BMJ Open

Parallel-group, randomised, controlled, non-inferiority trial of high-flow nasal cannula versus non-invasive ventilation for emergency patients with acute cardiogenic pulmonary oedema: study protocol

Onlak Ruangsomboon, Nattakarn Praphruetkit, Apichaya Monsomboon

To cite: Ruangsomboon O, Praphruetkit N, Monsomboon A. Parallel-group, randomised, controlled, non-inferiority trial of high-flow nasal cannula versus non-invasive ventilation for emergency patients with acute cardiogenic pulmonary oedema: study protocol. *BMJ Open* 2022;**12**:e052761. doi:10.1136/bmjopen-2021-052761

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-052761).

Received 23 April 2021
Accepted 20 June 2022

Department of Emergency Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

Correspondence to
Dr Onlak Ruangsomboon; doctor.mo@yahoo.com

ABSTRACT

Introduction High-flow nasal cannula (HFNC) is an innovative oxygen-delivering technique, which has been shown to effectively decrease the intubation risk in patients with hypoxaemic respiratory failure of various aetiologies compared with conventional oxygen therapy. Also, it has proved to be non-inferior to non-invasive positive pressure ventilation (NIPPV) in patients with hypoxaemic respiratory failure primarily due to pneumonia. Evidence on its benefits compared with NIPPV, which is the standard of care for patients with acute cardiogenic pulmonary oedema (ACPE) with hypoxaemic respiratory distress, is limited. Therefore, we planned this study to investigate the effects of HFNC compared with NIPPV for emergency patients with ACPE.

Methods and analysis In this single-centred, non-blinded, parallel-group, randomised, controlled, non-inferiority trial, we will randomly allocate 240 patients visiting the emergency department with ACPE in a 1:1 ratio to receive either HFNC or NIPPV for at least 4 hours using computer-generated mixed-block randomisation concealed by sealed opaque envelopes. The primary outcome is the intubation rate in 72 hours after randomisation. The main secondary outcomes are intolerance rate, mortality rate and treatment failure rate (a composite of intolerance, intubation and mortality). The outcome assessors and data analysts will be blinded to the intervention. These categorical outcomes will be analysed by calculating the risk ratio. Interim analyses evaluating the primary outcome will be performed after half of the expected sample size are recruited.

Ethics and dissemination This study protocol has been approved by the Siriraj Institutional Review Board (study ID: Si 271/2021). It has been granted the Siriraj Research and Development Fund. All participants or their authorised third parties will provide written informed consent prior to trial inclusion. The study results will be published in a peer-reviewed international journal and presented at national and international scientific conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first randomised controlled trial comparing high-flow nasal cannula with non-invasive positive pressure ventilation in patients with acute cardiogenic pulmonary oedema.
⇒ The study is a non-inferiority trial, the most appropriate design in comparing these two interventions.
⇒ The primary and main secondary outcomes are important objective clinical outcomes.
⇒ Potential limitations are the study being single-centre with unblinded interventions to the participants and healthcare providers.

Trial registration number TCTR20210413001.

INTRODUCTION

Background and rationale

Many patients present to the emergency department (ED) with acute cardiogenic pulmonary oedema (ACPE). Primary management includes reversing the specific underlying causes and conventional approaches to oxygen and ventilation therapy. Choices of oxygenation and ventilatory support include nasal cannula oxygen or face mask oxygen, non-invasive ventilation and invasive mechanical ventilation via endotracheal intubation.[1–6]

Non-invasive positive pressure ventilation (NIPPV) has been used and is well established for the management of cardiogenic pulmonary oedema because it has the ability to support either or both hypoxaemic and hypercapnic respiratory failure caused by cardiogenic pulmonary oedema.[7] NIPPV, if delivered as the initial respiratory support, has been shown to prevent endotracheal intubation and decreased mortality compared with conventional oxygen therapy.[8] Consequently,

it has been implemented as a recommendation in the European Society of Cardiology 2016 and Thai 2019 guidelines for the treatment of cardiogenic pulmonary oedema.[9 10]

Oxygenation via high-flow nasal cannula (HFNC) is a novel approach to oxygen and ventilation therapy, which delivers oxygenated air up to 60 L/min. HFNC can achieve a fraction of inspired oxygen (FiO_2) ranging from 21% to 100%. The flow levels are high enough to generate positive airway pressure, potentially decreasing entrapment of ambient air and providing support to reduce the work of breathing. Because conventional high-flow oxygen can be uncomfortable, modern HFNC systems integrate oxygen warming and humidification to enhance patient comfort.[11–14] There have been previous studies of HFNC in both adult volunteers and critically-ill patients with hypoxaemic respiratory failure mainly due to pneumonia with results generally supporting its tolerance by patients along with its efficacy in reducing the respiratory rate and improving oxygenation.[15–19] A previous randomised controlled trial assessing the efficacy of HFNC for mild cardiogenic pulmonary oedema in the ED reported significant improvement in respiratory rate compared with conventional oxygen.[20]

HFNC is more preferable to NIPPV because it is more tolerable for patients as it allows patients to talk and eat. It is also easier for healthcare providers to provide respiratory care and observe patients with HFNC compared with NIPPV. Although HFNC cannot create the same level of positive pressure as that of NIPPV, the efficacy of HFNC may be non-inferior to NIPPV. A previous randomised non-inferiority trial comparing HFNC and NIPPV in the ED for hypoxaemic respiratory failure found that HFNC was non-inferior to NIPPV in intubation and failure rates.[21] However, the primary cause of respiratory failure in that study was pneumonia. For cardiogenic pulmonary oedema, a retrospective study found a higher treatment failure rate from HFNC compared with that of NIPPV.[22] Another observational study in patients with heart failure after extubation reported a non-significant difference in failure rate between HFNC and NIPPV.[23] These previous studies were unpowered observational studies with risk of selection bias and potential unbalanced confounders. Also, they reported discordant results. A randomised trial with enough power to compare the efficacy of both treatment measures is needed to make a confirmatory conclusion.

Hypotheses and objectives

Although HFNC cannot provide the same level of positive pressure as NIPPV, which is the standard care, the authors hypothesise that HFNC might not be inferior to NIPPV in terms of intubation rate and treatment failure. Moreover, it may offer benefits with regards to convenience and better compliance.

Therefore, the primary aim of this randomised study is to determine if the use of HFNC results in a non-inferior intubation rate compared with NIPPV in patients admitted to ED with ACPE.

The key secondary aims are to evaluate the effects of HFNC compared with NIPPV on the rate of intolerance, mortality and overall treatment failure (a composite of intubation, intolerance and mortality). Also included as study outcomes are the length of hospital stay, changes of physiological variables and patient-reported dyspnoea scale. We will also evaluate the cost-effectiveness of HFNC compared with NIPPV, as well as the utility of the ROX (Respiratory rate OXygenation) index[24] and lung ultrasound scores[25] in predicting intubation after treatment with HFNC and NIPPV.

METHODS AND ANALYSIS

Study design and setting

This study is a non-blinded, non-inferior, parallel-group, single-centred, randomised controlled trial, in which patients with ACPE will be allocated in a 1:1 ratio to receive either HFNC or NIPPV for at least 4 hours. The trial protocol is reported according to the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) statement.[26] The trial procedures and schedules are summarised in figure 1 and table 1. The study will be conducted at the ED of Siriraj Hospital, Mahidol University, Bangkok, Thailand. Siriraj Hospital is the largest tertiary university hospital in Thailand, with 2200 inpatient beds and over 20 000 Emergency Severity Index triage level I-II ED visits annually.

Study population

Inclusion criteria

Patients will be recruited if they meet all the following criteria.

1. Adult patients (18 years of age and above) presenting with ACPE diagnosed by the attending ED physician by meeting all of the following criteria:[9 10]
   - History of acute dyspnoea.
   - Bilateral rales on physical examination.
   - At least one of the following signs on the initial chest radiograph: pulmonary venous congestion, cardiomegaly and interstitial oedema.[27]
2. Significant respiratory distress in need for non-invasive respiratory support measures by meeting all of the following:[9]
   - Respiratory rate (RR) >24 breaths/min.
   - Pulse oximetry (SpO_2) <92% when breathing at room air or arterial pressure of oxygen/FiO_2 <300 or SpO_2/FiO_2 <315 while on oxygen supplementation via standard nasal cannula or oxygen mask with reservoir bag.
   - Signs of respiratory distress, for example, accessory muscle use.

Exclusion criteria

Patients will be excluded if they meet one of the following criteria.

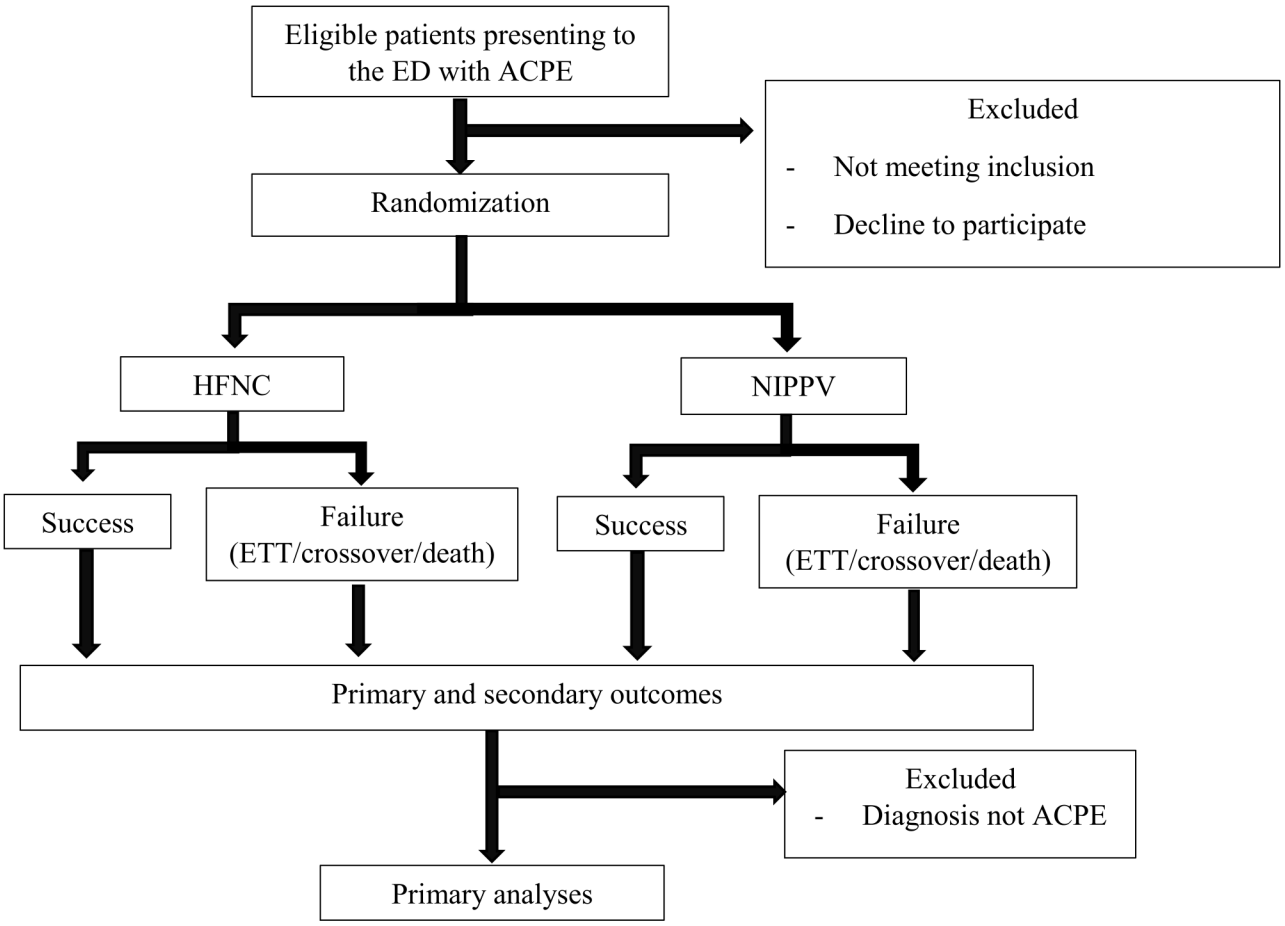

Figure 1 The study procedures. Success, successful weaning to a less invasive treatment measure, which are COT for HFNC and HFNC or COT for NIPPV; crossover, crossover to the other intervention without meeting the weaning criteria. ACPE, acute cardiogenic pulmonary oedema; COT, conventional oxygen therapy; ED, emergency department; ETT, endotracheal intubation; HFNC, high-flow nasal cannula; NIPPV, non-invasive positive pressure ventilation.

1. Respiratory failure needing immediate endotracheal intubation, defined as RR >35 breaths/min, SpO_2 <90% despite oxygen supplement at the highest level of FiO_2 possible via oxygen mask with reservoir bag and signs of severely increased work of breathing as determined by the attending physicians.
2. Patients with cardiac or respiratory arrest.
3. Patients with haemodynamic instability, defined as systolic blood pressure <90 mm Hg or mean arterial pressure <65 mm Hg with signs of poor tissue perfusion.
4. Patients with altered mental status, defined as a Glasgow Coma Scale score <13.
5. Agitated or non-cooperative patients.
6. Patients contraindicated to the use of NIPPV and HFNC, that is, at risk for aspiration, known or suspected pneumothorax.
7. Patients with other airway diseases as the primary provisional diagnosis.
8. Patients with chronic kidney disease stage V or end-stage renal disease.
9. Patients with ST-segment elevation myocardial infarction.
10. Patients with do-not-intubate order.
11. Patients with long-term non-invasive or invasive respiratory support.
12. Patients with a tracheostomy tube.
13. Pregnant patients.

Withdrawal criteria

1. Participants' request to withdraw from the trial.
2. Medical staffs' preference to withdraw from the trial for safety reasons.

Study outcomes

Primary outcome

The primary outcome is intubation rate within 72 hours after commencing the study intervention by meeting one of the criteria in box 1.

Secondary outcomes

1. Intolerance rate within 72 hours, defined as failure to tolerate the intervention due to intolerance and thus requiring crossover to another intervention or conventional oxygen therapy (COT) via standard nasal cannula or oxygen mask before successful weaning as defined in box 2.
2. All-cause mortality.

Table 1 Trial schedule and assessments at different time points

	Study period										
				Post-intervention							
Time point	**ED arrival**	**Enrolment**	**Allocation**	**1 hour**	**2 hours**	**4 hours**	**12 hours**	**24 hours**	**48 hours**	**72 hours**	**Close-out**
Trial process											
Eligibility screen		X									
Informed consent		X									
Allocation		X									
Assessments											
Patients' demographics			X								
Temperature	X										
Respiratory rate	X		X	X	X	X	X	X	X	X	
Blood pressure	X		X	X	X	X	X	X	X	X	
Pulse rate	X		X	X	X	X	X	X	X	X	
Pulse oximetry	X		X	X	X	X	X	X	X	X	
FiO_2			X	X	X	X	X	X	X	X	
GCS score			X	X	X	X					
Arterial blood gas			X	X							
MBS score			X		X	X					
Lung ultrasound score			X		X	X					
HFNC/NIPPV settings			X	X	X	X					
Treatment failure											x
Co-interventions											x
Complications											x
Hospital length of stay											x

FiO_2, fraction of inspired oxygen; GCS, Glasgow Coma Scale; HFNC, high-flow nasal cannula; MBS, modified Borg Scale; NIPPV, non-invasive positive pressure ventilation.

Box 1 Predefined criteria for intubation after non-invasive positive pressure ventilation or high-flow nasal cannula

⇒ Oxygenation failure: pulse oximetry <90% or arterial pressure of oxygen<60 mm Hg despite oxygen supplementation at fraction of inspired oxygen=1.0.
⇒ Ventilation failure: patients remain acutely hypercarbic (arterial pressure of carbon dioxide ($PaCO_2$) >50 mm Hg) and acidemic (pH <7.35) with lack of reduction in $PaCO_2$ and improvement in pH.
⇒ Failure to alleviate respiratory distress: respiratory rate >35 breaths/min and/or inability to reduce work of breathing or sustained increase in accessory muscle use.
⇒ Failure to protect the airway: inability to remove secretions, at risk of massive aspiration or deteriorating mental status.
⇒ Worsening medical conditions: cardiac or respiratory arrest, worsening haemodynamic status or any other life-threatening conditions as determined by the treating physicians.

3. Failure rate, a composite of intubation, intolerance and mortality rate, within 72 hours.
4. Adverse events due to NIPPV and HFNC.

Data collection

Details of the trial participants' assessments at different time points are illustrated in table 1. After enrolment, we will record patient demographics and medical history of ischaemic heart disease, congestive heart failure, valvular heart disease, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, hyperlipidaemia, current smoking, peripheral vascular disease, cerebrovascular disease, chronic kidney disease and immunocompromised status. Physiological variables, assessed using automated machines, will be recorded during the initial 4 hours and at 12, 24, 48 and 72 hours after study initiation. The ROX index will be retrospectively calculated from physiological variables and FiO_2 at each time point (formula: SpO_2/FiO_2 over respiratory rate).[24] Arterial gas results will be measured at baseline and at 1 hour after the treatment has been commenced, as per the standard protocol of care for patients receiving NIPPV or HFNC of the hospital. We will also assess the patient-reported dyspnoea scale rating using the Modified Borg Scale (MBS) score, which is a category ratio scale ranging from 0 to 10 with descriptive anchors to ensure ratio scaling.[28] Trained study investigators will ask the participants to mark the score on a form or speaking their answers. Moreover, settings of HFNC (airflow and temperature) and NIPPV (maximal inspired positive airway pressure (IPAP), expired positive airway pressure (EPAP) and expired tidal volumes) will be recorded.

Box 2 Predefined criteria for switching between non-invasive positive pressure ventilation (NIPPV), high-flow nasal cannula (HFNC) and conventional oxygen therapy (COT)

Switching from NIPPV to HFNC or COT; if one of the following criteria is met:
⇒ Intolerance with the mask, pressure, persistent asynchrony or inability to cooperate but without persistent or worsening hypoxaemia, respiratory acidosis and increased work of breathing,
⇒ Successful weaning; meeting the overall clinical improvement criteria, defined as respiratory rate (RR) ≤24 breaths/min, improved signs of increased work of breathing and the need for lower fraction of inspired oxygen (FiO_2) to maintain the desired pulse oximetry (SpO_2).

Switching from HFNC to COT; if one of the following criteria is met:
⇒ Intolerance with the nasal prongs, airflow or inability to cooperate but without persistent or worsening hypoxaemia, respiratory acidosis and increased work of breathing.
⇒ Successful weaning; meeting the overall clinical improvement criteria, defined as RR ≤24 breaths/min, improved signs of increased work of breathing and the need for lower FiO_2 to maintain the desired SpO_2.

Switching from HFNC to NIPPV; if
⇒ Intolerance with the nasal prongs, airflow or inability to cooperate with unimproved but not worsening hypoxaemia, respiratory acidosis and increased work of breathing and not meeting the predefined criteria for intubation in box 1.

Table 2 Point scoring for lung ultrasound findings in each position assessed[25]

Ultrasound finding	Score
Normal aeration: A-lines or B-lines <3 lines	0
Moderate damage: B-lines ≥3 lines	1
Serious damage: multiple confluence B-lines	2
Lung consolidation or pleural effusion	3

The lung ultrasound score will be measured at eight positions (left and right anterior upper, anterior lower, lateral upper and lateral lower lung region) on participants' chest wall while they are in a semi-supine position.[29] The finding from each position will be used to calculate the overall lung score at each time point according to table 2.[25 30–33] Lung ultrasound will be assessed by trained study investigators, and the findings videotaped for score calculation by another independent emergency ultrasound specialist blinded to the intervention and the interpretation of the first investigator. Their interpretations will be assessed for inter-rater reliability. The total duration for lung ultrasound assessment (excluding score calculation) at each time point shall not exceed 3 min to minimise the participants' possible distress and burden from the assessment process. Participants shall remain on the assigned intervention while they are being assessed.

The primary outcome will be assessed using chart review. We will also record complications associated with NIPPV and HFNC, such as nasal ulceration, facial ulceration, discomfort, aspiration and pneumothorax, as well as complications during the hospital stay, such as hospital-acquired pneumonia, hospital length of stay, a concurrent diagnosis other than ACPE, precipitating causes of ACPE and significant co-interventions, that is, diuretics, nitrates, antiplatelet with/without anticoagulant for treatment of acute coronary syndrome.

Recruitment, randomisation and treatment allocation

Adult patients presenting to the ED with signs and symptoms compatible with ACPE will be consecutively assessed for eligibility as per the trial inclusion and exclusion criteria by the attending ED physicians. Before enrolment, all patients will receive the standard therapy as determined by the attending physician, including concentrated supplemental oxygen therapy via standard nasal cannula or face mask. Management for ACPE will be delivered according to the standard guideline.[9 10] All other drug therapies will be given at the discretion of the treating medical staff. The medical and nursing staff providing clinical care for eligible patients will notify project researchers. The project investigators will confirm eligibility, undertake patient recruitment, consent and randomisation. Once consent has been obtained, participants will be allocated on a 1:1 basis by a computer-generated mixed block of size 2 and 4 randomisation and using sequentially-numbered sealed opaque envelopes. Participants will be randomised to one of the two groups. They will be given the allocated therapy of either HFNC or NIPPV for a minimum of 4 hours. Duration from time of eligibility assessment and study initiation will not exceed 20 min.

Blinding

Due to the nature of the intervention (either HFNC or NIPPV), participants and physicians taking care of the patients cannot be blinded. However, outcome assessors and data analysts will be blinded to the study group.

Interventions

Prior to the trial initiation, a hands-on workshop will be organised for all the study investigators, ED residents, ED nurses and attending physicians on airway management techniques with NIPPV and HFNC application, settings, monitoring and adjustment. After participants' enrolment, the study investigators will administer the trial intervention to the participants according to their allocated arm. The investigators will also provide the initial settings of HFNC and NIPPV. The attending physicians can make further adjustments in compliance with the study protocol. Should the participants require breaks from either HFNC or NIPPV sessions, oxygen via standard nasal cannula or oxygen mask with reservoir bag will be delivered.

HFNC

High flow oxygen will be delivered by Optiflow cannula using an Airvo flow source (Fisher & Paykel Healthcare). The initial flow will be set at 35 L/min and can be increased up to 60 L/min as tolerated by the participants. FiO_2 will be adjusted to keep SpO_2 at 94%–98% and maintain there for 4 hours.

NIPPV

Bi-level positive pressure ventilation will be delivered via Respironics (Phillips) with an initial IPAP of 8 cmH_2O and EPAP of 4 cmH_2O that can be increased up to 10 cmH_2O. IPAP may be increased up to 20 cmH_2O to achieve an expired tidal volume of 6–8 mL/kg ideal body weight or at 4 cmH_2O above EPAP. FiO_2 will be adjusted to keep SpO_2 at 94%–98% and maintain there for 4 hours.

Termination and weaning

Allocated oxygen treatment will be terminated if one or more of the intubation or switching criteria, as mentioned above, are met.

For successful treatment, non-invasive respiratory support will be maintained at least for 4 hours. Once the participants meet the overall clinical improvement criteria, defined as a RR ≤24 breaths/min, improved signs of increased work of breathing and the need for lower FiO_2 to maintain the desired SpO_2, both intervention settings can be weaned. If clinical improvement can be maintained after weaning is initiated and continued, the assigned intervention can be discontinued under the discretion of the treating physicians.

Protocol consistency

Before the trial initiates, the study protocol will be distributed to all ED residents, ED attending physicians and attending physicians of participating inpatient wards and intensive care units. The trial protocol, termination and intubation criteria and recording variables will be introduced, discussed and agreed on prior to the start of the trial. During the study, the management of ACPE will be delivered according to the standard guideline.[9 10] Medication, that is, intravenous diuretics, nitrates, will be given at the discretion of the treating physician.

Patient and public involvement

No patient involved.

Sample size calculation

Sample size calculation is based on an assumed intubation rate of approximately 6.3% and an upper 95% CI of a risk ratio for intubation of NIPPV compared with COT of 0.81.[34] Consequently, the risk ratio for intubation of COT compared with NIPPV would be 1.23. Under the fixed margin method, we defined that HFNC would be considered non-inferior to NIPPV if it could provide at least 50% of the efficacy of NIPPV with superiority over COT, thereby resulting in a non-inferiority margin of 11 percentage points. A sample size of 103 per arm is required such that a test of proportions with 0.025 one-sided level of significance and 90% power with a non-inferiority margin for intubation of 11%. A 15% increase in sample size is decided on to cover possible dropouts due to final diagnoses other than ACPE. Therefore, a total of 120 participants per group will be enrolled.

Statistical analysis

Primary and secondary analysis plan

All outcomes will be assessed by a modified intention-to-treat analysis, which includes all randomised participants minus those who are subsequently found to lack the diagnosis of ACPE.[35] After the participants are discharged,

two trial investigators, blinded to each participant's allocation, will independently review the final diagnoses and resolve their discordances through discussion; if it is not ACPE, participants will be excluded from the primary analysis. A flow diagram will be used to describe the number of eligible patients and the number of patients at each stage of the trial according to the CONSORT (Consolidated Standards of Reporting Trials) 2010 statement.[36] Demographics and baseline characteristics of all randomised participants will be summarised by treatment arms. Data will be analysed using SAS statistical software (V.9.2 or higher). Continuous variables will be presented as mean and SD or median and IQR. Categorical variables will be described as frequencies and percentages. Any statistically significant imbalances at baseline will be reported, although any difference between groups could only have occurred by chance with randomisation. Baseline characteristics of patients will be compared by the χ^2 or the Fisher''s exact test, and the two-sample Student's t-test or the Mann-Whitney U test as appropriate.

The primary endpoint, intubation rate, between the two study groups will be compared using risk ratio. A 0.025 one-sided CI, calculated using the adjusted score approximation method,[37] will be used to assess the non-inferiority of HFNC compared with NIPPV. The primary analysis of the primary endpoint will be performed without adjustment for baseline covariate imbalance. A sensitivity analysis of the primary endpoint will be performed adjusting for baseline covariates using a modified Poisson regression approach.[38] Secondary dichotomous outcomes between the two study groups except for safety events will also be compared using both adjusted and unadjusted risk ratio and assessed for non-inferiority as exploratory analyses. Analytical methods to adjust for contamination will also be employed as appropriate. Planned exploratory subgroup analyses will be performed to investigate if the treatment effect is modified by different initial severity of hypoxaemia and hypercapnia.

Unadjusted analyses of time-to-event for intubation, mortality and treatment failure events will also be presented with Kaplan-Meier curves and analysed using non-inferiority logrank test of median time-to-event as exploratory analyses.[39] Physiological variables, arterial gas results, patient-reported dyspnoea scale and the lung ultrasound score will also be compared between the study groups. These repeated quantitative outcomes will be compared using both unadjusted and adjusted analyses by analysis of covariance in a linear mixed model regression with a random intercept for subjects using an unstructured variance–covariance matrix. Kappa statistics will be used to calculate inter-rater reliability regarding lung ultrasound assessment. The safety set will include all patients randomised who have one of the study interventions applied. Analysis of safety events will be descriptive.

Both intention-to-treat and per-protocol analyses will be performed as recommended for non-inferiority trials.[40] Differences between the groups will be reported with associated p value and 95% CIs. All statistical analyses will be performed by blinded statisticians.

Interim analyses

For safety and efficiency reasons, interim analyses will be performed after half of the sample size is recruited and their outcomes have occurred. A flexible stopping rule was designed allowing stopping for efficacy, futility and safety. For efficacy, the primary endpoint will be analysed. If the intervention is superior to the control at a p value<0.001, consideration will be made to stop early for efficacy of the intervention. For futility, conditional power of demonstrating non-inferiority will be calculated. If the power is below 0.1, the trial may be considered futile and consideration to stop the trial for futility may be determined.[41] There is no predefined stopping rule for safety with regards to complications. Any significant potential harms and serious adverse events related to the interventions will be considered for stopping the trial.

Cost-effectiveness analyses

Resources used and the unit cost of each resource will be assessed from participants' hospital billings over their hospital stay. A cost-effectiveness analysis will be performed based on a healthcare institutional perspective. The direct costs considered include the cost associated with respiratory interventions according to the time spent on each type of intervention (capital cost, equipment, consumables, labour cost, etc), investigation (laboratory examinations, ECG, X-ray, etc), medication (diuretics, antibiotics, bronchodilators, etc), medical devices, procedures and hotel services at the ED, intensive care units and/or general medical wards. The outcomes considered as measures of effectiveness will be intubation rate. Cost-effectiveness comparisons will be analysed using incremental cost-effectiveness ratio.

Proposed further analyses

The predictive performance of the ROX index and the lung ultrasound score will be assessed for intubation and intolerance rate separately by each study arm. Discrimination will be reported using the area under the curve of the receiver operator characteristics curves and their 95% CIs. We will also evaluate the overall model performance with calibration plots and other statistical tests as appropriate. Clinical usefulness at cut-off values will also be assessed by sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, negative predictive value and positive predictive value. We will use both the recommended cutoffs from previous literature and the optimal cut-point of our data according to the Youden index.

Ethics and dissemination

Ethics approval and informed consent

The study was approved by Siriraj Institutional Review Board (study ID: Si 271/2021) and sponsored by Siriraj Research and Development Fund. Fisher & Paykel Healthcare will provide HFNC materials, which are Optiflow cannula and Airvo 2 machines. The company played

no role in the trial design and will not be involved in the data collection, analyses and manuscript preparation. The trial was registered in the Thai Clinical Trial Registry. Any amendments to the trial protocol will be reported. The trial will be conducted in compliance with the Declaration of Helsinki and Good Clinical Practice (GCP). All physicians and research nurses are required to obtain a GCP certification prior to their involvement in the study. All the study investigators have no other financial or non-financial conflicts of interest to declare.

To minimise the undue influence, project investigators, instead of the attending physicians, will provide information and obtain consent. Potential risks and benefits will be explained to the patients and their authorised third party. They will be given approximately 10 min to make their decision as the trial intervention should initiate within 20 min after the participants' eligibility is confirmed. Verbal consent from either the participants or their legal representatives will be initially acquired before trial inclusion with a written form obtained from the participants or their next of kin later when their' symptoms are stabilised. The risks associated with both NIPPV and HFNC are considered minimal as both treatment methods have shown well-established efficacy. Nonetheless, this risk will be minimised by excluding patients susceptible to complications from the study. Moreover, participants will be continuously monitored during their hospital stay for any potential risks and complications associated with the study interventions.

Data storage and management

All study data will be recorded on a case record form by the trial investigators. The data will be verified by the principal investigator (PI) for accuracy and completeness prior to having them uploaded and stored in an encrypted file on a web-based data management program, Research Electronic Data Capture (REDCap), by the department's research assistant. Electronically-recorded data will be double-checked with the case record forms by another research assistant for quality control. Only the research assistants and the PI will have access to the study data and participants' identifiable health records. The data will be stored for at least 10 years after the trial is finished. The PI will have access to the trial final data set and will be responsible for maintaining the confidentiality of the study participants and the security of the study data.

The study results will be presented at national and international scientific meetings and will be published in a peer-reviewed international journal.

DISCUSSION

Although NIPPV has been a standard non-invasive airway measure for patients with ACPE for it has been known to prevent endotracheal intubation, HFNC may be a feasible alternative with an efficacy that is non-inferior to that of NIPPV while also providing more convenience and better compliance to both the patients and healthcare providers, as well as minimising complications associated with the use of NIPPV.

Currently, to the best of our knowledge, there has been no published randomised controlled study assessing the efficacy of HFNC compared with NIPPV for ACPE that evaluates important clinical outcomes. Therefore, the results of this study will be of substantial value to the body of evidence in this research area. There can be an improvement in clinical decision-making and treatment guidelines regarding respiratory support for patients with ACPE, which may eventually lead to improved patients' overall clinical outcomes. Moreover, the present study focuses not only on the compared efficacy but is also complimented with a cost-effectiveness analysis. This will help guide a wider variety of decision-makers compared with trials involving efficacy alone as this study may contribute economic impact for hospitals and the healthcare system. Nonetheless, the present study has some limitations. First, it is a single-centred study, which may limit the generalisability of its findings. Second, the study intervention cannot be blinded to the participants or the attending physicians. Nevertheless, we will implement a strict treatment and termination protocol to prevent possible sources of bias. Also, the primary outcome is an objective outcome that involves minimal subjectivity of the treating physicians and the outcome assessors. Moreover, the study analyses will be performed in a blinded manner.

In conclusion, this study seeks to investigate if the use of HFNC for emergency patients with ACPE is non-inferior to NIPPV. Its results shall be of significant influence in developing clinical practice guidelines to optimise the management for patients with ACPE.

Acknowledgements The authors acknowledge the assistance of Professor Andrew Worster, MD, MSc, in providing valuable advice that led to substantial improvement of the protocol.

Contributors OR, NP and AM conceived the study idea, planned the design, methods and the study outcomes. OR wrote the first draft of the protocol. OR, NP and AM edited the protocol. All authors approved the final version of the protocol. OR takes responsibility for the protocol as a whole.

Funding This work is supported by Siriraj Research and Development Fund.

Competing interests Fisher & Paykel Healthcare will provide high-flow nasal cannula materials, which are Optiflow cannula and Airvo 2 machines for the trial.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request to the corresponding author.

ORCID iD

Onlak Ruangsomboon http://orcid.org/0000-0002-0848-7162

REFERENCES

1 Kallstrom TJ, American Association for Respiratory Care (AARC). AARC Clinical Practice Guideline: oxygen therapy for adults in the acute care facility--2002 revision & update. *Respir Care* 2002;47:717–20.
2 O'Driscoll BR, Howard LS, Davison AG, *et al*. Bts guideline for emergency oxygen use in adult patients. *Thorax* 2008;63 Suppl 6:vi1–68.
3 Keenan SP, Sinuff T, Burns KEA, *et al*. Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. *CMAJ* 2011;183:E195–214.
4 British Thoracic Society Standards of Care Committee. Non-Invasive ventilation in acute respiratory failure. *Thorax* 2002;57:192–211.
5 Rochwerg B, Brochard L, Elliott MW, *et al*. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J* 2017;50:1602426.
6 Giacomini M, Iapichino G, Cigada M, *et al*. Short-term noninvasive pressure support ventilation prevents ICU admittance in patients with acute cardiogenic pulmonary edema. *Chest* 2003;123:2057–61.
7 Bolton R, Bleetman A. Non-invasive ventilation and continuous positive pressure ventilation in emergency departments: where are we now? *Emerg Med J* 2008;25:190–4.
8 Vital FMR, Ladeira MT, Atallah AN. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. *Cochrane Database Syst Rev* 2013;5:CD005351.
9 Ponikowski P, Voors AA, Anker SD, *et al*. Esc guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of cardiology (ESC) developed with the special contribution of the heart failure association (HFA) of the ESC. *Eur Heart J* 2016;2016:2129–200.
10 Buakhamsri A, Chirakarnjanakorn S, Sanguanwong S, *et al*. Heart Failure Council of Thailand (HFCT) 2019 Heart Failure Guideline: Pharmacologic Treatment of Chronic Heart Failure - Part I. *J Med Assoc Thai* 2019;102:240–4.
11 Kernick J, Magarey J. What is the evidence for the use of high flow nasal cannula oxygen in adult patients admitted to critical care units? A systematic review. *Aust Crit Care* 2010;23:53–70.
12 Roca O, Riera J, Torres F, *et al*. High-flow oxygen therapy in acute respiratory failure. *Respir Care* 2010;55:408–13.
13 Dysart K, Miller TL, Wolfson MR, *et al*. Research in high flow therapy: mechanisms of action. *Respir Med* 2009;103:1400–5.
14 Gotera C, Díaz Lobato S, Pinto T, *et al*. Clinical evidence on high flow oxygen therapy and active humidification in adults. *Rev Port Pneumol* 2013;19:217–27.
15 Groves N, Tobin A. High flow nasal oxygen generates positive airway pressure in adult volunteers. *Aust Crit Care* 2007;20:126–31.
16 Parke R, McGuinness S, Eccleston M. Nasal high-flow therapy delivers low level positive airway pressure. *Br J Anaesth* 2009;103:886–90.
17 Sztrymf B, Messika J, Bertrand F, *et al*. Beneficial effects of humidified high flow nasal oxygen in critical care patients: a prospective pilot study. *Intensive Care Med* 2011;37:1780–6.
18 Schwabbauer N, Berg B, Blumenstock G, *et al*. Nasal high-flow oxygen therapy in patients with hypoxic respiratory failure: effect on functional and subjective respiratory parameters compared to conventional oxygen therapy and non-invasive ventilation (NIV). *BMC Anesthesiol* 2014;14:66.
19 Sztrymf B, Messika J, Mayot T, *et al*. Impact of high-flow nasal cannula oxygen therapy on intensive care unit patients with acute respiratory failure: a prospective observational study. *J Crit Care* 2012;27:324.e9–324.e13.
20 Makdee O, Monsomboon A, Surabenjawong U, *et al*. High-Flow Nasal Cannula Versus Conventional Oxygen Therapy in Emergency Department Patients With Cardiogenic Pulmonary Edema: A Randomized Controlled Trial. *Ann Emerg Med* 2017;70:465–72.
21 Doshi P, Whittle JS, Bublewicz M, *et al*. High-Velocity nasal insufflation in the treatment of respiratory failure: a randomized clinical trial. *Ann Emerg Med* 2018;72:73–83.
22 Koga Y, Kaneda K, Fujii N, *et al*. Comparison of high-flow nasal cannula oxygen therapy and non-invasive ventilation as first-line therapy in respiratory failure: a multicenter retrospective study. *Acute Med Surg* 2020;7:e461.
23 Chang C-J, Chiang L-L, Chen K-Y, *et al*. High-Flow nasal cannula versus noninvasive positive pressure ventilation in patients with heart failure after extubation: an observational cohort study. *Can Respir J* 2020;2020:1–9.
24 Roca O, Messika J, Caralt B, *et al*. Predicting success of high-flow nasal cannula in pneumonia patients with hypoxemic respiratory failure: the utility of the roX index. *J Crit Care* 2016;35:200–5.
25 Martindale JL. Resolution of sonographic B-lines as a measure of pulmonary decongestion in acute heart failure. *Am J Emerg Med* 2016;34:1129–32.
26 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al*. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
27 Wang CS, FitzGerald JM, Schulzer M, *et al*. Does this dyspneic patient in the emergency department have congestive heart failure? *JAMA* 2005;294:1944–56.
28 Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;14:377–81.
29 Yin W, Zou T, Qin Y, *et al*. Poor lung ultrasound score in shock patients admitted to the ICU is associated with worse outcome. *BMC Pulm Med* 2019;19:1.
30 Picano E, Pellikka PA. Ultrasound of extravascular lung water: a new standard for pulmonary congestion. *Eur Heart J* 2016;37:2097–104.
31 Platz E, Merz AA, Jhund PS, *et al*. Dynamic changes and prognostic value of pulmonary congestion by lung ultrasound in acute and chronic heart failure: a systematic review. *Eur J Heart Fail* 2017;19:1154–63.
32 Cortellaro F, Ceriani E, Spinelli M, *et al*. Lung ultrasound for monitoring cardiogenic pulmonary edema. *Intern Emerg Med* 2017;12:1011–7.
33 Platz E, Jhund PS, Girerd N, *et al*. Expert consensus document: reporting checklist for quantification of pulmonary congestion by lung ultrasound in heart failure. *Eur J Heart Fail* 2019;21:844–51.
34 Berbenetz N, Wang Y, Brown J, *et al*. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. *Cochrane Database Syst Rev* 2019;4:CD005351.
35 Abraha I, Montedori A. Modified intention to treat reporting in randomised controlled trials: systematic review. *BMJ* 2010;340:c2697.
36 Schulz KF, Altman DG, Moher D, *et al*. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMC Med* 2010;8:18.
37 Andrés AM, MÁ H, Tejedor IH. One-tailed asymptotic inferences for the relative risk: a comparison of 63 inference methods. *Commun. Stat. - Theory Methods* 2020;0:1–19.
38 McNutt L-A, Wu C, Xue X, *et al*. Estimating the relative risk in cohort studies and clinical trials of common outcomes. *Am J Epidemiol* 2003;157:940–3.
39 Jung S-H, Kang SJ, McCall LM, *et al*. Sample size computation for two-sample noninferiority log-rank test. *J Biopharm Stat* 2005;15:969–79.
40 Mauri L, D'Agostino RB. Challenges in the design and interpretation of Noninferiority trials. *N Engl J Med* 2017;377:1357–67.
41 Bratton DJ, Williams HC, Kahan BC, *et al*. When inferiority meets non-inferiority: implications for interim analyses. *Clin Trials* 2012;9:605–9.