Pilot and Feasibility Studies

STUDY PROTOCOL

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Impact of early continuous positive airway pressure in the delivery room (DR-CPAP) on neonates < 1500 g in a low-resource setting: a protocol for a pilot feasibility and acceptability randomized controlled trial

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Abstract

Background Preterm birth is the leading cause of childhood mortality, and respiratory distress syndrome is the predominant cause of these deaths. *Early* continuous positive airway pressure is effective in high-resource settings, reducing the rate of continuous positive airway pressure failure, and the need for mechanical ventilation and surfactant. However, most deaths in preterm infants occur in low-resource settings without access to mechanical ventilation or surfactant. We hypothesize that in such settings, *early* continuous positive airway pressure will reduce the rate of failure and therefore preterm mortality.

Methods This is a mixed methods feasibility and acceptability, single-center pilot randomized control trial of early continuous positive airway pressure among infants with birthweight 800–1500 g. There are two parallel arms: (i) application of continuous positive airway pressure; with optional oxygen when indicated; applied in the delivery room within 15 min of birth; transitioning to bubble continuous positive airway pressure after admission to the neonatal unit if Downes Score ≥ 4 (intervention), (ii) supplementary oxygen at delivery when indicated; transitioning to bubble continuous positive airways pressure after admission to the neonatal unit if Downes Score ≥ 4 (control). A two-stage consent process (verbal consent during labor, followed by full written consent within 24 h of birth) and a low-cost third-party allocation process for randomization will be piloted.

We will use focus group discussions and key informant interviews to explore the acceptability of the intervention, two-stage consent process, and trial design. We will interview healthcare workers, mothers, and caregivers of preterm infants. Feasibility will be assessed by the proportion of infants randomized within 15 min of delivery; the proportion of infants in the intervention arm receiving CPAP within 15 min of delivery; and the proportion of infants with primary and secondary outcomes measured successfully.

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Discussion This pilot trial will enhance our understanding of methods and techniques that can enable emergency neonatal research to be carried out effectively, affordably, and acceptably in low-resource settings. This mixed-methods approach will allow a comprehensive exploration of parental and healthcare worker perceptions, experiences, and acceptance of the intervention and trial design.

Trial registration The study is registered on the Pan African Clinical Trials Registry (PACTR) PACTR202208462613789. Registered 08 August 2022. https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=23888.

Keywords Preterm, Very low birthweight, VLBW, Africa, Neonatal, Continuous positive airway pressure, CPAP, Respiratory distress syndrome, Low-resource setting

Background

Preterm birth (< 37 weeks of gestation) is a global burden and complications of prematurity are the leading cause of death in children under the age of 5 [1]. In 2020, 13.4 million infants were born preterm and complications from preterm birth led to the death of nearly 1 million neonates worldwide, with the majority occurring in low- and middle-income countries (LMICs) like Uganda [1, 2]. The predominant reason for deaths in preterm infants is respiratory distress syndrome (RDS), with more than 50% of preterm infants born before 30 weeks of gestation developing RDS [3, 4]. The United Nations Sustainable Development Goals seek to reduce the global NMR to 12 deaths per 1000 live births by 2030 [5]. In Uganda, the Neonatal Mortality Rate (NMR) remains high at 22/1000 live births [6]. If the Sustainable Development Goal is to be reached, the mortality from preterm complications must be drastically reduced, and this will require novel approaches and dedicated and resource-appropriate neonatal care that appropriately address the challenges of healthcare provision in LICs.

Continuous positive airway pressure (CPAP) is an established and effective modality of respiratory support in preterm infants with RDS and is widely used in high-income countries (HICs) [7]. CPAP is a non-invasive type of respiratory support, that can be used without endotracheal intubation to support the breathing of preterm infants. Various types of machines can provide CPAP, including underwater bubble devices (bubble CPAP, BCPAP) and mechanical ventilators. BCPAP and ventilator-derived CPAP use different pressure sources. In ventilator CPAP, a variable resistance in a valve is adjusted to provide resistance to the flow of air. In BCPAP the positive pressure in the circuit is achieved by immersing the distal expiratory tubing in a water column to a desired depth rather than using a variable resistor. All CPAP works by providing a continuous level of positive pressure to the airways, which prevents end-alveolar collapse, maintains the functional residual capacity of the lungs, and supports gas exchange. This reduces apnoeas, work of breathing, and lung injury. In HICs, CPAP has been shown to reduce preterm mortality, reduce the need for mechanical ventilation, and reduce chronic lung disease [7]. CPAP is now the standard of care for RDS in HICs, with the option of mechanical ventilation and artificial surfactant in the event of respiratory failure. However, in LICs, mechanical ventilation and artificial surfactants are rarely accessible or affordable leaving limited treatment options for preterm infants with RDS.

Although conventional CPAP devices can cost from US$6,000 to US$10,000, various CE-marked Bubble CPAP (BCPAP) machines, with prices optimized for low-resource settings (< US$3000), are now available [8, 9]. BCPAP has been reported as a safe and effective method of delivering CPAP and has been shown to have comparable efficacy and safety [10–12]. Low-cost BCPAP for preterm infants was listed by the World Health Organization in 2012 as an area in need of implementation [13]. Due to their simplicity and affordability, commercially available, low-cost BCPAP devices have now been introduced in many neonatal units in LMICs [14, 15]. However, there have been no randomized trials conducted in LMICs that have evaluated the efficacy of BCPAP in preterm infants. Observation studies from Fiji, South Africa, and Malawi, showed a 26–78% reduction in in-hospital mortality following CPAP in preterm very low birthweight (VLBW, birthweight < 1500 g) infants [16–19]. The two South African studies used commercially available CPAP devices, whilst the studies from Malawi and Fiji used BCPAP. Pooled analyses of these four studies showed a 66% reduction in in-hospital mortality for VLBW infants following CPAP or BCPAP [20]. Our group also demonstrated a 44% reduction in in-hospital mortality in VLBW infants in a neonatal unit in Uganda following the implementation of the commercially available BCPAP [21]. Other studies in LICs have used locally assembled, homemade BCPAP, which is not believed to be a safe option as the pressures can be both unknown and unstable, and the increased work of breathing is not known [22–27]. Overall, available evidence suggests that commercially available BCPAP is a safe, effective, and affordable therapy for preterm infants with respiratory distress syndrome (RDS) in LMICs.

In HICs, the use of *early* CPAP, within 15 min of delivery, has been shown to decrease the need for mechanical ventilation by up to 45% and is now considered a safe alternative to intubation and surfactant for preterm infants [28–30]. Several studies of *early* CPAP have been carried out in middle-income countries where mechanical ventilation and surfactants are routinely available. Notably, in Iran and India, *early* CPAP and *early* BCPAP respectively, reduced the need for surfactant and mechanical ventilation in preterm infants [31, 32]. However, a randomized trial in Brazil, with access to MV and surfactant, reported that *early* CPAP did not reduce the need for MV; however, their control group received CPAP much earlier (median time 30 min) than CPAP is typically initiated in many low-resource settings [33].

In low-resource settings, even if BCPAP is available, access to mechanical ventilation or artificial surfactant for the treatment of RDS is often limited. Consequently, when BCPAP fails in the treatment of RDS, there are limited options for care and RDS is almost always fatal. The reduction in the need for surfactant and MV when *early* CPAP is used has the potential to reduce mortality from RDS in settings where these advanced treatments are not readily affordable or available. The impact of initiating *early* CPAP in settings where surfactant and MV are lacking has not yet been examined. One study in Malawi has already demonstrated that *early* BCPAP in the neonatal unit is feasible in preterm infants < 1300 g [34]. There is still a need for large high-quality studies on the efficacy, timing, and safety of BCPAP in VLBW infants in these settings. Our pilot randomized control trial seeks to evaluate the feasibility, acceptability, and safety of introducing *early* CPAP in the delivery room. Our subsequent trial will seek to determine whether, in a setting without artificial surfactant and mechanical ventilation, *early* CPAP can significantly impact mortality and morbidity in preterm infants.

Aims and objectives

Aim

The overall aim of this study is to assess the feasibility and acceptability of the trial design to aid the design of a future multi-center randomized controlled trial, which will evaluate the impact of *early* CPAP in the delivery room on the in-hospital mortality of VLBW infants in a low-resource setting.

Objectives

The objectives relate to assessing trial feasibility and acceptability and include the following:

1. To deliver a two-armed feasibility randomized control trial of *early* CPAP (within 15 min of delivery) in the delivery room to 100 very low birth weight infants (VLBW, < 1500 g)
2. To determine the acceptability of *early* CPAP to mothers, caregivers, and healthcare workers in a low-resource setting
3. To determine the post-intervention acceptability of using a two-stage consent process in neonatal emergencies in the delivery room in this setting
4. To evaluate the feasibility of a third-party allocation process for randomization by determining the time to randomization
5. To evaluate the feasibility of initiating *early* CPAP in the delivery room, in a low-resource setting in infants with birthweight 800–1500 g
6. To determine the safety of initiating *early* CPAP in a low-resource setting
7. To estimate the sample size to be used for future evaluation in the full trial
8. To assess the feasibility of primary and secondary outcome measures to be used in the full trial

Trial design

This is a mixed methods feasibility and acceptability, single-center randomized control trial of *early* CPAP in infants with a birthweight between 800–1500 g. The trial comprises two parallel arms: (i) application of continuous positive airway pressure; with a portable CPAP machine and RAM Cannula®; with optional oxygen when indicated; applied in the delivery room within 15 min of birth; and transitioning to bubble continuous positive airways pressure with RAM Cannula® after admission to the neonatal unit if the modified Downes Score (Supplement 1, [35, 36]) is ≥ 4 (intervention), (ii) supplementary oxygen at delivery when indicated; and transitioning to bubble continuous positive airways pressure with RAM Cannula® after admission to the neonatal unit if the Downes Score is ≥ 4 (control). The trial protocol aligns with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 checklist (Supplement 2) and has been developed collaboratively with our Trial Steering Committee (TSC) and our local preterm Community Advisory Board (CAB). The preterm CAB comprises families of preterm infants, healthcare workers with experience in caring for preterm infants, and local leaders. Refer to Fig. 1 for a visual representation of the study flow.

Setting

The study will be conducted in the neonatal unit (NNU) of Mbale Regional Referral Hospital (MRRH), a government hospital in eastern Uganda serving a population exceeding 4.5 million people. This dedicated level II NNU

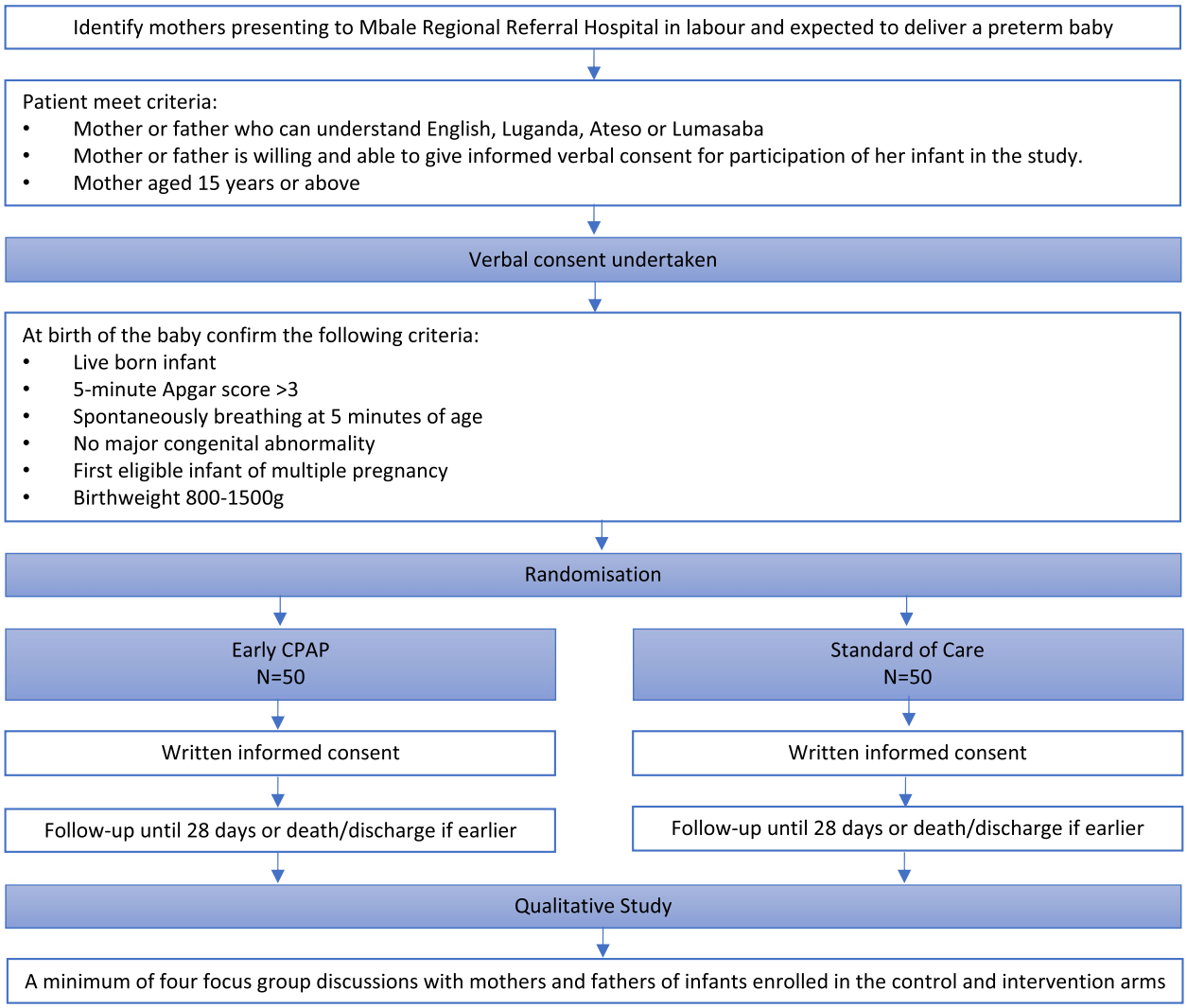

Fig. 1 Study flow chart showing feasibility design

admits approximately 2500 neonates annually, including around 450 VLBW infants. Neonates are admitted from the labor ward, and referred from surrounding facilities, and some neonates are brought in following home delivery. The NNU is staffed by a neonatologist, three neonatal clinical officers, one medical officer, and eight specialist neonatal nurses. MRRH NNU holds national recognition as a Centre of Excellence for neonatology, and through the implementation of Level II neonatal care has reduced the overall neonatal mortality from 48 to 12% since 2014 [21, 37]. The current in-patient mortality rate for VLBW infants is 26.5% [21]. All neonates enrolled in the DR-CPAP study will receive Level II neonatal care as defined by the Ugandan National Clinical Protocols for Managing Small and Sick Newborns.

Currently, MRRH-NNU has a 10-bed High Dependency Unit (HDU) where each bed is equipped with either a BCPAP or portable CPAP machine, and continuous pulse-oximetry monitoring. Six HDU beds are fitted with a BCPAP machine that can mix air and oxygen, while 4 HDU beds have a portable CPAP machine with the ability to add up to 2 L of oxygen as needed (Fig. 2). Every neonate on CPAP in HDU has continuous pulse-oximetry monitoring (LifeBox) to monitor for apnoea and allow for adjustment of the FiO_2. CPAP is routinely administered using RAM cannula® according to the size of the neonate.

For VLBW infants admitted to MRRH-NNU, it is standard care to commence CPAP for preterm infants with a Downe's score ≥ 4 (Supplement 1) [35, 36, 38]. Preference is to use a BCPAP machine, but a portable CPAP machine is used if a BCPAP machine is not available. Currently, portable CPAP machines are used in emergency management of RDS until a BCPAP is

Fig. 2 Types of CPAP used in Mbale Regional Referral Hospital Neonatal Unit (Diamedica Bubble CPAP (left), Diamedica portable CPAP (right)

available, ideally < 24 h. An additional 20 beds have access to oxygen therapy via standard nasal cannula, with these neonates having their oxygen saturations checked twice daily. Mechanical ventilation is unavailable in MRRH-NNU, and artificial surfactant is not routinely available, although occasionally patients are able to purchase this privately.

Kangaroo care is the continuous skin-to-skin contact between a caregiver and an infant immediately after birth [39, 40]. In MRRH-NNU, intermittent kangaroo care is initiated as soon as possible after delivery for all preterm infants. On occasions when neither the mother nor a caregiver is available to provide kangaroo care, a non-electric warming device (Warmilu™) is used to support thermoregulation until kangaroo care can be initiated. MRRH-NNU can routinely provide intravenous antibiotics, aminophylline, anticonvulsants, and fluids is possible in MRRH-NNU. Phototherapy is available and bedside ultrasound is routinely performed to examine for patent ductus arteriosus (PDA) at 72 h of age and intraventricular hemorrhage (IVH) at 7 days of age in VLBW infants.

For VLBW infants, feeding is initiated by nasogastric tube using expressed breastmilk and/or screened and pasteurized donor human milk if the mother's own milk is insufficient. Feeds are administered every 2 h, starting at 25 ml/kg/day and advancing by 25 ml/kg/day until the infant is gaining weight adequately (approximately 200 ml/kg/day). Once an infant is tolerating full feeds by nasogastric tube, gaining weight, and no longer requiring CPAP, they will transition to feeding by cup and spoon.

VLBW infants are discharged home when they no longer require respiratory support (CPAP or oxygen therapy) or intravenous medications, have safely received their first set of immunizations (Polio, Hepatitis B, and BCG), can maintain normothermia using kangaroo care, are gaining weight using expressed breastmilk taken by a cup and spoon, and weigh a minimum of 1200 g.

Eligibility criteria

Neonates who meet the study inclusion and exclusion criteria are eligible to participate (Table 1).

Participant identification and screening

A trial research assistant will be stationed in the neonatal unit 24 h a day and 7 days a week. When a mother presents to the labor ward and is anticipated to deliver a preterm infant, the research assistant will be informed. The research assistant will then screen the mother for

Table 1 The inclusion and exclusion criteria for the DR-CPAP trial

Inclusion criteria	Exclusion criteria
- Liveborn infant - Spontaneously breathing at 5 min of age - Infants born weighing 800–1500 g - Mother or father who can understand English, Luganda, Ateso, or Lumasaba - Mother or father who are willing and able to give informed, written consent for the participation of their infant in the study - Mother aged 15 years or above - Infants born at Mbale Regional Referral Hospital - Both a BCPAP and a portable CPAP machine are available at the time of recruitment	- 5-min Apgar score ≤ 3 - Need for ongoing ventilation at 5 min after birth - Second or later birth order of a multiple pregnancy when the first or an earlier birth order infant is eligible for participation - Mother and father who can not understand English, Luganda, Ateso or Lumasaba - Mother and father are not willing or are unable to give informed, written consent for participation of their infant in the study within 24 h of delivery - Infants with major congenital abnormality, e.g., gastroschisis, cyanotic heart disease, upper airway abnormality - Infants that receive surfactant during admission

pre-delivery eligibility criteria (Table 1) and approach her for verbal consent using the procedure described below. Upon obtaining verbal consent, a research assistant will be present at the delivery, initiating timing with a stopwatch at birth. If the entry criteria are fulfilled within 5 min after birth and after the determination of the birthweight, the neonate will be randomized (Fig. 1).

Two-stage consent

Clinical trials involving life-saving interventions often face challenges in obtaining prior written informed consent. It is recognized that preterm delivery is a neonatal emergency and a delay in study enrolment and thus treatment of the preterm infant through a consent procedure would be unacceptable. In addition, at the time of delivery, the mother will be recovering and may be potentially unwell herself. Recognizing these constraints, we acknowledge that it is likely to be neither acceptable nor possible to undertake the full informed consent procedure prior to enrolment. Conducting the full informed consent process could significantly delay the treatment allocation and be potentially detrimental to the infant's health. Consequently, we will use a modified form of deferred consent, which has received ethical approval for two trials involving severely ill children in Mbale RRH [41, 42].

In this trial, initial verbal consent for research, including randomization, will be initially gained from the mother and/or father when the mother is presenting in active labor and is expected to deliver a preterm baby. Full written consent will be sought from the mother and/or father after both the infant and the mother are stabilized, and it is confirmed that all inclusion and exclusion criteria are met.

Verbal consent will be obtained by a specially trained researcher. Mothers and/or fathers will be provided with a brief verbal description of the trial and will be given the opportunity to opt into the clinical research. The English version of the verbal consent script is included in Supplement 4. Prior to commencing the verbal consent script, permission from the mother and/or father will be sought to audio record the process. If they agree, the verbal consent process will be audio recorded, and the recording will be uploaded to the Mbale Clinical Research Institute (MCRI) server and stored securely with restricted access to only authenticated and authorized personnel. The undertaking of the audio recording was supported by our Community Advisor Board (CAB). While the audio recordings will not be routinely transcribed, they will be stored for 5 years on the secure server at MCRI, with transcription occurring if concerns or queries arise regarding the verbal consent process.

For infants meeting the inclusion and exclusion criteria, written, informed consent will be sought when the infant has been stabilized, treatment has been initiated and the mother has recovered and is able to receive, evaluate and discuss the information. All mothers will receive a patient information sheet (Supplement 5) in their preferred language containing details of the trial. For those unable to read, the patient information sheet will be read aloud. Mothers will be encouraged to ask questions before signing the consent form and their right of the mother to refuse to participate without giving reasons will be respected.

Fully informed written consent will always be obtained within 24 h. This will be obtained by the Research Assistant or Trial Medical Officer. At this point, the potential participant will be given ample time to consider participation, and the research assistant will involve the mother's family and her partner in the discussion. There will always be another person present during the informed consent process. The patient information sheet will be provided for the mother as well as her partner or next of kin.

Each participant will personally sign or thumbprint and date the latest approved version of the consent form before any further study-specific procedures are performed. It is recognized that some of our mothers and/or fathers may be illiterate or blind. In these instances, the patient information sheet will be read verbatim by the research assistant or trial medical officer and the mother and/or father will consent using their thumbprint. If a mother and/or father who is deaf can communicate via a relative using sign language and would like to participate, they will be able to.

Mothers and/or fathers who have provided verbal consent but are unwilling or unable to provide written informed consent within 24 h after delivery will result in the exclusion of the infant from the trial. No further data will be collected for these infants, and the data already collected will be destroyed. The infant will continue to receive the standard of care in the neonatal unit for the duration of their stay.

The patient information sheet and the consent form will be prepared in English and the three main local languages (Ateso, Lumasaaba, Luganda). The version used will be based on the mother's preference. The research assistant will use a flipchart to present study information to the mother, to facilitate understanding of what is being asked of them. This was shown to be highly effective and liked by the participants of an obstetric study in Mbale (18). For mothers who cannot read, the trial information will be presented in the preferred local language and in the presence of either a friend, a family member, or an independent individual capable of serving as an impartial

witness. Any questions about the study or the consent process will be explained in the mother's preferred language, and she will be encouraged to ask as many questions as they wish. The mother will be assured that she can provide consent at that time and can withdraw it at any time. If the mother is unable to write, then she will be invited to mark her consent on the consent form by placing a thumbprint, with the impartial witness completing the participant's name and date. The research assistant or trial medical officer will sign and date each completed consent form.

For the focus group discussions and key informant interviews, separate participant information sheets and consent forms will be prepared in English and the three main local languages (Ateso, Lumasaaba, Luganda). All mothers, caregivers, and healthcare workers identified as potential participants in the qualitative research will receive a participant information sheet in their preferred language containing details of the study. The English version of the healthcare worker participant information sheet is included in Supplement 6. For those unable to read, the participant information sheet will be read aloud. Participants will be encouraged to ask questions before signing the consent form and the right of a participant to refuse to participate without giving reasons will be respected.

Randomization

The trial will randomly assign neonates in a 1:1 ratio at birth to receive either *early* CPAP (intervention) or standard of care (control). Centralized "third-party" randomization and allocation will be used, with three researchers not involved in the study serving as the randomization coordinators. The lead coordinator will prepare a randomization schedule using http://www.randomization.com/ and store it securely on the MCRI server with exclusive access granted to the randomization coordinators only. Randomly permuted block randomization, using blocks of varying size (4, 6, and 8) will be used to ensure balance between the two arms and enhance concealment in group allocation.

After the identification and consent of a patient, the research assistant will request an allocation from the randomization coordinator by SMS. The coordinator will send the allocation to a study tablet device by email. This method, known for its affordability, speed, and reliability has been shown to be effective [43]. The time on the study phones and the study tablets will be synchronized and the time lapse between the SMS request and the receipt of the allocation will be recorded. Any failures in communication such as internet or phone service unavailability will be documented.

The investigators acknowledge that this method of randomization is novel, and although it is expected to be a more robust method of randomization, it is possible that it may limit the feasibility of initiating the intervention within 15 min of birth. After enrolling 20 participants, the timings of receiving the randomization code and initiating the intervention will be reviewed by the Trial Steering Committee and the Trial Management Group. If it is found that the receipt of the randomization code is found to be limiting the timeliness of the intervention, the randomization coordinator transitions to using serially numbered, sealed, and opaque envelopes. For each eligible patient, the next envelope in sequence will be opened for enrolment into the study.

Interventions

All participants All infants will receive Essential Newborn Care at delivery [44]. Any infants requiring resuscitation at birth will undergo standard neonatal resuscitation procedures (Helping Babies Breathe [45]). As described above, the decision to randomize occurs when the infant is spontaneously breathing 5 min after delivery, there are no major congenital abnormalities observed and the birthweight has been confirmed to be 800 g–1500 g. At this point, a randomization code will be requested. Until the randomization code is available, all infants will continue to receive standard care, including skin-to-skin and administration of oxygen therapy from 5 min of age to maintain pre-ductal oxygen saturation above 80% [46]. Once admitted to the neonatal unit, all infants, regardless of group assignment, will continue to receive the current standard of care under the responsibility of the neonatal team.

Intervention Once an infant is randomized to the intervention group, they will be started on CPAP immediately. The portable CPAP device will ideally be applied within 15 min of delivery using an appropriately sized nasal cannula (RAM cannula®) [32]. The portable CPAP device chosen delivers an FiO2 0.21 at an average pressure of 6 cm H_2O with 80% occlusion of the nares when using the preterm-sized RAM cannulae®. Optional supplementary oxygen from an oxygen cylinder will be added to the portable CPAP device to maintain pre-ductal oxygen saturations above 80% [46]. Infants in the intervention arm will be transferred to the NNU while on portable CPAP with or without oxygen and be changed over to BCPAP on admission to NNU if required (Downes score ≥ 4). As per local guidelines, the distending pressure will be initiated at 5 cm H_2O and adjusted between 2 and 8 cm H_2O depending on Downe's Score and the level of respiratory distress observed (Supplement 3). The FiO_2 will be adjusted from 0.21 to 0.95 to achieve

oxygen saturation of 90–93% in the preterm neonates [21, 47, 48]. These infants will be reviewed every 4 h and CPAP will be discontinued according to local guidelines for initiation of CPAP in neonates (Supplement 3, [35]).

Control Once an infant is randomized to the control group, they will continue to receive optional supplementary oxygen to maintain oxygen saturations above 80%. Oxygen will be administered with a standard oxygen cannula using an oxygen cylinder. If needed, neonates in the control arm will be transferred on oxygen to the NNU and transitioned to oxygen therapy at admission. Subsequently, they will continue to receive the current standard of care, which is the application of BCPAP if Downe's Score ≥ 4 [36, 38]. As per local guidelines, the distending pressure will be initiated at 5 cm H_2O and adjusted between 2 and 8 cm H_2O depending on Downe's Score and the level of respiratory distress observed. The FiO_2 will be adjusted from 0.21 to 0.95 to achieve oxygen saturations of 90–93% in the preterm infants [21, 47, 48].

Blinding

Due to the nature of the intervention, it is not possible to blind mothers, caregivers, or hospital staff. Permuted block randomization will be performed by a randomization coordinator (a researcher who is not involved in the study). The coordinator will prepare the randomization schedule using http://www.randomization.com/ and then it will be stored on a secure server at MCRI, with access limited to only two randomization coordinators. Only after obtaining verbal consent and confirming a patient's eligibility post-delivery, will the research assistant request an allocation code from the randomization coordinator, this will prevent selection bias. Trial data will be analyzed on an intention-to-treat basis including all eligible patients.

The independent assessments of the lung ultrasounds, echocardiograms, and cranial ultrasounds will be undertaken by three expert assessors, blinded to the clinical details and outcomes of the infants.

Data collection

One of the objectives of the feasibility study is to evaluate the most suitable primary and secondary outcome measures. Various outcome measures will be documented, including ultrasound imaging, anthropometric measurements, clinical data, and treatments required. Data collection will primarily be on electronic case report forms that will be created using the REDcap software package (Vanderbilt University, USA) on dedicated study tablets. The study data collected for each participant will be in two categories:

- Paper-based data containing personal information including address and personal identifiers and consent forms. These will be securely stored at the MCRI offices in Mbale in a separate location from the other data.
- All other data will be collected in the REDCap software which has been installed on encrypted, android tablets. These data will be automatically uploaded to a secure server based in MCRI, Mbale, Uganda when connected to the internet. Ugandan regulations will be adhered to when transferring data.

Medical records will be reviewed daily by the research team to collect data. The data collected are shown in Table 2.

Qualitative research

This project will undertake formative qualitative work to determine the acceptability of the trial design. The trial social scientist will oversee this process, which will be undertaken by the trial qualitative researcher. The qualitative researcher will be proficient in the local language and experienced in conducting qualitative research.

Key informant interviews (KII) with healthcare workers will consist of a minimum of 10 KIIs. To give representative views, the key informants will be purposively selected to include midwives, nurses, specialist and non-specialist doctors, and anesthetic officers. Ideally, we will select those with experience in providing neonatal care, care of preterm neonates, and/or management of preterm deliveries. Health worker acceptability of the trial design will be explored in three broad themes: (1) perceived usefulness of *early* CPAP in addressing preterm mortality, (2) ease of use of the portable CPAP, and (3) suitability of using *early* CPAP in a low-resource setting. We will summarize acceptability in the three themes using frequencies. Findings from the FGDs will be triangulated using information from the KIIs.

Focus group discussions (FGD) with the healthcare workers exposed to the trial will involve a minimum of four FGDs, each with up to twelve participants. The FGDs will include health workers in the labor suite and the neonatal unit who have been exposed to the trial. We will ensure that no FGD has less than six participants to guarantee the most reliable results. The study team will maintain a record of all healthcare workers present at the delivery, transfer, and admission of participants to the neonatal unit, and these healthcare workers will be invited to participate in FGDs.

Table 2 Maternal, perinatal, and neonatal data to be collected for each participant

Area	Data to be collected
Maternal	Age, parity, HIV status, antenatal attendance, last normal menstrual period, expected delivery date, time/date of rupture of membranes, time/date of onset of labor, dexamethasone administration, antibiotic administration
Birth	Time/date of birth, type of delivery, condition at birth, type of resuscitation required, medications administered at birth, time CPAP initiated if in the intervention arm
Neonatal	Time of admission to the neonatal unit, vital signs (heart rate, blood pressure, respiratory rate, oxygen saturation, and temperature), weight, length, and occipital-frontal circumference on admission to the neonatal unit, medications given at admission and during the stay, respiratory support given at admission and during the stay
Respiratory Distress Syndrome	The level of respiratory distress will be evaluated using the Downe's Score (Supplement 1) [36]. The Downe's score will be recorded every 4 h until CPAP is discontinued. Downe's score includes 5 criteria: respiratory rate, retractions, cyanosis, air entry, and grunting. Each of these is rated on a scale of 0, 1, 2. The total score is then evaluated as no respiratory distress (< 4), respiratory distress (4–7), and impending respiratory failure (> 7)
Cardiology	Evidence of haemodynamically significant patent ductus arteriosus (hsPDA) in echocardiogram performed at 72 h. The M-Turbo Sonosite™ will be used together with a p10x cardiac probe (4-8MHx). All doctors in the study will be trained by the study cardiologist to perform bedside echocardiograms. All practitioners who perform echocardiograms will follow the same protocol of standard transthoracic views including the subcostal, parasternal long and short axis views, and the ductal view. The ductal view will confirm the diagnosis of PDA. A local reading of the echocardiogram will be done by the clinical team and the neonate will be treated as per local protocols. Videos of each echocardiogram will be recorded and shared with the cardiologist for evaluation of the presence of hsPDA. A hsPDA will be defined if left-to-right shunting through the PDA is accompanied by two left atrial to the aortic root (LA:Ao) ratio of ≥ 1.5, and/or retrograde diastolic flow in the descending aorta, and/or a moderate to large PDA ≥ 1.5 mm, and/or increased LV end-diastolic diameter z-score for age, weight, and length. The cardiologist will be blinded to any demographic or clinical details of the neonate and the trial allocation group
Blood pressure	The diastolic and systolic blood pressure will be measured and recorded daily
Brain imaging	Cranial ultrasound examinations will be performed on day 1, day 3, day 7, and day 28 or at discharge if earlier. The ultrasound images will be evaluated for evidence and grade of any intraventricular hemorrhage. The M-Turbo Sonosite ™ will be used together with a curvi-linear (Cx11) probe. All doctors in the study will be trained to perform a cranial ultrasound by a senior neonatologist with extensive experience in performing and interpreting cranial ultrasounds. All practitioners who perform cranial ultrasounds will be taught to follow the same protocol and record a standard set of coronal and sagittal images via the anterior fontanelle Images with be saved and shared with the senior neonatologist for evaluation of the presence of IVH and cerebellar hemorrhage. The transverse cerebellar diameter (TCD) will be measured as an indicator of gestational age [49]. The neonatologist will be blinded to any demographic or clinical details of the neonate and the trial allocation group. The severity of the IVH will be graded using the following Papile criteria [50]: • *Grade 1:* Bleeding confined to the germinal matrix • *Grade 2*: Bleeding into the lateral ventricle but not causing ventricular distension • *Grade 3*: Bleeding into the lateral ventricle causing acute ventricular dilation • *Grade 4:* Haemorrhagic parenchymal infarction
Lung ultrasound	Lung ultrasound (LUS) will be performed on admission and daily thereafter until CPAP is discontinued. LUS will be evaluated for evidence of respiratory distress syndrome, consolidation, pleural effusion, and pneumothorax [51]. The M-Turbo Sonosite ™ will be used together with a high-resolution linear probe (SLAx). All doctors in the study will be trained to perform a lung ultrasound by an anaesthesiologist with experience in performing and interpreting lung ultrasounds. All practitioners who perform lung ultrasounds will be taught to follow the same protocol. Videos will be saved and shared with the anaesthesiologist for evaluation of the presence of lung pathology. The anesthesiologist will be blinded to any demographic or clinical details of the neonate and the trial allocation group. The LUS will be assessed for the presence or absence of pneumothorax and given a LUS score. The LUS will be scored by dividing each lung into 3 areas and scoring each area from 0 to 3 depending on the 4 different patterns that can be seen [51]
Nasal septal erosions	Evaluated at randomization to allow baseline documentation of the nasal septum in all infants. In the intervention infants, the septum will be evaluated when the portable CPAP is discontinued, either to stop CPAP completely or to change to BCPAP. The septum will then be evaluated daily until CPAP is weaned. Severity will be documented in the CRF with an accompanying photo. The septal erosions will be graded using the following criteria: 1. Nil 2. Erythema or pressure indentation 3. Superficial erosion 4. Septal necrosis
In hospital survival	Time and date of death or date of discharge will be recorded. Infants will be followed up until 28 days

FGDs with mothers and fathers will include a minimum of 4 FGDs of up to 12 participants each. These FGDs will be undertaken with mothers and fathers of infants enrolled in the trial to evaluate their acceptability of the two-step consent process. We will ensure that no FGD has less than 6 participants to guarantee the most reliable results. To give representative views, the participants will be purposively selected to include mothers and

fathers, various modes of delivery, and parents whose infants were enrolled in both the control and intervention groups. Once enough participants are available in the Neonatal Unit, a FGD will be organized.

Topic guides will be developed for the different KIIs and FGDs and will be modified according to the preliminary findings. Data will be collected in either a local language or English by a trained interviewer in a neutral location. All FGDs will be audio-recorded, transcribed, and translated independently. The transcripts will be analyzed using NVivo software.

Community and patient group involvement in project implementation

The MRRH-NNU has an established preterm Community Advisory Board (CAB), within which the trial community and patient group activities will be conducted. These activities will include meetings with mothers and caretakers of infants and key community members, at the beginning, midway, and the end of the study, where the trial design, protocol development, and acceptability of the DR-CPAP trial will be discussed.

Outcomes

Primary outcomes

The feasibility and acceptability outcomes of this pilot study are designed to inform the development of a larger trial, namely:

- To assess the *acceptability* of the DR-CPAP trial to mothers and healthcare workers in a low-resource setting
- To assess the post-intervention *acceptability* of using a two-stage consent process in neonatal emergencies in the delivery room in this setting
- To evaluate the *feasibility* of a third-party allocation process for randomization by determining the time to randomization and the number of patients randomized within 15 min of delivery
- To evaluate *feasibility* of initiating *early* CPAP in a low resource setting in infants with birthweight 800–1500 g within 15 min of delivery. We shall conclude feasibility when 80% of infants < 1500 g in the intervention arm are initiated on CPAP within 15 min of delivery
- To evaluate the *safety* of initiating *early* CPAP in a low-resource setting defined by the absence of increased in-hospital mortality rate during the study period compared to the baseline mortality rate for the study population in the previous 12 months, in addition to the feasibility outcome measures and adverse event reporting described below
- To estimate the sample size to be used for future evaluation in the full trial
- To assess the *feasibility* of outcome measures to be used in the future trial by evaluating the number of patients with primary and secondary outcomes measured successfully, including:
- Neonatal mortality-death before 28 days of age
- Total time on CPAP (days)
- High-grade (grades III and IV) intraventricular hemorrhage on cranial ultrasound before 7 days of age
- Hemodynamically significant patent ductus arteriosus on echocardiogram at 72 h of age
- Significant nasal septal erosions (superficial erosion or septal necrosis) daily until CPAP is weaned
- Pneumothorax on lung ultrasound
- Bronchopulmonary dysplasia—need for supplemental oxygen for ≥ 28 days
- Length of hospital stay (days)

Participants will be followed up daily until day 28 of age, or until death or discharge if this occurs earlier. The schedule and timings of enrolment, intervention, and outcome measures are summarized in Table 3.

Sample size

For a feasibility trial, it is not necessary to conduct sample size calculations to power the study [52]. A randomized sample size of $n = 100$ ($n = 50$ per arm) was considered appropriate for this feasibility and acceptability study. This pilot study will provide data to support sample size calculations for a subsequent trial. We anticipate that in the future, a total of 600 patients (300 per arm) would be required to achieve an 80% power in detecting a reduction in deaths by one-third from the current mortality rate of 27% (for infants < 1500 g) to 17% at a 5% level of significance level, assuming a 10% loss to follow-up.

Qualitative data

Acceptability of DR-CPAP to mothers, caregivers, and healthcare workers

This will be measured on (1) the perceived usefulness of DR-CPAP in addressing pre-term mortality, (2) ease of use of the DR-CPAP, and (3) suitability of using the DR-CPAP in a low-resource setting. These will be captured among the health workers exposed to the DR-CPAP using focus group discussions and key informant interviews. Interviews will be transcribed, translated, coded, and imported into the latest version of Nvivo software. Data will be coded using thematic coding and then analyzed and used for generating conclusions on the acceptability and feasibility of using DR-CPAP. Findings from the FGDs will be triangulated using information from the key informant interviews.

Table 3 Summary of enrolment, interventions, and assessments across the study period

	Responsible individual				
Study procedure	Trial research assistant	Trial medical officer	Cardiologist	Perinatal neurologist	Anesthesiologist
Initial approach and expression of interest	x				
Verbal consent	x				
Application of DR-CPAP	x				
Informed consent	x	x			
Demographic data collection	x	x			
Birth data collection	x	x			
Neonatal data collection	x	x			
Echocardiogram at 72 h		x	x		
Blood pressure at time of echo	x	x			
Cranial ultrasound days 1, 3, 7, and 28		x		x	
Lung ultrasound daily whilst on CPAP		x			x
Downe's Score 4 hourly whilst on CPAP	x	x			

Acceptability of using a two-stage consent process

The level of acceptability of using deferred consent will be analyzed using the proportion of mothers enrolled in the DR-CPAP study who uphold (do not withdraw) consent after the intervention. We will also conduct focus group discussions with mothers enrolled in the DR-CPAP study to capture their satisfaction, attitude, and perceptions of using the DR-CPAP. Interviews will be transcribed, translated, coded, and imported into the latest version of Nvivo software. Data will be coded using thematic coding and then analyzed.

Data analysis

The CONSORT reporting guidelines will be used to guide the presentation of trial outcomes. All quantitative data from the study will be analyzed descriptively in concordance with the CONSORT extension for pilot and feasibility trials [53]. All analyses will be performed with standard statistical software (SAS version 9.4 or later). The final analysis datasets, programs, and outputs will be archived as part of the Essential Documents set in accordance with Good Clinical Practice.

A statistical analysis plan (SAP), prepared by the study statisticians and agreed with the principal investigator (PI) and the trial management group (TMG), has been written. The key planned analyses are described below and the SAP, containing a detailed and comprehensive description of the pre-planned final analyses for the DR-CPAP trial, is included in Supplement 7. The results of the final analysis described within the SAP will be contained in a statistical analysis report. This report will be used as the basis of the primary research publications according to the study publication plan.

Feasibility of carrying out a larger trial

The feasibility and acceptability of the pilot trial will be evaluated to inform the progression to a large randomized controlled trial (RCT). A summary of these quantitative and qualitative data and predefined criteria are given below. The outcomes of the pilot will help refine the protocol for a future definitive RCT.

Acceptability and feasibility

In brief, analysis of primary feasibility and acceptability outcomes will include the following:

Acceptability of DR-CPAP to mothers, caregivers, and healthcare workers

The intervention will be considered acceptable when the majority of respondents perceive DR-CPAP to be useful in addressing preterm mortality; easy to use, and suitable for a low-resource setting. Their responses will help improve the acceptability of the protocol and the intervention for the future RCT.

Acceptability of using a two-stage consent process

The use of the two-stage consent process will be considered acceptable if ≥ 95% of mothers enrolled in the DR-CPAP study uphold (do not withdraw) consent after the intervention. The two-stage consent process will be considered acceptable when the majority of mothers are satisfied, have a positive attitude, and perceive the process

to be acceptable. Their responses will aid the refinement of the consent process for the future RCT.

Feasibility of enrolment in the study

The proportion of mothers in suspected preterm labor who are screened verbally consented, and recruited will be reported. Our criterion for success is the enrolment of ≥ 80% of eligible mothers.

Feasibility of third-party randomization within 15 min of delivery

The duration (in minutes) from the time of delivery of the infant to the time the SMS request is sent to the randomization coordinators; the time from the SMS request to the time the randomization allocation email is received from the randomization coordinator on the study tablet and the total time from birth to randomization will be used to evaluate the suitability of a third-party allocation process for randomization. We shall compute the mean and standard deviation of the duration of these times if normally distributed; otherwise, we shall report the median and interquartile range. We will also evaluate third-party randomization feasibility by determining the proportion of infants randomized within 15 min of delivery. We will conduct a one-sided *t*-test to determine if the mean duration (average time from birth to randomization allocation) is significantly less than 15 min. We shall conclude feasibility when ≥ 80% of infants are randomized within 15 min of delivery.

Feasibility of initiating DR-CPAP within 15 min of delivery

We shall measure the feasibility of initiating prophylactic CPAP in the delivery room (DR-CPAP) in infants with birth weight 800–1500 g using time from birth to the time of DR-CPAP initiation. Ideally, this is within 15 min of birth. For infants in the intervention arm, we will record the time that DR-CPAP is initiated and compute the average duration from delivery to initiation. We will conduct a one-sided *t*-test to test if the average DR-CPAP initiation time is less than 15 min. We will estimate the proportion of infants in the intervention who are initiated on DR-CPAP within 15 min of delivery. We shall conclude feasibility when ≥ 80% of infants < 1500 g in the intervention arm are initiated on DR-CPAP within 15 min of delivery. We will document any causes of delays in initiating DR-CPAP such as randomization, verbal consent, and resuscitation.

Study governance

The Trial Management Team comprises the PI, Trial Coordinator, and Research Assistants (RA). Weekly meetings will be held between the PI, Trial Coordinator, and Research Assistants. The TMG includes the PI, Trial Coordinator, co-investigators, and Collaborators, convening monthly to discuss project progress and management.

The project has undergone review by three research ethics committees. Initially, local approval was obtained from the Mbale Regional Referral Hospital Research Ethics Committee (MRRH-REC) for approval to undertake this research study (Approval ID: MRRH REC 123). MRRH-REC is mandated by the Uganda National Council of Science and Technology (UNCST) to offer Ethical Approval for research involving human subjects in Uganda. Subsequently, the trial was approved by UNCST (Approval ID: HS2605ES)**.** Lastly, in alignment with the funder's requirements, ethical opinion was sought from a UK Research and Ethics Committee, resulting in a favorable ethical opinion from the Liverpool School of Tropical Medicine Research Ethics Committee. Any amendments required will be approved by MRRH-REC and communicated to UNCST and the trial sponsor.

A Trial Steering Committee (TSC) has been appointed with an independent chairperson and two additional independent members, together with two study members: the PI and the senior study statistician. The independent TSC members were approved by the trial funder, all being neonatologists with experience in clinical research, and one member is based in East Africa. The TSC holds overall executive decision-making powers and strategic responsibility for the study in accordance with its charter. Due to geographic distances between the partner organizations this meeting will be conducted via teleconference/Zoom.

The TSC convened three times during the protocol creation to provide advice and guidance on trial design. Throughout the project, the TMG will meet with the TSC every 6 months to discuss trial progress and seek advice on key methodological issues, safety, progress, and dissemination.

Safety

All research and clinical staff involved in the care of the study participants will be trained on the safe application and use of both the portable CPAP and the bubble CPAP machines that are in use in Mbale RRH-NNU.

The safety of the infants participating in this study is paramount. Safety data on the infants will be collected (including adverse events (AEs) and serious adverse events (SAEs)). The key participants in this study are VLBW infants, and adverse events that could be influenced by the trial interventions are outcomes of the study. Data on these events will be recorded on the Case Report Forms (CRFs).

All SAEs will be reported to the PI/Sponsor within 24 h of the research team becoming aware of it. Although

neonatal death is one of the outcomes of this study and is likely to be a common outcome (current mortality for this high-risk group is 27% in MRRH-NNU), it will still be considered as a serious adverse event (SAE) and reported to the required regulatory authority within 7 days of becoming aware of the event.

Given the high risk of co-morbidities in infants < 1500 g, events that occur that are life-threatening or other important medical events will not require expedited reporting as an SAE to regulatory and/or governance bodies, i.e., MRRH-REC, Sponsor unless it is considered to be potentially related to the study interventions. SAEs that will require expedited reporting will include but are not limited to, pneumothorax, hypoxia not relieved by supplementary oxygen, severe respiratory distress defined as Downe's Score of 8–10, and respiratory arrest. All related SAEs will be followed until there is a resolution or the event is considered stable and collated for reporting. Other unrelated SAEs will be recorded but will not require the following.

Dissemination

We have developed a comprehensive dissemination strategy that aims to share the trial results not only with the local preterm community but also with national policymakers, the national newborn steering committee, and academic audiences. A detailed scientific report will be crafted and submitted to a widely accessible scientific journal. The writing team will consist of the principal investigator and members of the trial team. All writing team members will comply with internationally agreed requirements for authorship and will review and approve the final manuscript prior to submission. Results will be presented locally and will be disseminated nationally by presentation at an annual scientific conference.

To ensure broader coverage, we will host at least two online webinars to share the outcomes of the study. These webinars will be shared with preterm support groups in Uganda, advertised on social media, and promoted through the Uganda Paediatric Association and the National Neonatal Sub-Committee. Additionally, a local dissemination event involving key stakeholders and preterm support groups will also be organized.

Discussion

This pilot trial aims to enhance our understanding of methods and techniques to conduct emergency neonatal research effectively, affordably, and acceptably in low-resource settings. Given that, nearly all neonatal deaths occur in LICs, with three-quarters of neonatal deaths happening within the first 7 days after birth and the highest risk of death is on the first day of life, improving our approach to this area of research is paramount to reducing global neonatal mortality [54, 55]. Collaborating with families and healthcare workers caring for sick and small neonates is essential in this endeavor. The mixed-methods approach adopted in this trial provides a robust platform for exploring parental and healthcare worker perceptions, experiences, and acceptance of both the intervention and the trial design. Specifically, this pilot trial will test the feasibility of a low-cost third-party allocation process for randomization, a method, known for its affordability, speed, and reliability [40]. Although stratification by weight (< 1000 g, 1000– < 1500 g) was not undertaken in this pilot, our randomization procedure supports this approach and will be considered in the larger RCT. We will describe our experience of adopting such a method for emergency neonatal research in a low-resource setting. Through focus group discussions and key informant interviews, we will improve our understanding of the maternal, caregiver, and healthcare worker perceptions of the use of early CPAP in the delivery room. This will be key to ensuring the acceptability and uptake of both a larger trial and the future uptake of the intervention if it proves to be beneficial. Neonatal emergency research is often neglected, in part due to the challenges of acquiring informed consent at a challenging time. Our pilot study will explore if the two-step consent process is acceptable to mothers and fathers in this emergency situation, and allow us to ensure a suitable method of consent can be used in our future trial and other similar neonatal emergency trials. Although this is a pilot trial, and therefore not powered to detect differences in outcomes between the randomization groups, it will explore the feasibility of measuring all potential outcomes to support the design of a future larger trial. Overall, the insights gained from this pilot trial will offer critical knowledge on the acceptability and feasibility of methods and outcomes, serving as the groundwork for a definitive randomized control trial in the future.

Trial status

This paper refers to protocol version 1.3 dated 13 October 2023. Recruitment began in April 2023 and is anticipated to be complete by the end of April 2024. Post-intervention assessments are therefore expected to be complete by the end of June 2024.

Abbreviations

BCPAP	Bubble continuous positive airway pressure
CPAP	Continuous positive airway pressure
DR-CPAP	Delivery room continuous positive airway pressure
FGD	Focus group discussion
HIC	High-income country
IVH	Intraventricular hemorrhage
KII	Key informant interview
LMIC	Low- and middle-income country
MCRI	Mbale Clinical Research Institute
MRRH	Mbale Regional Referral Hospital

NMR	Neonatal mortality rate
NNU	Neonatal Unit
PDA	Patent ductus arteriosus
PI	Principal investigator
RCT	Randomized controlled trial
RDS	Respiratory distress syndrome
TMG	Trial Management Group
TMT	Trial Management Team
TSC	Trial Steering Committee
VLBW	Very low birthweight

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40814-024-01552-x.

Additional file 1: Supplement 1: The Downes Scoring system (adapted from Ehret et al). Supplement 2: Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 checklist. Supplement 3: Guideline for initiation of CPAP in neonates (adapted from Ehret et al.). Supplement 4: The English version of the verbal consent script. Supplement 5: Patient information sheet. Supplement 6: English version of the healthcare worker participant information sheet. Supplement 7: A detailed and comprehensive description of the pre-planned final analyses for the DR-CPAP trial.

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Sponsor
The trial sponsor will be Mbale Clinical Research Institute (MCRI).

Authors' contributions
KB conceived the trial. KB, JMS, AN, and FO designed the trial and wrote the protocol. KB, JMS, AN, FO, AgN, CH, JN, AHS, KL, AD, JW, and POO critically reviewed the study protocol before submission for ethical approval. KB, JMS, FO, MM, GA, and AD designed the data collection tools. KB, AN, AgN, and MM designed the topic guides for the qualitative research. KB wrote the first draft of the manuscript and all authors critically revised, read, and approved the final manuscript.

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Availability of data and materials
Study materials are available upon request.

Declarations

Ethics approval and consent to participate
The study has been given ethical approval bythe Mbale Regional Referral Hospital research ethics committee (MRRH-REC, 123) and Uganda National Council of Science and Technology (UNCST, HS2605ES)**.** In alignment with the funder's requirements, ethical opinion was sought from a UK Research and Ethics Committee, resulting in a favorable ethical opinion from the Liverpool School of Tropical Medicine Research Ethics Committee.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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