2 Incidence and highest grade of intraventricular hemorrhage (IVH): Assessed by ultrasound scan between DOL 3 and 7.

2.2.3 Retinopathy of prematurity (ROP): Assessed as the worst stage by an ophthalmologist in patients <1500 grams at birth.

2.2.4 Bronchopulmonary dysplasia (BPD): Defined as continued use of supplemental oxygen at 28 days of life.

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2.2.5 Surgical Necrotizing Enterocolitis (NEC stage IV): Defined as the need for any surgical intervention for a patient with clinical signs of necrotizing enterocolitis.

2.2.6 Determine the incidence of clinically diagnosed pneumothorax: Diagnosed with a positive transillumination sign.

2.2.7 Determine the effect of Vayu bCPAP + Caffeine + LISA **vs.** current standard respiratory support on hospital survival.

2.3 **Tertiary aims**: Evaluate the implementation of the intervention bundle using the RE-AIM Framework.

2.3.1.1 **R**each: Measured by evaluating the proportion of eligible subjects successfully treated with the intervention.

2.3.1.2 **A**doption: Measured by providers' perception of the intervention (s) and implementation strategy.

2.3.1.3 **I**mplementation fidelity: Measured by the degree of adherence to the implementation strategy.

2.3.2 Determine the cost-effectiveness of the individual and bundled intervention.

2.4 Exploratory aims: During the standardization phase, we will explore the impact of Vayu bCPAP and caffeine citrate on

2.4.1 The difference in Silverman Anderson Score.

2.4.2 The difference in the 7-day AOP incidence.

2.4.3 The difference in the hospital Survival.

3.0 Eligibility Criteria:

There are different inclusion and exclusion criteria for each component of the intervention bundle.

3.1 <u>Criteria for receiving the Vayu bCPAP.</u>

3.1.1 **Inclusion Criteria**

- Birth weight between 750 and 2000 grams or gestational age between 24- and 35 weeks.
- Silverman Anderson Score ≥3.
- Parents provided informed consent.

3.1.2 **Exclusion criteria**

- Major congenital or genetic anomalies
- Active pulmonary hemorrhage

- Major craniofacial anomalies that preclude the successful use of CPAP

3.2 Criteria for receiving Caffeine. Subjects will also receive the Vayu bCPAP per indications in section 3.1.

3.2.1 **Inclusion criteria**

- Birth weight between 750 and 1250 grams or gestational age <32 weeks (prophylactic treatment).
- Birth weight between 1251 to 2000 or gestational age between 32 to 35 weeks without an identifiable source/cause of apnea. (Symptomatic treatment).
- Admitted to a study site within 24 hours of life.
- Parents provided informed consent.

3.2.2 **Exclusion criteria**

- Cardiac arrhythmia
- Bilirubin encephalopathy
- Confirmed seizures.

3.3 Criteria for receiving surfactant via the LISA procedure. Subjects will also receive the Vayu bCPAP and caffeine per indications in sections 3.1 and 3.2, respectively.

3.3.1 **Inclusion Criteria**

- Birth weight between 750 and 2000 grams or gestational age between 24- and 35 weeks.
- Silverman Anderson Score ≥5 before or after CPAP treatment.
- Admitted to a study site within 24 hours of life.
- Parents provided informed consent.

3.3.2 **Exclusion Criteria**

- Major congenital or genetic anomalies.
- Active pulmonary hemorrhage.
- Major craniofacial anomalies that preclude the successful use of CPAP.

4.0 Study Design

The study will utilize an effectiveness-implementation hybrid type I study design with two phases. **See Figure 1**. In a hybrid type I study, the effectiveness of the intervention is tested, and the implementation process is explored.

Phase 1 is the standardization (normalization) of Vayu bCPAP and caffeine**.**
Phase 2 is the implementation of LISA.

- Design for Phase 1:
  - Prospective cohort design where we will standardize/normalize using the Vayu bCPAP and Caffeine at each study site. During this phase, we will also standardize the study monitoring and data collection procedures. Additionally, we will confirm that all the 2 Kenyan sites have an Ophthalmologist who is trained to assess and treat ROP, so during standardization we will access the equipment that they need from Indiana University.
- Design for Phase 2:
  - A stepped-wedge cluster randomized controlled trial to implement the LISA procedure for surfactant administration.

Figure 1: The study design.

	Phase 1		**Phase 2**								
Sites	**Standardization phase**		**Stepped Wedge Cluster Trials**								
	Study procedures	*Study Intervention(s)*	*Step 1*	*Step 2*	*Step 3*	*Step 4*	*Step 5*	*Step 6*	*Step 7*	*Step 8*	*Step 9*
1											
2											
5											
4											
5											
6											
7											
8											

Table Legend:

	Implement a combination of data collection, vital signs monitoring, blood culture, head ultrasounds, and eye screening.
	Implementation of study intervention that is not currently available at each study site.
	Vayu bCPAP + Caffeine control period of the stepped-wedge phase.
	Vayu bCPAP + Caffeine + LISA.

Study sites:

The study will be conducted in eight hospitals in the Central African Republic, Ghana, Kenya, and Nigeria. Each country will contribute two sites. The study sites are the highest-level newborn units in the region. They are in metropolitan cities and are major referral centers capable of providing critical neonatal care, including neonatal resuscitation, CPAP, optimal thermoregulation, and enteral and intravenous nutritional and antibiotic therapy. The study sites are:

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1. Korle-Bu Teaching Hospital (KBTH), Accra, Ghana
2. Komfo Anokye Teaching Hospital (KATH), Ghana
3. Tamale Teaching Hospital, Ghana
4. Community Hospital Centre (CHUC), Bangui, Central African Republic.
5. Federal Teaching Hospital Ido-Ekiti (FETHI) Nigeria.
6. University of Ilorin Teaching Hospital (UITH), Nigeria
7. Mama Lucy Kibaki Hospital, Nairobi, Kenya.
8. Coast General Teaching and Referral Hospital, Kenya.

The sites cater to low-income families. Typical payment for services includes out-of-pocket payments and health insurance (private or government) that is not always available to everyone.

The role of the site PI includes the following:

- Ensure all institutional ethics and other regulatory approvals are completed and kept current.
- Recruit and manage research personnel.
- Supervise the training and retraining of all clinical staff involved in the study.
- Facilitate communication between the clinical and research team.
- Ensure the safety of study participants and maintain the confidentiality of all research-related documents, especially those that contain personalized health information.
- Communicate with and supervise data management.
- Meet with the study PI's from other sites and the co-PIs every two weeks.
- Meet with the wider PRETERM Africa study team every month.
- Conduct weekly meetings with the onsite clinical and research teams to address research or patient safety concerns, participant enrollment, and other research-related activities.

5.0 Enrollment/Randomization

5.1 **Screening and recruitment:** All admitted patients to the newborn units of the study sites will be screened for eligibility based on the study inclusion and exclusion criteria. For patients (mothers/ primary care givers) who are eligible, they will have the opportunity to read or be read the informed consent in English or Swahili and have an opportunity to ask the research assistants any questions they may have. It will be explained that participation is voluntary and can be terminated at any time without reason and without any penalty. If the potential participant has any questions, they will be answered in English or Swahili to ensure that they understand the research and their potential role in it. Consent will be

confirmed with the patient's signature or a thumbprint. In case of a thumbprint, a literate witness (other than the member of the research team obtaining consent) will be asked to sign. Finally, the member of the research team obtaining consent will sign the form and give a copy of the information sheet to the patient.

We estimate that approximately 40 minutes will be taken to consent the participant and that will be the only time required of the participant during the trials most of the data collection will happen via health records/ patient files.

Screening and recruitment will happen day and night (24 hours) to ensure that all eligible patients who need these interventions can access them in a timely manner.

5.2 Randomization scheme:

- **Phase 1**:
  - No randomization will be conducted as this will be a prospective cohort design.
- **Phase 2**:
  - Randomization will occur at the study site level and within four strata: sites with higher-than-median infant mortality and sites with lower-than-median infant mortality, crossed with sites with higher-than-median recruitment potential and sites with lower-than-median recruitment potential.

6.0 Study Procedures

These procedures follow the screening, determination of eligibility and consenting phase of the study.

6.1 **Procedure for Phase 1**:

6.1.1 **Step 1: Study policies, procedures, and monitoring implementation**: In this step, we will introduce the data collection procedure for the study. We will collect data on pregnancy, birth, resuscitation, hospital course, results from blood culture if obtained, and study outcomes using a standardized case report form. We will also implement routine cardiopulmonary monitoring and blood cultures when antibiotics are indicated. We will implement head ultrasound and ROP screening procedures for participants <1500 grams at birth or those at high risk of intracranial

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bleeding or ROP. We will collect cardiopulmonary data from standard monitoring devices during this phase.

6.1.2 **Step 2: Introduction of study interventions** in this step, we will implement the Vayu bCPAP and/or caffeine at each site, depending on what they currently use as a standard of care. Eligible consenting study participants will be placed on the Vayu bCPAP and/or treated with caffeine where indicated.

At the time of this proposal submission, the current capacity at each site as it pertains to the study interventions is as follows:

Table 1: Characterization of study sites by current routine use of study intervention component.

Site	Available bundle components that are currently being used routinely.
Community Hospital Centre (CHUC), Bangui, CAR	Caffeine
Korle-Bu Teaching Hospital (KBTH), Ghana	Vayu bCPAP and oral caffeine
Komfo Anokye Teaching Hospital (KATH), Ghana	Vayu bCPAP and oral caffeine
Tamale Teaching Hospital, Ghana	Vayu bCPAP and oral caffeine
Mama Lucy Kibaki Hospital, Nairobi, Kenya	Vayu bCPAP
Coast General Teaching and Referral Hospital, Kenya	Vayu bCPAP
Federal Teaching Hospital Ido-Ekiti (FETHI) Nigeria	None
University of Ilorin Teaching Hospital (UITH), Nigeria	None

Description of study interventions for Phase 1

For this study, the low-cost standardized CPAP we will utilize is the Vayu bubble CPAP System (Global Health Innovation, Medford, MA, USA) Vayu bCPAP.[27] **The Vayu bubble CPAP** is a low-cost CPAP device that delivers humidified, filtered, pressurized, and oxygen-enriched air to the patient. (Figure 2) The Vayu bCPAP utilizes a novel venturi oxygen blender that can adjust the fraction of inspired oxygen between 30 and 100% oxygen.[18] The Vayu bCPAP has an advantage over the locally customized CPAP or low-flow oxygen commonly available at the study sites, which cannot blend oxygen. It was specifically designed to overcome the existing challenges of low-resource settings. Its utility has been evaluated in small before and after studies, as well as in qualitative studies that evaluated perception by nurses.[20,21] While Vayu bCPAP was designed

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for LMICs, there is a continued need for high-quality trials on its effectiveness to support its dissemination.

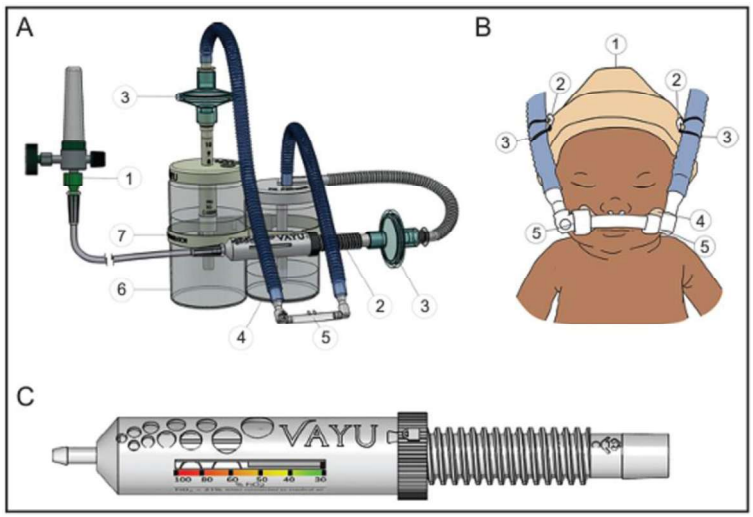

Figure 2: A: The bubble CPAP system composed of (1) an external pressurized oxygen source; (2) Venturi blender; (3) 2 bacterial and viral filters, one on the inspiratory limb and one on the expiratory limb; (4) a humidifier; (5) nasal prongs; (6) a water column with an adjustable wand to control the delivered pressure from 4 to 10 cm H2O; and (7) warmer bracket that stabilizes the system and allows it to be placed inside infant radiant warmers. B: The patient interface, composed of (1) hat; (2) 2 safety pins, (3) 2 rubber bands, (4) hook tape moustache, and (5) loop tape strips. C: The Venturi blender is the distinguishing feature of the bubble CPAP system; it delivers 30– 100% oxygen by mixing pressurized oxygen and ambient air

Caffeine citrate is a methylxanthine used to treat AOP for over 20 years. In high-income countries, CC is the mainstay treatment for AOP because it has a better side effect profile, a wider therapeutic index, a longer half-life, and does not require therapeutic drug monitoring.[23,24,28–31] Caffeine Citrate can be administered intravenously or orally. The dosing regimen for intravenous and oral caffeine is the same: 20mg/kg as a loading dose, followed by a maintenance daily dose of 5mg/kg. Unlike the other methylxanthines (aminophylline and theophylline), caffeine citrate does not require therapeutic drug monitoring.

Using the same procedure as during the pre-implementation phase, we will collect data on pregnancy, birth, resuscitation, hospital course, results from blood culture if obtained, and study outcome using a standardized case report form. We will also collect cardiopulmonary data from standard monitoring devices during this phase. We will also conduct standard screening for complications of prematurity, including head ultrasounds and eye exams for babies <1500 grams.

6.2 **Procedure for phase 2**: In addition to receiving the Vayu bCPAP and caffeine, patients will receive surfactant using the LISA procedure.

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6.2.1 **Less Invasive Surfactant Administration** (**LISA**): This involves the administration of surfactant through a thin catheter to a patient spontaneously breathing on CPAP. The procedure steps include confirming CPAP is appropriately placed, performing direct or video laryngoscopy to identify the glottic opening, and passing a thin catheter through the vocal cords into the trachea. The laryngoscope blade is then removed with the thin catheter held in place against the palate. A syringe is then attached to the thin catheter, and surfactant is slowly instilled into the lungs in micro-boluses over 1 to 3 minutes, coordinating each micro-bolus with the patient's inspiratory effort. (Figure 3)

Using the same procedure as during the pre-implementation phase, we will collect data on pregnancy, birth, resuscitation, hospital course, results from blood culture if obtained, and study

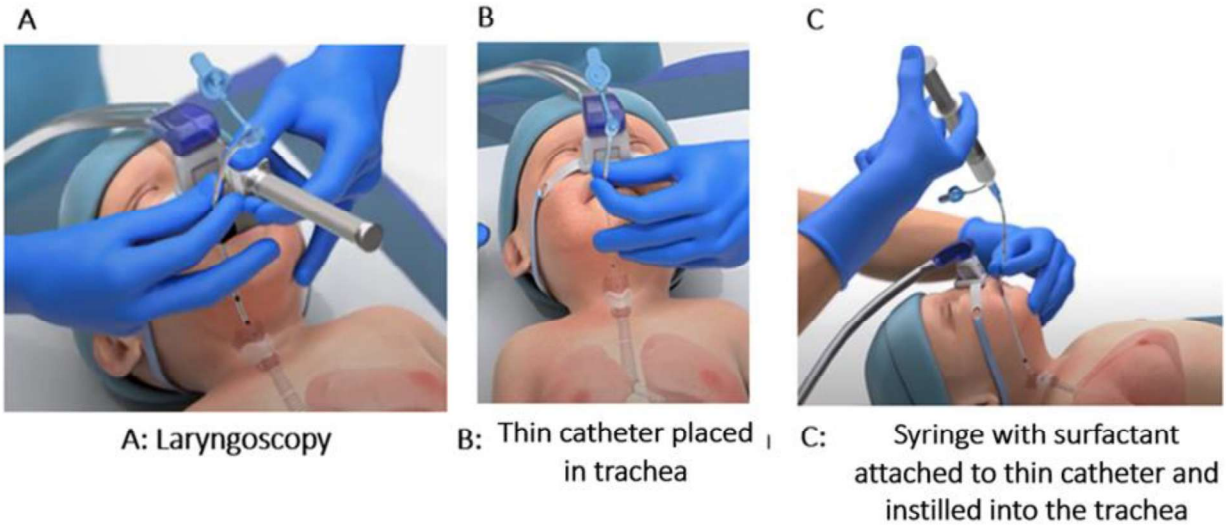

Figure 3: Less Invasive Surfactant Administration (LISA)

outcomes using a standardized case report form. Additionally, we will collect specific data points on the LISA procedure to document adherence to the implementation strategy and document adverse events**.** We will also collect cardiopulmonary data from standard monitoring devices during this phase. We will also conduct standard screening for complications of prematurity, including head ultrasounds and eye exams for babies <1500 grams.

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Stopping or escalation rules for Vayu bCPAP and caffeine are outlined below.

For Vayu CPAP:

CPAP is the highest level of respiratory support available in most of the study sites. Traditionally, if a patient fails CPAP, they get intubated and placed on a mechanical ventilator. If available, the indication for escalation to a mechanical ventilator is as follows:

a. The persistence of the Silverman Anderson Score >4, the need for a fraction of inspired oxygen of 100% with saturations persistently lower than 90% for >30 min, and all other aspects of CPAP management have been optimized (including prong size and position, minimizing CPAP pressure leak).
b. Apnoea unresponsive to caffeine therapy and need for stimulation, which is either frequent (6 episodes in 6 hours requiring vigorous stimulation) or severe (more than one episode requiring positive pressure ventilation in 12 hours). These infants will require mechanical ventilation if available or referred to a hospital that has this service.

For the surfactant replacement therapy through the LISA procedure:

During the procedure, if catheterization of the trachea is not possible within 20–30 seconds on the first attempt, remove the laryngoscope, allow recovery on Vayu bCPAP as required, and then attempt tracheal catheterization again. The maximum number of catheterization attempts should be 3, after which the procedure should be abandoned.

After the procedure, the indications to escalate are as follows:

a. The persistence of the Silverman Anderson Score >4, the need for a fraction of inspired oxygen of 100% with saturations persistently lower than 90% for >30 min, and all other aspects of CPAP management have been optimized (including prong size and position, minimizing CPAP pressure leak).
b. Apnea unresponsive to caffeine therapy and need for stimulation, which is either frequent (6 episodes in 6 hours requiring vigorous stimulation) or severe (more than one episode requiring positive pressure ventilation in 12 hours).

Infants will be reassessed for other potential complications of prematurity e.g. sepsis or intraventricular haemorrhage etc that could be causing the deterioration and managed according to the Kenya Paediatric and Neonatal Protocols.

These have been adopted from the Ministry of Health Kenya's i.e. Basic Paediatric Protocols for ages up to 5 years, 5th Edition November 2022 and ii. Management of Apnoea of Prematurity, National Guideline, 2023. Context-relevant evidence to inform these cut-offs is limited in Africa.

7.0 Study Calendar

Phase 1 of the study will be separated into two steps. This will allow sites a staggard introduction to the study interventions, policies, and procedures. Also, it will enable all the sites to be at the same stage before the stepped-wedge study period begins.

i. Step 1 of Phase 1 will entail normalizing the study data collection process, consistent use of cardiopulmonary monitoring, head US and ROP screening, and blood culture procedure.

ii. Step 2 of Phase 1 will entail normalizing the use of the Vayu bCPAP and/or caffeine, depending on what bundle component the sites already utilize. Sites will finalize their implementation strategy.

Site-specific implementation:

1. **CAR site**:
    a. They currently use caffeine routinely. Thus, step 2 of phase 1 will focus on implementing Vayu CPAP.
2. **Ghana sites**:
    a. They currently use oral caffeine and Vayu bCPAP. Thus, step 2 will focus on implementing study monitoring and screening, while step 1 will be to understand baseline performance.
3. **Kenya sites**:
    a. They are currently using Vayu bCPAP routinely. The use of caffeine remains intermittent due to the systemic procurement challenges. Thus, phase 1 will focus on implementing caffeine routinely and the study monitoring procedures.
4. **Nigerian sites**:
    a. They do not routinely use Vayu bCPAP or caffeine. Thus, step 2 will focus on implementing Vayu bCPAP and Caffeine into routine clinical use.

Because each site has a different timeline for obtaining ethical approval, the time to complete phase 1 will vary by site. We estimate that the shortest time to complete phase 1 will be ~4 months, while the most prolonged time could be 9 months.

Figure 4: Study timeline

	Phase 1		Phase 2								
Sites	**Standardization phase**		**Stepped Wedge Cluster Trials**								
	Study procedure	*Study Intervention*	*Step 1*	*Step 2*	*Step 3*	*Step 4*	*Step 5*	*Step 6*	*Step 7*	*Step 8*	*Step 9*
1											

	Period	Duration (months)	Number of periods	Total time (months)
	Data collection and monitoring	~2-3	1	2 to 3
	Vayu bCPAP and/or caffeine	3 to 6 months	1	3 to 6
	Stepped Wedge Phase	3	9	27
Total study period				**32 to 36**

8.0 Reportable Events

The primary outcome (mortality) is expected, given the study population (critically ill-hospitalized premature infants). We will closely monitor this outcome. However, if this event occurs as a direct consequence of the intervention, we will classify it as a serious adverse event and report it. The local site investigator will promptly notify their respective ethics committee and the PI of any unanticipated, serious adverse events related to the research activity. The PI will notify the Indiana University (IU) Institutional Review Board (IRB) promptly after receiving the report. Written reports will be filed electronically and per the timeline below.

Table 2: Potential adverse event, timing, and method of reporting.

Type of unanticipated problems	Initial Notification (Phone, Email, Fax)	Written Report
Death or life-threatening event attributed to the investigative device, drug, or procedure.	Five business days	Within five business days
All other SAEs are attributed to the investigative device, drug, or procedure.	Five business days	Within five business days
Unanticipated problems related to the research	Five business days	Within five business days
Unanticipated problems related to the research, Protocol deviations	Five business days	Within five business days

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The following will be classified as serious adverse events from CPAP therapy.

1. Pneumothorax: Diagnosed clinically by transillumination or radiographically by X-ray.
2. Pneumomediastinum: Diagnosed clinically by transillumination or radiographically by X-ray.
3. Pulmonary hemorrhage: Diagnosed clinically with worsened respiratory status (oxygen saturation, respiratory rate, and work of breathing) and continuous bleeding from the mouth and nose that is not from direct trauma to soft tissue in the mouth. It can also be diagnosed radiologically.
4. Grade III or IV pressure necrosis around nostrils and distortion of the nasal septum.
5. Grade III or IV pressure necrosis around the head/ears.
6. Head molding.

The following will be classified as adverse events from caffeine therapy.

1. Tachycardia: A persistent increase in heart rate that prompts the managing physician to reduce the dose or stop the drug.
2. Abnormal movement that is concerning seizure activity necessitating stopping the drug by the managing clinician.

The following will be classified as serious adverse events from LISA therapy.

1. Pneumothorax: Diagnosed clinically by transillumination or radiographically by X-ray.
2. Pneumomediastinum: Diagnosed clinically by transillumination or radiographically by X-ray.
3. Pulmonary hemorrhage: Diagnosed clinically with worsened respiratory status (oxygen saturation, respiratory rate, and work of breathing) and continuous bleeding from the mouth and nose that is not from direct trauma to soft tissue in the mouth. It can also be diagnosed radiologically.
4. Bradycardia and desaturation that requires positive pressure ventilation.
5. Bradycardia and desaturation that requires chest compression and positive pressure ventilation.
6. Major airway injury: esophageal or tracheal tear
7. Cardiac arrest that leads to death.

Management of complications: The complications of the study interventions are the same as those of the underlying respiratory disease (RDS, sepsis). The study sites typically have the capacity to manage these complications, however, not to the fullest capacity. For pneumothorax, each site has the capacity to perform a needle decompression, but not all can place a chest tube.

Pneumomediastinum is typically managed conservatively. Pulmonary hemorrhage can be managed by increasing the continuous distending pressure (increasing CPAP pressure) or by intubation and mechanical ventilation, which, unfortunately, is very limited in the study sites. In addition, there will be provision for insurance of all trial participants in case of adverse effects from proposed interventions.

9.0 Data Safety Monitoring

We will have a data safety monitoring board (DSMB) for this study. The following will be monitored as part of the Data Safety Monitoring Plan (DSMP): Adverse event data, mortality rate, results of related studies that may impact subject safety, and procedures designed to protect subjects' privacy. The DSMB will monitor the study's progress when 25%, 50%, and 75% of the trial subjects have reached hospital discharge.

10.0 Study Withdrawal/Discontinuation

A parent may decide to withdraw their child from the study at any time without prejudice to their care. For any subject who has withdrawn, no clinical information other than basic demographic information and the reason for withdrawal will be collected. Study subjects may also be discontinued from the study at the discretion of the local PI with stated reasons. If the PI becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded and reported per policy.

11.0 Statistical Considerations

The 2023 admission and mortality data on babies ≤2000 grams from the study sites indicated an average in-hospital mortality rate of ~35%. There was considerable variability in the admissions and mortality rates amongst sites, which resulted in an inter-cluster correlation (ICC) calculated to be 0.5.

Sample size:

Primary Aim: Determine the impact of Vayu bCPAP + Caffeine + LISA **vs.** Vayu bCPAP + Caffeine on neonatal survival. Table 3 provides the sample size with the resultant expected effect size (absolute and relative reduction in mortality) using an alpha of 5%, an ICC of 0.5, and a power of 80%.

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Table 3: Sample size and effect size estimates for the stepped-wedge phase of the study.

Sample size	Baseline mortality	Resulting mortality with intervention	An absolute reduction in mortality	A relative reduction in mortality
864	0.35	0.237	-0.112	32.1%
936	0.35	0.242	-0.108	30.9%
1008	0.35	0.246	-0.104	29.8%
1080	0.35	0.249	-0.101	28.8%
1152	0.35	0.252	-0.097	27.9%
1224	0.35	0.255	-0.094	27.0%
1296	0.35	0.258	-0.092	26.3%
1368	0.35	0.260	-0.089	25.6%
1440	0.35	0.263	-0.087	24.9%
1512	0.35	0.265	-0.085	24.3%

We plan to recruit the highest number of subjects (1512). However, given the variations in admission potential and mortality rates, we apportioned each site's recruitment number commensurate with their recruitment capacity. This will ensure all sites complete recruitment at the same time. (Table 4).

Table 4: Sample size estimates per center during the stepped-wedged phase of the study.

Site location	Total number of estimated subjects
Korle Bu Teaching Hospital	328
Komfo Anokey Teaching Hospital	312
Mama Lucy Kibaki Hospital	224
Kilifi County Hospital	152

Tamale Teaching Hospital	136
CHUC	160
University of Ilorin	136
Federal Medical Center Ekiti	64
Total estimated sample	**1512**

Secondary Aim: Determine the effect of Vayu bCPAP + Caffeine + LISA **vs.** current standard respiratory support on hospital survival. We anticipate recruiting 30 to 50 subjects from each site who do not routinely use Vayu bCPAP and/or Caffeine in the standardization phase, resulting in an average of 150 subjects receiving standard care respiratory support. We will perform a one-to-many matching with enrolled subjects who received the Vayu bCPAP + Caffeine + LISA. Using an alpha of 0.5% and ICC of 0.5, we will have 80% power to detect a decrease in mortality of 18%.

Statistical analytic approach:
We will compare the maternal and neonatal demographics and clinical information between the patients who received the locally customized bubble CPAP and Vayu bCPAP. These characteristics will be compared using standard descriptive statistics, a two-sample t-test or Wilcoxon rank-sum test for continuous variables, and $\chi 2$ test or Fisher's exact test for categorical variables.

Primary Objective: To determine the impact of Vayu bCPAP + Caffeine + LISA **vs.** Vayu bCPAP + Caffeine on neonatal mortality at discharge.

We will analyze the impact of LISA using a mixed model that accounts for the random effect of location and a fixed effect for time, and the impact of time on the treatment (i.e., the length of time the treatment has been in effect at that location), again specifying our outcome is binary. We will also include controls for birthweight and initial Silverman Anderson Score.

Secondary Objectives:

1. To determine the impact of Vayu bCPAP + LISA **vs**. the locally customized CPAP device on neonatal mortality at discharge.

   We will employ propensity score matching to match each neonate in the control group with the closest neonate in the LISA group, based on birthweight, initial Silverman Anderson Score, AOP rate, and location. We will then ensure balanced values for our matching variables

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(covariates) before performing a chi-square to determine whether there are differences in the probability of mortality between stages.

2. To evaluate the implementation of the intervention bundle using the RE-AIM Framework.

   - **Reach**: This will be calculated by the proportion of eligible subjects that received the study intervention in the indicated timeframe.

   - **Adoption**: This will be measured via adoption, acceptability, and suitability survey instruments for the bundle components. Survey results will inform the need for individual or focused group discussions.

   - **Implementation fidelity**: During the stakeholder-driven implementation strategy development, we will create a policy and procedure checklist that will be used to monitor adherence to the developed strategy.

3. To determine the cost-effectiveness of the individual and bundled intervention.

- **Analysis Type**: Intention-to-treat (ITT) will be performed. The ITT analysis will include all study participants, employing appropriate statistical methods and addressing missing data through imputation techniques.

- **Adjusted analysis**: At the end of each period, we will reassess our planned sample sizes to ensure we have enough power to detect the level of changes we are observing based on the level of variation that is intrinsic to the locations (i.e., we will have better estimates of the ICC). We may also adjust the number of neonates included for analysis at larger locations if we cannot recruit as many as hoped from the smaller locations. We will also consider whether to use one-to-one or one-to-many matching for our final set of analyses based on the effect sizes and coefficients of variation we observe. If the variation between groups is large, we may need to use one-to-many matching. In this case, every neonate in the LISA group will be matched with the closest neonate in the pre-trial group, with those in the pre-trial group replaced after each match. If treatment effects are small but the trial results in a low coefficient (if the ICC < 0.1 in the mixed models), we may pool all the neonates regardless of location.

12.0 Data Management

The data manager will oversee key study activities and ensure compliance with the Data Protection Act. The REDCap system will be managed by the data management team. The team in conjunction with the Indiana IT administrator will set up the system, implement security access controls and ensure compliance with Indiana IT procedures and policies.

The data manager will also configure android tablets and assign access rights to the research assistants. The data manager will be responsible for designing the data questionnaire using REDCap. Additionally, they will monitor the data entry for accuracy and completeness, checking for inconsistencies, missing data, outliers, evidence of rounding off measurements and implementing quality control checks. All issues identified during routine monitoring will be discussed with the research assistants and corrective measures taken promptly.

Data Entry

- We will collect demographic data on the mother and baby. We will also collect pregnancy, delivery, resuscitation, initial stabilization, general management, Silverman Anderson Score on the locally customized bubble CPAP and the Vayu bCPAP, clinical outcome data, and study outcome data.
- We will also collect recorded images of brain ultrasound scans and images of recordings from the video laryngoscope that will be used for the study procedure.
- Data collected and stored on multiparameter monitors will also be collected.
- We will extract data from medical records and case report forms.

Data will be collected using android-based tablets that are password protected and fitted with the IU-supported REDCap. REDCap is a secure web-based database, offline, android based mobile app for data collection. It is compliant with GDPR and other regulatory requirements (https://www.project-redcap.org/). REDCap handles database access, file access and data synchronization. It ensures data security, with data synchronization and storage to the Indiana University servers. Data will be collected offline and uploaded to the Indiana University servers at the end of the day or the soonest time point by the study coordinator. In case data synchronization and upload is not possible, the principal investigator will be notified for further advice on what should be done.

To access data on the Indiana University server, the study investigators will be required to request for access and right through the Indiana University IT department after which the data to be shared will be discussed and agreed upon. Anonymised data will be stored on the Indiana University server.

Quality control

The research assistants will be senior nurses with a minimum qualification of Diploma in Nursing and to have at least 2 years' experience of working in a newborn baby unit or conducting clinical research among newborn babies.

In Kenya, both caffeine administration and CPAP use are nurse-led interventions and are standard of care for very preterm and very low birthweight infants in Kenya. The nurses alongside the medical officers, clinical officers and consultant paediatricians/neonatologists on

the newborn units will therefore be trained and retrained on these procedures throughout the duration of the study, with structures in place to assure continuity beyond the study, and more importantly, to assure patient safety. For LISA, only medical officers and consultant paediatricians/neonatologists will be trained and retrained to conduct this procedure.
We will use a theory-guided approach to develop a site-specific implementation strategy. This strategy will inform the development of a standard operating procedure, including patient safeguards. Other safeguards include using cardiorespiratory monitors during the LISA procedure, creating a stopping rule, and restricting the LISA procedure to a specific cadre of clinicians.

All research assistants will be required to be GCP certified. They will undergo training on obtaining informed consent, interviewing skills and data entry using the REDCap software.

The following quality assurance steps will be used: 1) built-in range checks and 2) database testing by a study team before moving to implementation phase.

The following quality control methods will be used: [e.g., 1) Data validation of Redcap data records, and 2) extraction and cleaning of data used for analysis every three months.

All collected data will be monitored remotely by the data manager for any missingness, anomalies or inaccurate data which will be flagged for the study coordinator to confirm with the hospital site teams and data corrected where necessary.

We will retrain and support any research assistants who make consistent errors. During the study, we will randomly sample about 5-10% to check for accuracy.

13.0 Privacy/Confidentiality Issues

Security measures to protect subject identities include using coded files to unlink research records from names and other identifiers, locked storage areas, and password-protected computer files. Subjects' names are linked to their IDs, as noted above. Access to computer systems housing sensitive information is strictly regulated. Credentials permitting access to these systems are granted only to essential investigators and research personnel. All systems are secured from external attacks through hardware and software firewalls and are updated with necessary security patches as they become available. Related hardware and backup storage media are maintained in a secure environment to which only essential personnel have physical access. All consent and research procedures will be compliant with Subpart B of the Code of Federal Regulations Title 45, Part 46 - Protection of Human Subjects with Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research (66 FR 56778, Nov. 13, 2001).

Research staff (including the research assistants) will be fully trained to maintain confidentiality when handling participant data with an aim to maintain anonymity.

No identifiable data will be used for future studies without obtaining IRB approval or determination of exemption. The Investigator will obtain a data use agreement between the provider (the PI) of the data and any recipient researchers (including others at IU) before sharing a limited dataset accessed.

14.0 Follow-up and Record Retention

Each study participant will be involved in the study for the duration of their hospital stay. All paper documents will be scanned and stored in REDCap, alongside primary data collection which will be done on REDCap. Paper records will be kept for 5 years after the study is completed in a secure filing cabinet under lock and key in study office at Mama Lucy Hospital and at the Aga Khan University-Mombasa Research Office (MRO). Electronic records will be maintained for five years after the results of the study are published. De-identified data will be kept in a data repository and will be available to researchers based on a review of applications.

15.0 Data sharing

Data will be available based on request and review by the senior team of collaborators. The senior team of collaborators will review applications to use the study data. This team will comprise the three co-PIs and the eight site PIs.

Applications will be considered from clinical, academic and potentially commercial bodies involved in newborn care technologies, all of which must be purely for research and educational purposes. All interested groups will be required to complete a proposal form with details of study justification, research questions and reasons for data points required. These will be reviewed by the team of senior collaborators, discussed with the applicant (s) and once revisions have been made as recommended by the team, this will be signed off by the primary co-PI. Thereafter the data sharing agreement will be signed and data will be made available to the applicant. A record of the process will be outlined and shared with all senior investigators. A record will be compiled for all studies seeking to use these data for secondary analyses and each one will have a unique identifier. All data sharing agreements will have a time limit for the completion of the analysis and write up and if not met then the agreement will be withdrawn. Academic researchers may be requested to cover the costs for data retrieval and transfer, to support administrative aspects of this process.

The release of data to external users must comply with the ethics committee approvals. The procedure required for confidentiality and data security will be clearly documented. The data sharing agreement will address the approach that will be used for intellectual property, publication, authorship and acknowledgement. It will include a requirement that research publications and other outputs based on the data are reported to the co-PIs and that the Open Philanthropy be acknowledged in outputs. The researchers accessing the data must agree not to

transfer data to another unauthorized third-party. Arrangements for secure data archiving will be made and the costs of data retrieval detailed.

16.0 Community and stakeholder engagement

During the setting up, conducting and completion of the study we will engage with existing parent groups and champions whose infants have been admitted onto the newborn units at Mama Lucy Kibaki Hospital and Coast General Teaching and Referral Hospital. With them we will co-design the community engagement strategy for the study, relevant for tertiary level facilities where patients will be referred from communities often a long distance from the hospitals. This will include media awareness sessions as well as hospital-based meetings with diverse groups including those mothers with disabilities. This will enable use to understand the community norms, their perceptions of the study interventions that we seek to implement ad evaluate and how best to deliver these in the two tertiary level hospitals in Kenya serving predominantly urban populations with diverse religious and cultural beliefs.

Stakeholder engagement will involve convening a series of meetings with health care providers and policy makers from the hospitals, county health management teams, referring health facilities and community health promoters.

Feedback to the participant will focus on the impact of adding surfactant to the care provided to the infants and infant outcomes from the study. This will be done through targeted meetings. Feedback to the stakeholders will include standardization of the use of CPAP in the hospitals to reduce infant mortality and study outcomes on the additional use of surfactant. This will be through dissemination at hospital level, County and sub-county level, and national/international child health scientific meetings.

17.0 Disclosure statement

The principal investigator, co-principal investigator, and each individual site principal investigator do not have any financial or personal interest in the sponsors of the study. They also have no financial or personal interest related to this study to disclose.

The cost of caffeine and surfactant used for the study will not be borne by the study participants. Study sites will not bear the cost of purchasing any study-related material. The study has provided funds to cover any medical expense that is determined by the managing clinicians as a direct result of the study intervention or procedure.

18.0 Compliance Statement

The design, conduct, recording, and reporting of this study will be in accordance with the international ethical and scientific quality standards on good clinical practice. We will follow good clinical practice guidelines.

19.0 Ethical considerations

Ethical approval will be sought from the Aga Khan University Institutional Scientific and Ethics Review Committee (ISERC) and the National Commission for Science, Technology and Innovation (NACOSTI). Further approval will also be sought from Indiana University. In-country approval for the sites in CAR, Ghana and Nigeria will also be obtained.

20.0 Expected application of the results

The results of this study will be used to inform practice in the hospitals on the additional use of surfactant to the already present standard of care CPAP and contribute towards generation of policy related data to support the uptake and implementation of both care practices.

21.0 Budget

Subrecipient Centre of Excellence for Women and Child Health

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Name	Role	Appt Type	FTE 1	FTE 2	FTE 3	Base Salary	Fringe Rate	Year 1 Months	Year 1 Salary	Year 1 Fringe	Year 2 Months	Year 2 Salary	Year 2 Fringe	Year 3 Months	Year 3 Salary	Year 3 Fringe	Total
Personnel																	
Co- PI, Helen Nabwera	Co-PI	12-month	0.08	0.08	0.08	158,064	0.00%	1.0	12,645	0	1.0	12,645	0	1.0	12,645	0	37,935
TBD Site 1	Site PI	12-month	1.00	1.00	1.00	12,000	0.00%	12.0	12,000	0	12.0	12,000	0	12.0	12,000	0	36,000
TBD Site 2	Site PI	12-month	1.00	1.00	1.00	12,000	0.00%	12.0	12,000	0	12.0	12,000	0	12.0	12,000	0	36,000
TBD Site 1	Research Assistants	12-month	1.00	1.00	1.00	12,000	0.00%	12.0	12,000	0	12.0	12,000	0	12.0	12,000	0	36,000
TBD Site 1	Research Assistants	12-month	1.00	1.00	1.00	12,000	0.00%	12.0	12,000	0	12.0	12,000	0	12.0	12,000	0	36,000
TBD Site 2	Research Assistants	12-month	1.00	1.00	1.00	12,000	0.00%	12.0	12,000	0	12.0	12,000	0	12.0	12,000	0	36,000
TBD Site 2	Research Assistants	12-month	1.00	1.00	1.00	12,000	0.00%	12.0	12,000	0	12.0	12,000	0	12.0	12,000	0	36,000
TBD Site 1	Data Manager	12-month	1.00	1.00	1.00	8,400	0.00%	12.0	8,400	0	12.0	8,400	0	12.0	8,400	0	25,200
TBD Site 2	Data Manager	12-month	1.00	1.00	1.00	8,400	0.00%	12.0	8,400	0	12.0	8,400	0	12.0	8,400	0	25,200
Ken, Prisca-AKU	Finance Grant Officers	12-month	0.10	0.10	0.10	31,200	0.00%	1.2	3,120	0	1.2	3,120	0	1.2	3,120	0	9,360
Subtotal Salaries & Wages									104,565	0		104,565	0		104,565	0	313,695
TOTAL SALARIES & FRINGE BENEFITS									104,565			104,565			104,565		313,695
Travel																	
Domestic Travel - Co-PI Travel									4,000			4,000			4,000		12,000
Foreign Travel									0			0			0		0
Subtotal Travel									4,000			4,000			4,000		12,000
Other Direct Costs																	
Clinical Supplies include:Caffeine Drug, Vayu CPAP, Blood Cultures, Clinical Care									52,000			0			0		52,000
Training Workshop									2,000			2,000			2,000		6,000
Office Supplies, Laptop, Office Space Cost									12,000			6,500			6,500		25,000
Shipping CPAP and Ethics Approvals									6,000			0			0		6,000
Subtotal Other Direct Costs									72,000			8,500			8,500		89,000
TOTAL DIRECT COSTS									180,565			117,065			117,065		414,695
Indirect Costs																	
MTDC																	
Indirect Base (TDC-equipment-participant support-fee remissions-subcontract>$25K)									180,565			117,065			117,065		414,695
TOTAL INDIRECT COST							10.00%		18,057			11,707			11,707		41,471
TOTAL PROJECT COSTS									198,622			128,772			128,772		456,166

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APPENDIX 1: PRETERM AFRICA TRIAL CASE REPORT FORM (Pre_LISA PHASE)

PRETERM Africa Trial Case_Report_Form (Pre_LISA PHASE)	
ADMIN INFORMATION	
Study ID: _____ **Admit Date & Time**: (dd/mm/yy):___/___/____ | ___: ___(hh:mm)	**Admit Dr**: _____ **Unit/Ward**: _____
MATERNAL DEMOGRAPHICS & DELIVERY INFORMATION	
Age: _____ y ☐UKN **MOD:** ☐Vaginal ☐ Cesarean Section	**Antenatal steroids**: ☐Yes ☐No ☐UKN **# of steroid doses**: _____
Pregnancy complications: ☐Diabetes Mellitus ☐Oligohy ☐Polyhy ☐Chorio ☐PPROM ☐PIH ☐No complications **Other Specify:** _____ **Duration of labor:** _____hr ☐N/A (No labor) ☐ UKN **Duration of membrane rupture:** _____ hrs ☐UKN **Was fluid/liquor meconium stained**: ☐Yes ☐No ☐UKN **Resuscitation**: ☐ Dry&Stim ☐Bag Mask ☐Intubation ☐Chest Compression ☐Adrenaline ☐ Blood/IVF ☐ Unk (all that apply) **CPAP started in the delivery room**: ☐Yes ☐No ☐UKN. **5 Min APGAR:** _____ ☐UKN **Delayed Cord Clamping** (>30 sec): ☐Yes ☐No ☐UKN	
BABY DEMOGRAPHICS & CLINICAL INFORMATION	
Sex: ☐ F ☐M ☐UKN **Pregnancy**: ☐ Singleton ☐ Twins ☐ Triplet ☐ ≥4 **Birth/Admit weight**: _____g ☐UKN **GA**: _____ wks. ☐UKN **GA By**: ☐LMP ☐1st Trim US ☐2nd/3rd Trim US ☐ Ballard ☐Unk (select all that apply)	**DOB**: (dd/mm/yyyy): ___/___/____ **TOB**: _____: _____ (military time) **Ballard GA**: _____ wks. ☐ Not performed **Place of birth:** ☐Inborn Out born ☐Hosp ☐ Home **Admission glucose:** _____ mg/dl ☐UKN **Admission Temp:** _____ °C ☐UKN
RDS ASSESSMENT AND CARE:	
Nasal Cannula/Prongs before CPAP: ☐Yes ☐No ☐UKN	**Anderson Silverman Score 2 hours AFTER CPAP:** _____ **Anderson Silverman Score 6 hours AFTER CPAP:** _____ **Anderson Silverman Score 12 hours AFTER CPAP:** _____
Anderson Silverman Score BEFORE CPAP: _____ (highest score) **Hour of life CPAP started:** _____	
Blended oxygen used: ☐Yes ☐No ☐UKN	**DOL 0 Received:** ☐Caffeine ☐Aminophylline ☐None
Highest FiO2: _____, **Lowest FiO2:** _____,	**First 7 d Received:** ☐Caffeine ☐Aminophylline ☐None
CPAP started in the DR: ☐Yes ☐No	
CPAP: ☐Yes ☐No **Type of CPAP machine**: _____	**Highest level of CPAP pressure**: _____cmH_2O

Start Date: ___/___/___ Stop Date: ___/___/___ Start Date: ___/___/___ Stop Date: ____/____/___ Start Date: ___/___/___Stop Date: ___/___/____	**Surfactant administered:** ☐Yes ☐No ☐UKN **Methods of surfactant administration:** ☐LISA ☐LMA ☐ InSuRe (≤2H on ventilator) ☐ Ventilator (>2 hours on the ventilator)
Nasal Cannula: ☐Yes ☐No	**Ventilator:** ☐Yes ☐No ☐ Not available
Start Date: ___/___/___ Stop Date: ___/___/___ Start Date: ___/___/___ Stop Date: ___/___/___	Start Date: ___/___/___ Stop Date: ___/___/___ Start Date: ___/___/___ Stop Date: ____/____/____
CLINICAL OUTCOMES	
ROP: ☐Yes Worst Stage_____ ☐No ☐UKN/ND. **IVH by US**: ☐Yes Worst Grade_____ ☐No ☐UKN/ND. **Positive blood culture**: ☐Yes ☐No ☐ UKN **Antibiotics exposure**: ☐Yes ☐No ☐ UKN **Surgeries**: ☐Yes ☐No ☐ UKN **Surgery type**: _____ **Discharge weight**: _____ (g) ☐UNK or N/A	**PDA by ECHO**: ☐Yes ☐No ☐ UKN **NEC**: Medical☐ Surgical☐ None☐. **Resp support at 28 days of life**: ☐Yes ☐No ☐ UKN *Support Type*: ☐Prongs/Cannula ☐ CPAP ☐Vent **Pneumothorax**: ☐Yes ☐No ☐ UKN **Pulmonary hemorrhage**: ☐Yes ☐No ☐ UKN
PATIENT DISPOSITION	
Hospital Outcome: ☐Home ☐DAMA ☐Died ☐Transferred to another hospital. **Outcome Date**: (dd/mm/yyyy): ___/___/____ **Primary Cause of Death***: _____*Cardiopulmonary arrest is not a cause of death **Cause of death determined by autopsy**: Yes ☐ No ☐	
Form completed by: _____ **Date**__/___/__ **Form reviewed by consultant:** _____ **Date**__/___/__	

APPENDIX 2: PRETERM AFRICA TRIAL CASE REPORT (LISA PHASE)

PRETERM Africa Trial Case_Report_Form (LISA PHASE)	
ADMIN INFORMATION	
Study ID: _____ **Admit Date & Time**: (dd/mm/yy):___/___/____ | ___: (hh:mm)	**Admit Dr**: _____ **Unit/Ward**: _____
MATERNAL DEMOGRAPHICS & DELIVERY INFORMATION	
Age: _____ y ☐UKN **MOD:** ☐Vaginal ☐ Cesarean Section	**Antenatal steroids**: ☐Yes ☐No ☐UKN **# of steroid doses**: _____
Pregnancy complications: ☐Diabetes Mellitus ☐Oligohy ☐Polyhy ☐Chorio ☐PPROM ☐PIH ☐No complications **Other Specify:** _____ **Duration of labor:** _____hr ☐N/A (No labor) ☐ UKN **Duration of membrane rupture:** _____ hrs ☐UKN **Was fluid/liquor meconium stained**: ☐Yes ☐No ☐UKN **Resuscitation**: ☐ Dry&Stim ☐Bag Mask ☐Intubation ☐Chest Compression ☐Adrenaline ☐ Blood/IVF ☐Unk (all that apply) **CPAP started in the delivery room**: ☐Yes ☐No ☐UKN. **5 Min APGAR:** _____ ☐UKN **Delayed Cord Clamping** (>30 sec): ☐Yes ☐No ☐UKN	
BABY DEMOGRAPHICS & CLINICAL INFORMATION	
Sex: ☐ F ☐M ☐UKN **Pregnancy**: ☐ Singleton ☐ Twins ☐ Triplet ☐ ≥4 **Birth/Admit weight**: _____g ☐UKN **GA**: _____ wks. ☐UKN **GA By**: ☐LMP ☐1st Trim US ☐2nd/3rd Trim US ☐ Ballard ☐Unk (select all that apply) **Admission Temp:** _____ ºC ☐UKN	**DOB**: (dd/mm/yyyy): ___/___/____ **TOB**: _____: _____ (military time) **Ballard GA**: _____ wks. ☐ Not performed **Place of birth:** ☐Inborn Out born ☐Hosp ☐ Home **Admission glucose:** _____ mg/dl ☐ UKN
RDS ASSESSMENT AND CARE:	
Nasal Cannula/Prongs before CPAP: ☐Yes ☐No ☐UKN	**Anderson Silverman Score 2 hours AFTER CPAP:** _____ **Anderson Silverman Score 6 hours AFTER CPAP:** _____ **Anderson Silverman Score 12 hours AFTER CPAP:** _____
Anderson Silverman Score BEFORE CPAP: _____ (highest score) **Hour of life CPAP started:** _____	
Blended oxygen used: ☐Yes ☐No ☐UKN	**DOL 0 Received:** ☐Caffeine ☐Aminophylline ☐None
Highest FiO2: _____, **Lowest FiO2:**_____,	**First 7 d Received:** ☐Caffeine ☐Aminophylline ☐None

CPAP: ☐Yes ☐No	**Highest level of CPAP pressure**: _____ cmH_2O
Start Date: ___/___/___ Stop Date: ___/___/___ Start Date: ___/___/___ Stop Date: ____/____/___ Start Date: ___/___/___ Stop Date: ___/___/____	**Type of CPAP machine**: _____
Nasal Cannula: ☐Yes ☐No	**Ventilator:** ☐Yes ☐No ☐ Not available
Start Date: ___/___/___ Stop Date: ___/___/___ Start Date: ___/___/___ Stop Date: ___/___/___ Start Date: ___/___/___ Stop Date: ___/___/___	Start Date: ___/___/___ Stop Date: ___/___/___ Start Date: ___/___/___ Stop Date: ____/____/____ Start Date: ___/___/___Stop Date: ___/___/____
CLINICAL OUTCOMES	
ROP: ☐Yes Worst Stage_____ ☐No ☐UKN/ND. **IVH by US**: ☐Yes Worst Grade_____ ☐No ☐UKN/ND. **Positive blood culture**: ☐Yes ☐No ☐ UKN **Antibiotics exposure**: ☐Yes ☐No ☐ UKN **Surgeries**: ☐Yes ☐No ☐ UKN **Surgery type**: _____ **Discharge weight**: _____ (g) ☐UNK or N/A	**PDA by ECHO**: ☐Yes ☐No ☐ UKN **NEC**: Medical☐ Surgical☐ None☐. **Resp support at 28 days of life**: ☐Yes ☐No ☐ UKN *Support Type*: ☐Prongs/Cannula ☐ CPAP ☐Vent **Pneumothorax**: ☐Yes ☐No ☐ UKN **Pulmonary hemorrhage**: ☐Yes ☐No ☐ UKN
PATIENT DISPOSITION	
Hospital Outcome: ☐Home ☐DAMA ☐Died ☐Transferred to another hospital. **Outcome Date**: (dd/mm/yyyy): ___/___/____ **Primary Cause of Death***: _____ *Cardiopulmonary arrest is not a cause of death **Cause of death determined by autopsy**: Yes ☐ No ☐	
Form completed by: _____ **Date**__/___/__ **Form reviewed by consultant:** **Date** / /