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Respiratory support with standard low-flow oxygen therapy, high-flow oxygen therapy or continuous positive airway pressure in adults with acute hypoxaemic respiratory failure in a resource-limited setting: protocol for a randomised, open-label, clinical trial – the Acute Respiratory Intervention StudiEs in Africa (ARISE-AFRICA) study

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ABSTRACT

Rationale Acute hypoxaemic respiratory failure (AHRF) is associated with high mortality in sub-Saharan Africa. This is at least in part due to critical care-related resource constraints including limited access to invasive mechanical ventilation and/or highly skilled acute care workers. Continuous positive airway pressure (CPAP) and high-flow oxygen by nasal cannula (HFNC) may prove useful to reduce intubation, and therefore, improve survival outcomes among critically ill patients, particularly in resource-limited settings, but data in such settings are lacking. The aim of this study is to determine whether CPAP or HFNC as compared with standard oxygen therapy, could reduce mortality among adults presenting with AHRF in a resource-limited setting.

Methods This is a prospective, multicentre, randomised, controlled, stepped wedge trial, in which patients presenting with AHRF in Uganda will be randomly assigned to standard oxygen therapy delivered through a face mask, HFNC oxygen or CPAP. The primary outcome is all-cause mortality at 28 days. Secondary outcomes include the number of patients with criteria for intubation at day 7, the number of patients intubated at day 28, ventilator-free days at day 28 and tolerance of each respiratory support.

Ethics and dissemination The study has obtained ethical approval from the Research and Ethics Committee, School of Biomedical Sciences, College of Health Sciences, Makerere University as well as the Uganda National Council for Science and Technology. Patients will be included after informed consent. The results will be submitted for publication in peer-reviewed journals.

Trial registration number NCT04693403.

Protocol version 8 September 2023; version 5.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This trial is being conducted in resource-limited areas of Uganda (very limited or no access to Intensive Care Services) which are representative of resource-limited settings.
⇒ A hard endpoint, namely mortality, will be used to evaluate the efficacy.
⇒ We propose a stepped wedge design, a pragmatic methodology that can reconcile the need for robust evaluations with ethical and/or logistical constraints.
⇒ The blinding of patients and investigators to the interventions during the study is not possible.

INTRODUCTION

Background and rationale

The most common reason for intensive care unit (ICU) admission globally is respiratory support for acute hypoxaemic respiratory failure (AHRF). Research evidence for recommendations in patients with AHRF has been mainly gathered from investigations in

high-income countries (HICs).[1 2] This evidence may not be applicable to resource-limited settings.[3]

Continuous positive airway pressure (CPAP) is a simple to use and affordable technique for noninvasive ventilatory support. In a study conducted in a small sample of patients with AHRF in an HIC, CPAP achieved early physiological improvement.[1] More recent studies suggest its potential in reducing intubation rates in COVID-19-related AHRF.[4]

The Boussignac CPAP device (Vygon) is an open system which is easy to use and compatible with all non-invasive ventilation (NIV) face masks. Pressure is generated by a standard gas flow passing through microcapillaries (located all around the CPAP device) increasing its speed and generating turbulence, therefore, creating a 'virtual valve'. This technique offers multiple advantages for respiratory support in addition to not needing a ventilator or electricity to work.[5 6] Although different CPAP systems were used in previous studies, the Boussignac is particularly well suited for constrained settings and situations.[7]

High-flow oxygen through a nasal cannula (HFNC) may also offer an efficient alternative in patients with hypoxaemia. During HFNC, heated and humidified oxygen is delivered to the nose at flow rates as high as 60 L/min, allowing clinicians to better match the inspiratory demands of patients with AHRF. These high-flow rates also generate low levels of positive pressure in the upper airways, and the fraction of inspired oxygen (FiO_2) can be adjusted by changing the fraction of oxygen in the driving gas. HFNC has been shown to result in better comfort and oxygenation than standard oxygen therapy delivered through a face mask in patients with AHRF.[8] In a study conducted in patients with AHRF in an HIC, HFNC achieved better survival as compared with standard oxygen and NIV.[9] In COVID-19-related AHRF, HFNC also proved useful in reducing intubation rate in HICs.[10] A recent HFNC device integrates a flow generator (Airvo, Fisher and Paykel) that uses ambient air to deliver high flow of warmed and humidified gases to spontaneously breathing patients, a feature particularly interesting in resource-limited settings.

To our knowledge, the effect of Boussignac CPAP and HFNC on major outcomes has not been assessed in adults with AHRF in resource-limited settings.

Hypothesis

We hypothesise that both CPAP (using the Boussignac device) and HFNC (using the Airvo device) may prove useful in reducing mortality in AHRF patients in resource-limited settings where the access to invasive mechanical ventilation (MV) and/or highly skilled acute care workers is scarce.

OBJECTIVES

Primary objective

The primary objective is to assess the efficacy of CPAP or HFNC in improving 28-day survival in patients with AHRF.

Secondary objectives

Secondary objectives are to determine the feasibility, safety, tolerance and comfort of CPAP and HFNC and evaluate the impact of CPAP and HFNC on morbidity, including the need for intubation, ventilator-free days, organ dysfunction and hospital length of stay.

CLUSTER	P1	P2	P3	P4	P5	P6	P7	P8	P9
1	OXYGEN	HFNC	HFNC	HFNC	HFNC	HFNC	HFNC	HFNC	HFNC
		CPAP	CPAP	CPAP	CPAP	CPAP	CPAP	CPAP	CPAP
2	OXYGEN	OXYGEN	HFNC	HFNC	HFNC	HFNC	HFNC	HFNC	HFNC
			CPAP	CPAP	CPAP	CPAP	CPAP	CPAP	CPAP
3	OXYGEN	OXYGEN	OXYGEN	HFNC	HFNC	HFNC	HFNC	HFNC	HFNC
				CPAP	CPAP	CPAP	CPAP	CPAP	CPAP
4	OXYGEN	OXYGEN	OXYGEN	OXYGEN	HFNC	HFNC	HFNC	HFNC	HFNC
					CPAP	CPAP	CPAP	CPAP	CPAP
5	OXYGEN	OXYGEN	OXYGEN	OXYGEN	OXYGEN	HFNC	HFNC	HFNC	HFNC
						CPAP	CPAP	CPAP	CPAP
6	OXYGEN	OXYGEN	OXYGEN	OXYGEN	OXYGEN	OXYGEN	HFNC	HFNC	HFNC
							CPAP	CPAP	CPAP
7	OXYGEN	OXYGEN	OXYGEN	OXYGEN	OXYGEN	OXYGEN	OXYGEN	HFNC	HFNC
								CPAP	CPAP
8	OXYGEN	OXYGEN	OXYGEN	OXYGEN	OXYGEN	OXYGEN	OXYGEN	OXYGEN	HFNC
									CPAP

Figure 1 Trial design. CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula; P, period.

ANCILLARY STUDIES

There are three ancillary studies in patients included in the ARISE trial, with the following objectives: (1) to scrutinise their lung ultrasound profile[11]; (2) to examine their respiratory sample biology[12] and (3) to assess the oxygen consumption, economic and environmental impact of the three respiratory support strategies.

METHODS AND ANALYSIS

Trial design

The ARISE-AFRICA study is a cluster, randomised, controlled trial using a stepped wedge design (figure 1)[13] at participating hospitals in Uganda. Hospitals will be divided into eight different clusters. At baseline, all hospitals will simultaneously start with the control period (standard oxygen). The order in which a cluster will move to the intervention period (CPAP or HFNC) will be randomised. At the end of every study period, the CPAP and HFNC treatment will be implemented in an additional cluster after training. From that point on, the CPAP and HFNC treatment will be part of the standard care in that cluster. All patients included during the intervention period will be randomised on an individual basis between CPAP and HFNC. Every cluster will participate for the entire study period. The anticipated duration of each period is 1–2 months, but this time frame could be adjusted based on the actual number of patients enrolled during the first month. The blinding of patients and investigators to the interventions during the study is not possible given the nature of the interventions.

Study setting

The trial will be conducted at 17 trial sites across Uganda. Enough patients will be randomised to bring the total number of evaluable patients to at least 504 in the entire trial programme (see the 'Sample size and its justification' section). To achieve the required number of patients within the given timelines, we are considering one to three hospitals per cluster to actively participate in the trial.

Eligibility criteria

Inclusion criteria

All consecutive patients 18 years of age or older will be enrolled if they meet the following criteria:

- De novo acute respiratory distress, as defined by dyspnoea, use of accessory respiratory muscles and a respiratory rate of 25 breaths per minute or more.
- Hypoxaemia, as defined by a ratio of the partial pressure of arterial oxygen (PaO_2) to the FiO_2 of less than 300 mm Hg. FiO_2 will be measured by a portable oxygen analyser that will be introduced in the non-rebreather face mask or estimated from the 3% formula[14] if the oxygen analyser is not available. If arterial blood gases are not available, an SpO_2/FiO_2 ratio <315 will be considered for inclusion.[15 16]
- Informed consent was obtained in accordance with local regulations.

Non-inclusion criteria

- Exacerbation of asthma, chronic obstructive pulmonary disease or another known or suspected chronic respiratory disease.
- Absolute contraindications to CPAP or HFNC, including any of the following: patient not cooperating or opposing the technique, pneumothorax not drained, chest wound blowing, uncontrollable vomiting, upper gastrointestinal bleeding, craniofacial trauma, severe upper airway obstruction, traumatic tetraplegia at the initial phase.
- Cardiac arrest; severe ventricular arrhythmia; shock defined by the need for vasopressors (dopamine >5 µg/kg/min or epinephrine or norepinephrine at any dose).
- Altered consciousness (Coma Glasgow Score below 12 points).
- Do not intubate order, do not resuscitate order or decision to limit full care taken before obtaining informed consent.
- Refusal to participate, prior enrolment in the trial, participation in another interventional study on respiratory distress.

Study interventions

In all groups

Within 3 hours after the validation of selection criteria, patients will be assigned to the allocated strategy (oxygen or CPAP or HFNC) after having signed informed consent. In all groups, the oxygen flow will be adjusted to maintain an oxygen saturation level of 92% or more, as measured by means of pulse oximetry (SpO_2). All patients with suspected cardiac insufficiency will receive diuretics as required. Infectious causes will be treated with antibiotics, according to the Uganda Clinical guidelines. Staff at the site will administer the respiratory support under the supervision of the site investigator. Any omission of study treatment will be recorded in the case report form (CRF) to monitor treatment compliance.

Standard oxygen treatment

Patients assigned to the standard treatment group will receive oxygen delivered through nasal prongs, face masks or a non-rebreather face mask (choice depending on the need) until endotracheal intubation, death or fulfilment of oxygen delivery cessation criteria (an SpO_2 above 92% without oxygen and a respiratory rate below 25 cycles/min).

CPAP treatment

Patients assigned to the CPAP plus oxygen group will receive periods of CPAP in addition to the standard treatment. All study centres will use a Boussignac device (Vygon) connected to an oro-nasal mask composed of a transparent mask and a soft inflatable cushion. CPAP will be started at 7.5 cm H_2O. The level will be decreased to

5 cm H_2O or increased to 10 cm H_2O as needed based on the clinical response and tolerance. For at least the first 6–12 hours, CPAP will be given continuously and then discontinuously (for at least 6 hours/day) based on patient tolerance.[1] CPAP will be continued until endotracheal intubation, death or fulfilment of the following cessation criteria: SpO_2 above 92% and respiratory rate below 25 cycles/min with FiO_2 of 30% or less and a CPAP level of 5 cmH_2O. The criteria for oxygen delivery cessation will be the same as in the standard therapy group.

HFNC treatment

In the HFNC group, oxygen will be delivered through a heated humidifier (Airvo-2/3, Fisher and Paykel Healthcare) and applied continuously through large-bore binasal prongs, with a gas flow rate of 50 L/min and adjusted based on the clinical response. FiO_2 will be adjusted for the target SpO_2. HFNC will be continued until endotracheal intubation, death or fulfilment of the following cessation criteria: SpO_2 above 92% and respiratory rate below 25 cycles/min with a FiO_2 of 30% or less and a gas flow of up to 30 L/min. The criteria for oxygen delivery cessation will be the same as in the standard therapy group.

Endpoints

Primary endpoint

The primary endpoint for efficacy at the end of the study is 28-day mortality. The choice of survival as the primary efficacy endpoint is based on the persistently high mortality of AHRF in low-income settings. Mortality is indisputably a critical endpoint to consider in these patients.

Secondary endpoints

Percentage of patients with criteria for intubation at day 7

The predetermined criteria for endotracheal intubation and MV will include respiratory failure, circulatory failure or neurological failure and will be established as follows[9]:

- Respiratory failure: signs of persisting or worsening respiratory failure, defined by at least two of the following criteria: a respiratory rate above 40 cycles/min, lack of improvement of signs of respiratory-muscle fatigue, development of copious tracheal secretions, acidosis with a pH below 7.35, SpO_2 below 90% for more than 5 min without technical dysfunction, or intolerance to CPAP or HFNC.
- Circulatory failure: shock defined by the need for vasopressors (dopamine >5 µg/kg/min or epinephrine or norepinephrine at any dose).
- Neurological failure: deterioration of neurological status with a Glasgow Coma Scale below 12 points.

Organ failures free days at day 7

We will use the proposed modified SOFA (MSOFA), which is derived from the original SOFA score and does not require specific laboratory equipment, is calculated easily at the patient bedside and is available for daily reassessment in low-resource settings.[17 18] The worst value for each individual organ system (ie, respiratory, cardiovascular, renal, coagulation and hepatic) components within the past 24 hours (at baseline and once daily until day 7) will be recorded where possible, considering that majority of patients may not get urinary catheters. Organ failure will be deemed present when the MSOFA≥3 for the organ.

Percentage of patients intubated at day 28 and ventilator-free days at day 28

Invasive MV is defined as the use of endotracheal or tracheostomy tube assisted ventilation. One point will be given for each calendar day during the measurement period, that is, from the first day of randomisation to day 28 that patients were both alive and free of invasive MV. Zero value is given for patients who died both before extubation and day 28. A patient extubated on day 2 of the study and remaining alive and free of the ventilator for the remainder of the 28-day study period would receive a ventilator-free day score of 26, whereas the patient receiving MV until death on day 2 would receive a score of 0.

Tolerance of CPAP/HFNC

We will assess the percentage of patients with facial skin necrosis, aspiration or sinusitis, up to day 28. The patient discomfort and dyspnoea will also be assessed during the first 7 days of treatment. Respiratory patient discomfort and dyspnoea will also be assessed using an unmarked Visual Analogue Scale from 'no discomfort' to 'maximal imaginable discomfort', and using a Likert scale model indicating marked improvement (+2), slight improvement (+1), no change (0), slight deterioration (−1) and marked deterioration (−2).

Sample size and its justification

According to Hussey and Hughes,[19] the power calculation for a stepped wedge design depends on the number of clusters, number of steps, the number of participants per cluster, strengths of the desired treatment effect, variability and significance level α. Sample size of the study was calculated to detect a clinically relevant effect on the 28-day mortality rate (primary outcome). Assuming a mortality of 80% in the population that is treated with standard oxygen therapy,[20] we calculated that enrolment of at least 504 patients would provide the study with >80% power to show an absolute difference of 20 percentage points in the primary outcome between the standard-oxygen group and either the CPAP or HFNC group, at a two-sided alpha level of 0.05, considering a stepped wedge design with eight clusters, nine periods and a coefficient of variation of 0.15.[19]

Recruitment

The expected duration of patient's enrolment is 10 months starting from March 2023. The chronogram of the study is as follows: (1) November 2019: approval by an independent ethics committee; (2) January 2021: winning grant award; (3) March 2023–January 2024: inclusion of patients; (4) 2024–2025: end of inclusions, monitoring by the participating centres and research

work by the investigators; cleaning and closure of the database; blind review to screen for protocol violation, to define intention-to-treat (ITT) and per-protocol (PP) analysis populations and (5) 2024–2025: data analysis, writing the manuscript and submission for publication.

Allocation of intervention and data collection

The order in which a cluster will move to the intervention period will be randomised before the trial starts, using a computer-generated list. In addition to cluster-level randomisation, all patients included during the intervention period will further be randomised 1:1 on an individual basis between CPAP and HFNC as follows. A computer-generated randomisation list will be prepared prior to enrolment of the first patient into the trial. No patient can be enrolled twice. Patients will be randomised by block to treatment in a fixed manner. To minimise the risk of patient characteristics imbalance between the treatment's arms, the individual randomisation will be minimised on the following criteria: cluster; diagnosis of cardiogenic pulmonary oedema (yes/no/test not performed); moderate-to-severe hypoxaemia (yes/no) and hypercapnia (yes/no/blood gas not performed).

Data will be entered into the e-CRF via a web browser by a trained investigator or research assistant at each centre. The participating centres have access to e-CRF forms via a web-based data collection system (unique identification and password by user).

Statistical methods

All analyses will be performed according to a predefined statistical analysis plan, using R V.4+ (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed $p<0.05$ should indicate statistical significance. A flow diagram will describe the progress of the two groups of patients throughout the different phases of the trial (enrolment, allocation, received interventional strategies, follow-up and data analysis). The primary endpoint analysis will be performed on an ITT basis. In case of premature interruption or withdrawal from the study, patients will not be substituted. Missing values will be described, and according to their nature and frequency, multiple imputation methods shall be applied. A PP analysis will be conducted as a supportive sensitivity analysis to investigate PP-excluded patients and check the robustness of the results in those patients without substantial protocol deviation. There is no planned interim analysis. All secondary endpoint analyses will be conducted on both ITT and PP populations.

Descriptive analyses

Descriptive statistical analyses will be conducted regarding the trial groups in terms of demographics, history and baseline characteristics. Quantitative variables will be presented as mean (±SD) or median (25th–75th percentiles) according to the normality of their distribution and qualitative variables will be presented as numbers (%). Comparisons between randomised groups will be conducted by use of the χ^2 test or the Fisher's exact test, according to expected numbers in crossings, for categorical variables and by use of t-tests or non-parametrical Mann-Whitney tests (pairwise comparisons), and analysis of variance or Kruskal Wallis tests (global comparisons for >2 groups) for quantitative variables, as appropriate. Pairwise comparisons within groups (ie, across time points) will be conducted using tests for paired data, that is, McNemar tests for qualitative data, and t-tests for paired data or Wilcoxon signed ranks tests for continuous data, as appropriate.

Analysis of the primary endpoint

The primary endpoint will be the 28-day mortality rate. Stepped wedge cluster trials present several challenges related to intracluster correlation, the correlation between data repeated over time and the need to monitor underlying temporal trends. Accordingly, the analysis of the primary endpoint and other binary secondary endpoints will be based on mixed-effects logistic regression models, entering as fixed effects the control/intervention period and a time term to account for a potential underlying trend in mortality rates over the study period, and a random effect accounting for the centre level. A potential interaction term between time and intervention will be tested to identify a possible learning curve. Treatment-effect heterogeneity across clusters and varying secular trends across clusters will also be investigated by introducing the intervention and time terms as random slopes, respectively.[21] Prespecified supportive analyses will be performed to take into account possible changes in clinically important confounding factors over time by further adjusting for such demographic and clinical characteristics and possible seasonal variations. As the primary analysis, the intervention period will be analysed as a whole with no distinction made by treatment type (ie, CPAP/HFNC), thus assessing the efficacy of experimental treatment regardless of the nature of the randomised therapeutic modality. In case of statistical significance at the $p<0.05$ level, pairwise comparisons will be led at the $p<0.017$ level (Bonferroni correction for test multiplicity) between (1) intervention (CPAP) and control periods, (2) intervention (HFNC) and control periods and (3) between intervention (CPAP) and (HFNC) periods. There are no planned interim analyses with the potential to stop the trial early. Mortality endpoints will also be assessed based on time-to-event data, using methods appropriate for censored data (Kaplan-Meier curves and Cox proportional hazards models).

Analysis of secondary endpoints

The analysis of continuous secondary endpoints will be based on mixed-effects linear regression models, following similar modelling principles such as those previously described for the primary endpoint. A bilateral alpha of 5% will be used for all comparisons relating to secondary endpoints.

Predetermined subgroup analyses

We plan to perform a subgroup analysis of the primary endpoint in patients with the following characteristics:

- Diagnosis of cardiogenic pulmonary oedema.
- Moderate-to-severe hypoxaemia (PaO_2/FiO_2 ratio <200 or SpO_2/FiO_2 ratio <235 in the absence of arterial blood gases).[15 16]
- Hypercapnia (PaCO2>45 mm Hg) in the presence of arterial blood gases.

Data monitoring

The trial steering committee will supervise the progression and monitoring of the study. Study monitors will regularly monitor all centres on site to check protocol adherence and accuracy of the recorded data. An investigator or research technician at each centre will be responsible for daily patient screening, patient enrolment, adherence to protocol and completion of the eCRF. A data safety monitoring board will oversee the overall safety of the trial participants.

Patient and public involvement

Patients and/or the public were not involved in the development of this study, but we plan to have focused group discussions with patient survivors, community leaders, hospital and trial staff at the end of the study.

ETHICS AND DISSEMINATION

Ethical approval

The study has been approved by an independent ethics committee (Research and Ethics Committee, School of Biomedical Sciences, College of Health Sciences, Makerere University) under the registration number SBS-699 and the Uganda National Council of Science and Technology (UNCST) registration number HS523ES.

Consent to participate

Patients will be included after signing a written informed consent. If the patient is not able to understand the information given in the consent, they can be included if a next of kin consents. Eligible patients unable to receive information and for whom a substitute decision maker is not present can still be included through a process of deferred consent. Permission to keep the patient in the study will be sought from the patient after recovery, or from next of kin at their earliest availability, whichever occurs first

Dissemination policy

Findings will be published in peer-reviewed journals and presented at national and international meetings. Communications, reports and publication of the results of the study will be placed under the responsibility of the principal investigator, senior principal investigator and the steering committee. Reporting will adhere to the Consolidated Standards of Reporting Trials extension for stepped wedge cluster randomised trials reporting guidelines, and rules of publication will follow the international recommendations as for The Uniform Requirements for Manuscripts (ICMJE, April 2010).

Confidentiality

During and after the clinical study, all data collected about the study participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be anonymised. Under no circumstances will the names and addresses of the subjects be shown.

Access to data

Investigators will make the documents and individual data required for monitoring, quality control and audit of the study available to dedicated persons, in fulfilment with the law.

Data statement

The trial steering committee will work to make study data available on legitimate requests, in respect for compliance with the applicable regulations.

DISCUSSION

We here propose the first prospective multicentre study to assess standard oxygen, CPAP and HFNC in adults with AHRF in sub-Saharan Africa.

The care for the critically ill patient revolves around prompt diagnosis of organ dysfunction with a view to the restoration of normal homeostasis and resolution of the primary cause of organ failure. Typically, this takes place in ICU. ICU care is quite expensive, both in resource-limited and resource-rich countries. In patients with AHRF, the need for invasive MV is associated with high mortality, especially in LICs, given the scarce availability of invasive MV.[22 23] Observational series[24 25] and small randomised trials (confined to children)[26] suggest that administration of ventilatory support through a mask may be effective in resource-limited settings. However, there is no clinical study data in adults to support this evidence. Human and material constraints are major barriers to the care of critically ill patients in resource-limited settings,[27] advocating the need for a frugal approach.[7 28 29] Furthermore, the scarcity of ICUs in LICs contributes to a high mortality among acutely ill patients. In a recent study by Kwizera *et al* of 328 adults with AHRF presenting to a Mulago national referral hospital (in Kampala, Uganda) and needing respiratory support, only 6% obtained admission to the ICU. The remainder received low-flow oxygen by face mask or nasal prongs during hospitalisation. The majority of patients (80%) had lower respiratory tract infections (pneumonia) and in-hospital mortality was 77%.[20] These patients were referrals from district hospitals all over the country, places where they would have obtained quicker care.

We have chosen not to assess NIV, that is, bilevel assistance delivered by ventilators because this technique requires more advanced training and material, which may be challenging in many resource-limited settings. In

addition, recent reports suggest that this approach may be associated with excessive tidal volumes during AHRF,[30] the latter being potentially involved in lung injury.[31] Some recent studies performed in resource-rich settings do not suggest any benefit of NIV during de novo AHRF[9] and the 2017 European Respiratory Society/American Thoracic Society NIV clinical practice guideline made no recommendation regarding the use of NIV for acute de novo respiratory failure.[32]

The methodology of the study is innovative. Unlike previous trials of respiratory support in adults with AHRF in resource-limited settings, our study will be prospective, controlled and randomised. We will use a stepped wedge design, an innovative research methodology that is gaining popularity for evaluating interventions. This design features the random and sequential transition of clusters from control to intervention until all clusters have experienced the intervention. It is a practical study design that balances the need for rigorous evaluations with ethical and logistical considerations. We chose this design because based on current evidence, we expect CPAP or HFNC will do better than harm in a limited-resource country with little access to invasive MV; therefore, there is little likelihood for the need to 'deimplement' the intervention at the end of the study.

In conclusion, the ARISE-AFRICA study will provide meaningful information for the optimal care of adult patients with AHRF in sub-Saharan Africa.

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Contributors AK and AMD designed the study and wrote the manuscript, in collaboration with DK. EA provided substantial contributions to the conception and design of the study, wrote the statistical analysis plan and estimated the sample size. DO, JK, GK, DNanyunja, CS, DNyakato and CO revised the work and approved the final version of the manuscript. All authors agreed to submit the present version and to be accountable for all aspects of the work.

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Disclaimer These organisations had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data or decision to submit results.

Competing interests AMD reports fees (lectures and research) from Fisher and Payckel. EA reports personal fees from GBT, personal fees from Hemanext, both unrelated to the present study.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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