BMJ Open

Helmet noninvasive ventilation for COVID-19 patients "Helmet-COVID": study protocol for a multicenter randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-052169
Article Type:	Protocol
Date Submitted by the Author:	07-Apr-2021
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Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, RESPIRATORY MEDICINE (see Thoracic Medicine), COVID-19

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Abstract

Introduction

Noninvasive ventilation delivered by helmet is has been used for respiratory support of patients with acute hypoxemic respiratory failure due to COVID-19 pneumonia. The aim of this study is to compare helmet noninvasive ventilation with usual therapy versus usual therapy alone to reduce the mortality.

Methods and analysis

This is a multicenter, pragmatic, parallel, randomized controlled trial that will compare helmet noninvasive ventilation with usual care to usual care alone in 1:1 ratio. A total of 320 patients will be enrolled in this study. The primary outcome is 28-day mortality. The primary outcome will be compared between the two study groups in the intention to-treat and per-protocol cohorts. An interim analysis will be conducted for both safety and effectiveness.

Ethics and dissemination

Approval will be obtained from the research ethics board of each participating institution. Our findings will be published in peer-review journals and presented at relevant stake holders' conferences and meetings.

Trial registration number NCT04477668

Article Summary

Strengths and limitations of this study

- This trial compares helmet NIV to usual care for respiratory support of patients with acute hypoxemic respiratory failure due to COVID-19 pneumonia.
- The trial is a multi-center, pragmatic, parallel randomized controlled trial.
- The main limitations include the unblinded design due to the nature of the intervention.

Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a pandemic resulting in over 131 million cases and approximately 2.9 million fatalities as of April 5, 2021.[1] The resulting Coronavirus Disease 2019 (COVID-19) leads to severe pneumonia and acute respiratory distress syndrome (ARDS) among other organ injury.[2] ARDS may occur in up to 5% of infected patients.[3-5] Invasive mechanical ventilation was used widely because of concerns about noninvasive ventilation safety and efficacy early in the pandemic. However, noninvasive ventilation (NIV) use increased with time, including mask NIV and helmet NIV.

NIV has been shown to be physiologic benefits in patients with acute hypoxemic respiratory failure (AHRF) secondary to pulmonary edema, atelectasis, or pneumonia.[6] It has been shown to improve arterial oxygenation by increasing functional residual capacity, shifting the tidal volume to a more compliant part of the pressure-volume curve, thus reducing both the work of breathing and the risk of tidal opening and closure of the airways.[7] NIV is commonly provided through nasal or oro-nasal interfaces. The resulting aerosol generation may increase the risk of transmission of pathogens to healthcare providers, raising concerns about the use of NIV in patients with viral pneumonia.[8] Helmet NIV has been used for AHRF including patients with COVID-19 pneumonia. The helmet surrounds the patient's entire head to supply oxygen and is sealed with a soft, airtight collar that wraps around the neck. Due to this design, it has advantages over the nasal and oro-nasal interfaces. These include less air leaks, no skin or nasal bridge injuries, no eye irritation, fitting for different facial contours,[9] and hypothetically less dissemination of aerosols in the environment.

Evaluation of helmet NIV as a respiratory support modality started more than two decades ago.[10] Helmet NIV has been investigated as a treatment for different forms of AHRF in adults in various settings, such as pre-hospital ambulance, emergency department and ICU.[7 11-15] However, clinical studies are relatively scarce and small in size. Their primary outcomes were

improvement in oxygenation and requirement for intubation. A systematic review concluded that there was insufficient scientific evidence to recommend helmet NIV in AHRF due to the limited number of trials available.[6]

However, the evidence on helmet NIV for AHRF is growing. A systematic review of randomized controlled trials (RCTs) and observational studies published before June 2016 found 11 studies involving 621 patients.[16] Compared with controls, the use of the helmet was associated with lower hospital mortality (odds ratio, 0.43; 95% CI, 0.26-0.69), intubation rate (odds ratio, 0.32; 95% CI, 0.21-0.47), and complications (odds ratio, 0.6; 95% CI, 0.4-0.92).[16] Moreover, there was no significant difference in gas exchange and ICU stay.[16] A meta-analysis of four RCTs (377 patients) showed that helmet NIV significantly increased the ratio of arterial oxygen partial pressure to fraction (percent) of inspired oxygen (PaO_2/FiO_2) (+73.4; 95% CI, 43.9-102.9) and decreased arterial carbon dioxide levels (-1.92; 95% CI, -3.21 to -0.63), intubation rate (relative risk, 0.21; 95% CI, 0.11-0.40) and in-hospital mortality rate (relative risk, 0.22; 95% CI, 0.09-0.50) compared to standard oxygen therapy.[17] In a more recent systematic review and network meta-analysis that included 25 studies (published up to April 2020) and 3804 patients with AHRF, treatment with helmet NIV (risk ratio, 0.40; 95% credible interval (CrI), 0.24-0.63; absolute risk difference, −0.19; 95% CrI, −0.37 to −0.09; low certainty) and face mask NIV (risk ratio, 0.83; 95% CrI, 0.68-0.99; absolute risk difference, −0.06; 95% CrI, −0.15 to −0.01]; moderate certainty) were associated with a lower risk of mortality compared with standard oxygen.[18] Moreover, helmet NIV (risk ratio, 0.26; 95% CrI, 0.14-0.46; absolute risk difference, −0.32; 95% CrI, −0.60 to −0.16; low certainty), face mask NIV (risk ratio, 0.76; 95% CrI, 0.62-0.90; absolute risk difference, −0.12; 95% CrI, −0.25 to −0.05); moderate certainty) and high-flow nasal oxygen (RR, 0.76 [95% CrI, 0.55-0.99]; absolute risk difference, −0.11; 95% CrI, −0.27 to −0.01; moderate certainty) were associated with lower risk of endotracheal intubation compared with standard oxygen.[18]

Data on helmet NIV in AHRF related to COVID-19 are emerging. A recent RCT conducted in patients admitted to 4 Italian ICUs with COVID-19 and moderate to severe AHRF found that treatment with helmet NIV did not result in significantly fewer days of respiratory support at 28 days from randomization (primary outcome) as compared with high-flow nasal oxygen alone (mean difference 2 days, 95% CI, -2 to 6, p=0.26).[19] Nevertheless, the intubation rate was significantly lower in the helmet group than in the high-flow nasal oxygen group (30% vs 51%; p=0.03).[19] Additionally, the median number of days free of invasive mechanical ventilation within 28 days was significantly higher in the helmet group than in the high-flow nasal oxygen group (28 versus 25 days; mean difference, 3 days; 95% CI, 0-7; P = 0.04).[19] The hospital mortality was 24% in the helmet group and 25% in the high-flow nasal oxygen group.[19]

As the efficacy of helmet NIV to improve outcomes in severe AHRF due to COVID-19 pneumonia has not been clearly established, the aim of this study is to compare helmet NIV with usual care versus usual care alone to reduce mortality. We hypothesize that helmet NIV will reduce 28-day all-cause mortality in patients with suspected or confirmed severe COVID-19 pneumonia and AHRF.

Methods and analysis

Trial design

This is an investigator-initiated, pragmatic parallel RCT that will compare helmet NIV with usual care to usual care alone in 1:1 ratio in patients with suspected or confirmed COVID-19 pneumonia and AHRF. The trial is sponsored by King Abdullah International Medical Research Center, Riyadh, Saudi Arabia, has been registered with ClinicalTrials.gov (NCT04477668) and will be conducted across multiple centers in Saudi Arabia. Training and in-service education on helmet NIV use as well as on protocol implementation will be provided to all participating centers. The competency of the bedside respiratory therapists will be checked by experienced respiratory care supervisors and intensivists.

Sample size

In a large observation study of patients with AHRF and ARDS, hospital mortality was 34.9% (95% CI, 31.4-38.5%) for patients with mild ARDS, 40.3% (95% CI, 37.4%-43.3%) for those with moderate ARDS, and 46.1% (95% CI, 41.9%-50.4%) for those with severe ARDS.[20] Assuming a mortality rate of 40% in patients with COVID-19 pneumonia and moderate to severe ARDS treated with usual care, we calculated that enrollment of 304 patients (152 in each group) would provide the study with 80% power to show an absolute difference of 15% in the primary outcome between the usual care group and helmet NIV group at a two-sided alpha level of 0.05.[21] To account for 5% loss to follow-up, the total number of patients needed in the trial is 320 patients.

Participant eligibility

The trial will enroll ICU patients with suspected or confirmed COVID-19 pneumonia who have AHRF. Detailed inclusion and exclusion criteria can be found in **Table 1**.

Informed consent

Informed consent will be obtained from the potential trial participants or their surrogate decision maker. A hybrid model of consent will be used where a priori consent is obtained if possible, otherwise delayed consent model will be obtained as per local approval.

Trial interventions

Helmet group

A helmet (Subsalve, USA or its equivalent), which is made of transparent latex-free polyvinyl chloride, will be applied to patients randomized to the intervention group as per the manufacturer instructions. It will be immediately connected to an ICU ventilator in pressure support (PS) mode with positive end-expiratory pressure (PEEP) using a conventional respiratory circuit joining two port sites to allow inspiratory and expiratory flow. The starting

settings is PS 8-10 cm H2O, PEEP 10 cm H2O with FiO_2 100%, targeting flow rate ≥50 L/min with an Inspiratory rise time 50 msec and end flow/cycling off 50% of maximal inspiratory flow. PEEP can be increased by 2 cm every 3 minutes to achieve SpO2≥90% at FIO_2 ≤ 60%, and PS can be increased by 2 cm every 3 minutes to achieve respiratory rate ≤ 25/min and disappearance of accessory muscle activity. The maximal allowed PS + PEEP is 30 cm H_2O. Helmet should be continuously applied for at least 48 hours.[19] More details of helmet application, set up and weaning can be found in the **Supplementary File**. Some patients may not tolerate the helmet. The physician or the respiratory therapist will explain the procedure to the patient. In case the patient continues to refuse the helmet, this with be documented in case report form. Dexmedetomidine may be used to improve compliance with the helmet. However, other intravenous sedatives such as benzodiazepines or intravenous narcotics should generally not be used. Patient then can be managed according to the usual care. Detailed data about tolerance will be collected.

Control group

In the control group, patients will receive usual care according to the clinical practices of each site. This may include oxygen provided high flow nasal cannula or NIV provided by nasal mask, face mask or total mask.

Decision to Intubate

The decision to intubate enrolled patients will be at the discretion of the treating team. There will be no involvement from the research team in this decision. However, the protocol provides guidance on assessing patients for the need of endotracheal intubation throughout NIV treatment (helmet NIV or usual care) according to the following:

Assess the patient within 4 hours and at frequent intervals throughout NIV treatment for

- Neurologic deterioration *(not attributed to sedation)*
- Persistent or worsening respiratory failure of NIV:
    - oxygen saturation <88%
    - respiratory rate >36/min
    - PO_2/FiO_2 ratio <100
    - a persistent requirement of FiO_2 ≥70%
- Intolerance of face mask or helmet
- Airway bleeding
- Copious respiratory secretions
- Respiratory acidosis with pH <7.25
- Hemodynamic instability
- Significant radiologic worsening

Co-Interventions

Patients who required endotracheal intubation will be managed by the primary team with lung protective strategy with tidal volumes of 6 mL/kg of ideal body weight and titration of PEEP to achieve oxygen saturation of 88% to 95% at the lowest possible FiO_2. Daily interruption of sedation, awakening and breathing trials, and early mobilization will be performed per the ICU standard care.[22] Management of COVID-19 will be as per local protocols; physicians are advised to follow the related clinical practice guidelines set by the Saudi Critical Care Society,[23] the Surviving Sepsis Campaign,[24 25] and the World Health Organization.[26] The study protocol does not mandate a particular therapy, however corticosteroids, immune modulators and

antiviral therapy will be all recorded. Conservative fluid management is recommended where neutral balance should be targeted and intravenous resuscitation should be reserved for shock treatment in both groups and fluid balance will be recorded.

Blinding

Due to the nature of the study intervention, blinding will not be possible.

Recruitment schedule and enrollment procedures

Schedule of assessments is detailed in **Table 2**. All non-intubated subjects will be screened upon admission to the ICU. Screening evaluations must be completed before randomization. A screening log will be kept to monitor and report the size of the patient population from which eligible patients have been randomized.

Co-enrollment in another RCT is permissible as long as inclusion in the other RCT would not confound the results of this trial and after discussion with the steering committees of the other studies.

Data collection

Baseline data on demographics, admission diagnosis and clinical information will be collected to. Clinical information will include Acute Physiology and Chronic Health Evaluation (APACHE) II score,[27] source of admission, ICU admission category (elective, emergency or non-surgical), ICU admission diagnosis (as defined by the APACHE III severity of illness scoring system) and co-morbidities (as defined by the APACHE II severity of illness scoring system).

During ICU and hospital stay, collection of clinical information will be recorded until discharge from ICU or 28 days after randomization.

Outcomes

The primary outcome will be 28-day all-cause mortality. Secondary outcomes will include requirement for endotracheal intubation within 28 days, ICU mortality, hospital mortality, ICU-free days at day 28, ventilator-free days at day 28, renal replacement therapy-free days at day 28, vasopressor-free days at day 28, skin pressure injuries, tolerance of helmet (>1-hour use), 180-day mortality (Follow-up study), and 180-day EuroQoL (EQ)-5D-5L[28] (Follow-up study).

There will be follow up at day 180 and data about vital status, functional status (EuroQoL (EQ)-5D-5L), length of stay in hospital, date and cause of death will be recorded. For participants discharged from hospital prior to day 180, vital status at time of discharge will be recorded. For patients who have been discharged from hospital, follow up will be conducted by telephone. Hospital mortality will be censored at 180 days from the date of enrollment.

Data analysis

A formal statistical analysis plan will be agreed upon and placed in the public domain before the study database is locked for the analysis of the primary outcome. The primary outcome will be compared in the intention to-treat and per-protocol cohorts (effectiveness analysis) using the chi-square test. Results will be reported as relative risk with 95% CI. Kaplan–Meier curves will be plotted to assess the time from enrollment to death in the hospital and will be compared by means of the log-rank test. A two-tailed P value <0.05 will be considered to indicate statistical significance. SAS software, version 9.2 (SAS Institute) will be used for all the analyses. A detailed statistical analysis plan will be published subsequently.

A priori analysis will be done for the following subgroups:

I. Patients with moderate ARDS (PaO_2/FIO_2 ratio 100-200) and patients with severe ARDS ($PaO_2/FIO2$ ratio <100)

II. Obese patients (body mass index >30 kg/m^2) and patients with body mass index ≤30

III. Patients aged >65 years and ≤65 years

IV. APACHE II score higher or lower than the median of enrolled patients

For the occasional randomized patient who is withdrawn from the trial and allows use of data, the patient's data will be included in the group to which he/she was allocated as per the intention-to-treat principle and the reason of withdrawal will be documented.

Trial management and monitoring

The study Steering Committee members will be responsible for overseeing the conduct of the trial, for upholding or modifying study procedures as needed, addressing challenges with protocol implementation, formulating the analysis plan, reviewing and interpreting the data, and preparing the manuscript. This will be achieved through meetings (in-person or by conference calls) at least quarterly.

Several measures are taken to minimize, observe and document any potential safety concerns. First, any unexpected safety concerns will be reported immediately to the Steering Committee. Second, an independent Data Safety Monitoring Board will be monitoring the safety of the trial. Lastly, interim analyses will be conducted after recruiting 1/3 and 2/3 of the total patients and the interim test statistics will be the primary outcome analysis for both safety and effectiveness. The Data Safety Monitoring Board will use formal stopping rules based on the primary endpoint of 28-day mortality. The trial may be stopped for safety ($p<0.01$) or effectiveness ($p<0.001$). There will be no plans to terminate the trial for futility. We will account for alpha spending by the O'Brien Fleming method and the final p value will be considered at 0.048. The principles used in the conduct of safety monitoring and reporting in this trial are those outlined by Cook et al.[29]

In this trial, reporting of serious adverse events will be restricted to events that are not captured as study outcome and are considered to be related to the helmet NIV (possibly, probably or definitely).[29] These may include skin ulceration at the neck seal, patient intolerance (i.e., claustrophobia), barotrauma (development of pneumothorax), cardiovascular events (i.e., cardiac arrest and hypotension with drop in blood pressure to systolic <90 mm Hg) and device complications (i.e., helmet deflation).

Ethics and dissemination

The study will be conducted according to the principles of the latest version of Good Clinical Practice (GCP) and in accordance with all relevant local ethical, regulatory, and legal requirements. A manuscript with the results of the primary study will be published in a peer-reviewed journal. Separate manuscripts will be written on secondary aims, and these will also be submitted for publication in peer reviewed journals as well.

Discussion

The importance of this study stems from the current pandemic situation as different treatment modalities are being sought to answer important clinical questions. Available literature on the evaluation of helmet NIV as a respiratory support modality in COVID-19 patients is limited. Table 3 provides the list of ongoing RCTs on helmet NIV. This study aims to contribute to the existing literature and in turn influence clinical practice.

The first patient was enrolled in February 2021 and we aim to recruit more sites across the region. As of April 5, 2021, we have enrolled 50 patients. There are several sites that are processing IRB approvals.

The main limitation to our study is inability to blind the given allocation due to the nature of the intervention.

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Acknowledgements

The authors would like to thank the Data Safety & Monitoring Board: Chair: Dr. Nicholas S. Hill (Professor of Medicine, Chief of Pulmonary, Critical Care and Sleep Division, Tufts Medical Center, Boston, Massachusetts, USA), DSM members: Dr. Stefano Nava (Professor of Respiratory Medicine University of Bologna, Chief of the Respiratory and Critical Care Sant' Orsola Hospital Bologna, Specialist in Respiratory Medicine and Intensive Care Medicine, University of Bologna, Italy), Dr. James Mojica (Vice Chief and Clinical Director of Pulmonary & Critical Care, Director, The Sleep Center at Spaulding, Massachusetts General Hospital, USA) and Dr. Michael Harhay (Assistant Professor of Epidemiology and Medicine-Pulmonary and Critical Care, Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania USA).

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Funding The study is funded by King Abdullah International Medical Research Center (RC 20/306/R). The study sponsor does not have any role in the study design, collection, management, analysis, and interpretation of data as well as writing of the report.

Competing interests None declared

Ethics approval

The study has been approved by the Institutional Review Board (IRB) of Ministry of National Guard Health Affairs (MNGHA) and the respective Institutional Review Boards of all the other centers.

Patient consent for publication Not required.

Provenance and peer review Not commissioned, externally peer reviewed.

Table 1. Eligibility Criteria

Inclusion Criteria	1. Suspected or confirmed COVID-19* 2. Aged ≥ 14 years old. ICUs that use other age cut-off for adult patients will adhere to their local standard (16 or 18 years) 3. Acute hypoxemic respiratory failure based on PaO2/FIO2 ratio < 200 despite supplemental oxygen with a partial /non-rebreathing mask at a flow rate >10 L/min or above 4. Able to follow instructions (e.g. squeeze hand on command, eye contact with care provider, stick out tongue on command,etc.)
Exclusion Criteria	1. Prior intubation during this hospital admission 2. Cardiopulmonary arrest 3. Glasgow coma scale < 12 4. Tracheostomy 5. Upper airway obstruction 6. Active epistaxis 7. Requirement for more than one vasopressor to maintain mean arterial pressure > 65 mm Hg. 8. Pregnancy 9. Imminent intubation 10. Patients with do-not-intubate orders (or equivalent) 11. Enrolled in another trial for which co-enrolment is not approved including trials on mechanical ventilation 12. Patients already treated with helmet 13. Patients with chronic carbon dioxide retention (CO2>45)
Eligible non-randomized	1. Patient or substitute decision- maker declines consent 2. ICU physician or other treating clinician declines consent

***A** suspected/probable COVID-19 case is defined as: At least two of the following symptoms: fever (measured or subjective), chills, rigors, myalgia, headache, sore throat, new olfactory and taste disorder(s) **OR** at least one of the following symptoms: cough, shortness of breath, or difficulty breathing **OR** severe respiratory illness with at least one of the following: Clinical or radiographic evidence of pneumonia, **OR** ARDS **AND** no alternative more likely diagnosis. A confirmed COVID-19 case is defined as: Detection of SARS-CoV-2 RNA in a respiratory specimen using a molecular amplification detection test such as rt-PCR.

Table 2. Schedule of assessments in the trial

Task	Screening	Randomization	Baseline	Day 1-28	180-Day Follow up
Assess eligibility to enter study	X				
Assess ability to gain consent & follow-up	X				
Consent	X				
Demographics & eligibility checklist	X	X	X		
Laboratory data			X	X	
Vital signs			X	X	
Vital status up to Day 28 in the ICU				X	X
Vital and functional status					X
Discharge date from ICU, from hospital				X	X
Adverse events				X	
Protocol violation				X	

Table 3. List of ongoing registered clinical trials on helmet noninvasive ventilation

Trial	Registration	Interventions	Design	Countries	N
Helmet Non-Invasive Ventilation for COVID-19 Patients (Helmet-COVID)	NCT04477668	Helmet vs. standard of care	Multicenter RCT	Saudi Arabia	320
Comparison of High Flow Nasal Cannula (HFNC), Face-mask Non-Invasive Ventilation (NIV) & Helmet NIV in COVID-19 ARDS Patients (NIV COVID19)	NCT04715243	High flow nasal cannula (HFNC) vs. helmet NIV vs. mask NIV	Multicenter RCT	Oman	360
Helmet CPAP Versus HFNC in COVID-19 (COVID HELMET)	NCT04395807	HFNC vs. helmet CPAP	Single center RCT	Sweden	120
COVIDNOCHE Trial (HFNO Versus CPAP Helmet) in COVID-19 Pneumonia (COVIDNOCHE)	NCT04381923	HFNC vs. helmet CPAP	Single center RCT	USA	200
Early CPAP in COVID-19 Patients With Respiratory Failure. (EC-COVID-RCT)	NCT04326075	Early helmet CPAP vs. current clinical practice	Single center RCT	Italy	900

Helmet-NIV Protocol

Setup and preparation

- Use unheated, low-compliance, dual limb breathing circuit.
- Insert a bacterial/viral filter at the expiratory port of the ventilator.
- Carry out the required preoperational check.
- To avoid patient-ventilator asynchrony, explain the application and the procedure of the helmet to the patient.
- Insert the earplugs into patient ears.
- Use the under-arm pads to avoid strap pressure.

Initial setup

- Can be used with a ventilator or NIV machines.
- Set up the ventilator on Pressure Support Ventilation (PSV).
- PSV 8-10 cm H2O pressure, positive end-expiratory pressure (PEEP) 10 cm H2O pressure, FiO2 100%.
- Flow rate >50 L/min, inspiratory rise time 50 msec, End Flow/Cycling off 50% of maximal inspiratory flow.

Titration

- Increase PEEP by 2-3 cm H2O every 3 minutes to achieve SpO2 ≥ 92% on FiO2 ≤ 60%
- Higher PEEP than what is used on face mask NIV is allowed and tolerated.
- Increase PS by 2-3 cm every 3 minutes to achieve respiratory rate (RR) ≤ 25/min or clear patient comfort.
- The maximal allowed PS + PEEP is 30 cm H_2O.
- Helmet should be applied continuously for at least 48 hours.
- Titrate FiO2 to ≤60% as soon as possible.

Sedation

- Dexmedetomidine may be used to improve compliance with the helmet. However, other intravenous sedatives such as benzodiazepines or intravenous narcotics should not be used.

Weaning when clinical condition allows

- Titrate PS by 2 cm H2O every 3 hours if RR ≤ 25/min.
- Titrate PEEP by 2 cm H2O every 3 hours if SpO2 >92% on <60% FiO2.
- If RR ≤25/min on PSV ≤8 cm and SpO2 >92% on FiO2 ≤50% and PEEP ≤8 cm H2O, the helmet can be discontinued and patient switched to high-flow nasal cannula, or oxygen supply at O2 at 6L/min or higher.
  Helmet NIV could be resumed at any time if the respiratory rate was greater than 25 breaths/min and/or SpO2 was lower than 92% on FiO2 of ≥60% .

Nursing Care

- Perform oral care/suction before helmet application.
- Place a nasogastric tube before helmet application if felt necessary by treating physician.
- A suction Yankauer for suctioning and a straw for drinking can be introduced through the patient port without removing the helmet.

- Intravenous sedation (Dexmedetomidine or others) can be used at the discretion of the treating physician to assure patient comfort.

Equipment required

- Mechanical ventilator (BP 840, PB 980, Servo-I, Drager V 500, Astral and V680)
- Unheated Double lumen circuit
- Bacterial/viral filter
- Subsalve helmet or equivalent
- Under arm pads (any kind)
- Ear plugs

General recommendations to consider intubation for patients on NIV (assessed within 4 hours and at frequent intervals throughout NIV treatment):

- Neurologic deterioration (not attributed to sedation)
- Persistent or worsening respiratory failure of NIV:
    - oxygen saturation <88%
    - respiratory rate >36/min
    - P/F ratio <100
    - a persistent requirement of FiO2 ≥70%
- Intolerance of face mask or helmet
- Airway bleeding
- Copious respiratory secretions
- Respiratory acidosis with pH <7.25
- Hemodynamic instability
- Significant radiologic worsening

Humidification

Appropriate level of humidification can be achieved via bubble humidifier with external oxygen flow of 5 L/Min entrained into the ventilator circuit proximal to the patient helmet.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	6
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	8-10
	2b	Specific objectives or hypotheses	10
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	10
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	not applicable
Participants	4a	Eligibility criteria for participants	11
	4b	Settings and locations where the data were collected	10
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	11-12
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	15
	6b	Any changes to trial outcomes after the trial commenced, with reasons	not applicable
Sample size	7a	How sample size was determined	11
	7b	When applicable, explanation of any interim analyses and stopping guidelines	15
Randomisation:			10
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	10
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	14

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	15
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	not applicable
	13b	For each group, losses and exclusions after randomisation, together with reasons	not applicable
Recruitment	14a	Dates defining the periods of recruitment and follow-up	not applicable
	14b	Why the trial ended or was stopped	not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	not applicable
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	not applicable
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	not applicable
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	not applicable
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	16
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	17
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	17
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	not applicable
Other information			
Registration	23	Registration number and name of trial registry	6
Protocol	24	Where the full trial protocol can be accessed, if available	21
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Helmet noninvasive ventilation for COVID-19 patients "Helmet-COVID": study protocol for a multicenter randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-052169.R1
Article Type:	Protocol
Date Submitted by the Author:	05-Jul-2021
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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Intensive care, Respiratory medicine, Infectious diseases
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, RESPIRATORY MEDICINE (see Thoracic Medicine), COVID-19

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Helmet noninvasive ventilation for COVID-19 patients "Helmet-COVID": study protocol for a multicenter randomized controlled trial

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Abstract

Introduction

Noninvasive ventilation delivered by helmet is has been used for respiratory support of patients with acute hypoxemic respiratory failure due to COVID-19 pneumonia. The aim of this study is to compare helmet noninvasive ventilation with usual care versus usual care alone to reduce the mortality.

Methods and analysis

This is a multicenter, pragmatic, parallel, randomized controlled trial that compares helmet noninvasive ventilation with usual care to usual care alone in 1:1 ratio. A total of 320 patients will be enrolled in this study. The primary outcome is 28-day all-cause mortality. The primary outcome will be compared between the two study groups in the intention-to-treat and per-protocol cohorts. An interim analysis will be conducted for both safety and effectiveness.

Ethics and dissemination

Approvals are obtained from the Institutional Review Boards (IRBs) of each participating institution. Our findings will be published in peer-review journals and presented at relevant conferences and meetings.

Trial registration number NCT04477668 registered on July 20, 2020 **Article Summary**

Strengths and limitations of this study

- This trial compares helmet NIV to usual care for respiratory support of patients with acute hypoxemic respiratory failure due to COVID-19 pneumonia.
- The trial is a multi-center, pragmatic, parallel randomized controlled trial.
- The main limitation is the unblinded design due to the nature of the intervention.

Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a pandemic resulting in over 181 million cases and approximately 3.9 million fatalities as of June 29, 2021.[1] The resulting Coronavirus Disease 2019 (COVID-19) leads to severe pneumonia and acute respiratory distress syndrome (ARDS) among other organ injury.[2] ARDS may occur in up to 5% of infected patients.[3-5] Early in the pandemic, invasive mechanical ventilation was widely used because of concerns about noninvasive ventilation safety and efficacy. However, noninvasive ventilation (NIV) use increased with time, including mask NIV and helmet NIV.

NIV has been shown to be physiologic benefits in patients with acute hypoxemic respiratory failure (AHRF) secondary to pulmonary edema, atelectasis, or pneumonia.[6] It has been shown to improve arterial oxygenation by increasing functional residual capacity, shifting the tidal volume to a more compliant part of the pressure-volume curve, thus reducing both the work of breathing and the risk of tidal opening and closure of the airways.[7] NIV is commonly provided through nasal or oro-nasal interfaces. The resulting aerosol generation may increase the risk of transmission of pathogens to healthcare providers, raising concerns about the use of NIV in patients with viral pneumonia.[8] Helmet NIV has been used for AHRF including patients with COVID-19 pneumonia. The helmet surrounds the patient's entire head to provide positive pressure and supply oxygen and is sealed with a soft, airtight collar that wraps around the neck. Due to this design, it has advantages over the nasal and oro-nasal interfaces. These include less air leaks, no skin or nasal bridge skin injuries, no eye irritation, fitting for different facial contours,[9] and hypothetically less dissemination of aerosols in the environment. However, helmet interface may be associated with increase in dead space (especially if the settings are not used appropriately), claustrophobia, discomfort, and difficulty in access for suction and feeding.

Evaluation of helmet NIV as a respiratory support modality started more than two decades ago.[10] Helmet NIV has been investigated as a treatment for different forms of AHRF in adults in various settings, such as pre-hospital ambulance, emergency department and ICU.[7 11-15] However, earlier clinical studies are relatively scarce and mostly small in size, and often used improvement in oxygenation and intubation rate as primary outcomes.[6]

However, the evidence on helmet NIV for AHRF is growing. A systematic review of randomized controlled trials (RCTs) and observational studies published before June 2016 found 11 studies involving 621 patients.[16] Compared with controls, the use of the helmet was associated with lower hospital mortality, intubation rate, and complications.[16] Moreover, there was no significant difference in gas exchange and ICU stay.[16] A meta-analysis of four RCTs (377 patients) showed that helmet NIV significantly increased the ratio of arterial oxygen partial pressure to fraction of inspired oxygen (PaO_2/FiO_2) and decreased arterial carbon dioxide levels, intubation rate and in-hospital mortality compared to standard oxygen therapy.[17] In a more recent systematic review and network meta-analysis that included 25 studies (published up to April 2020) and 3804 patients with AHRF, mortality and intubation rate were lower with helmet NIV compared to standard oxygen by more than 50%, while the effect of mask NIV and high-flow nasal oxygen were modest compared to standard oxygen.[18] Helmet NIV was superior to both mask NIV and high-flow nasal oxygen, while mask NIV and high-flow nasal oxygen were not different in their effects on mortality and intubation rate.[18] One study reported the cost-effectiveness of helmet NIV compared to mask NIV.[19]

Data on helmet NIV in AHRF related to COVID-19 are emerging. A recent RCT conducted in 4 Italian ICUs on patients with COVID-19 and moderate to severe AHRF found that treatment with helmet NIV did not result in significantly fewer days of respiratory support at 28 days from randomization (primary outcome) as compared with high-flow nasal oxygen alone (mean difference 2 days, 95% CI, -2 to 6, p=0.26).[20] Nevertheless, the intubation rate

was significantly lower in the helmet NIV group compared to the high-flow nasal oxygen group (30% vs 51%; p=0.03).[20] Additionally, the median number of days free of invasive mechanical ventilation within 28 days was significantly higher in the helmet NIV group than in the high-flow nasal oxygen group (28 versus 25 days; mean difference, 3 days; 95% CI, 0-7; P = 0.04).[20] The hospital mortality was 24% in the helmet NIV group and 25% in the high-flow nasal oxygen group.[20]

As the efficacy of helmet NIV to improve outcomes in severe AHRF due to COVID-19 pneumonia has not been clearly established, the aim of this study is to compare helmet NIV with usual care versus usual care alone to reduce 28-day all-cause mortality. We hypothesize that helmet NIV will reduce 28-day all-cause mortality in patients with suspected or confirmed severe COVID-19 pneumonia and AHRF.

Methods and analysis

Trial design

This is an investigator-initiated, pragmatic parallel RCT that will compare helmet NIV with usual care to usual care alone in 1:1 ratio in patients with suspected or confirmed COVID-19 pneumonia and AHRF. Randomization is performed using a computer-generated schedule using variable block sizes (4 or 6) and is stratified by site. The trial is sponsored by King Abdullah International Medical Research Center, Riyadh, Saudi Arabia, has been registered with ClinicalTrials.gov (NCT04477668) and is conducted across multiple centers in Saudi Arabia. Training and in-service education on helmet NIV use as well as on protocol implementation are provided to all participating centers. The competency of the bedside respiratory therapists is supervised by experienced respiratory care supervisors and intensivists.

Sample size

In a large observation study of patients with AHRF and ARDS, hospital mortality was 34.9% (95% CI, 31.4-38.5%) for patients with mild ARDS, 40.3% (95% CI, 37.4%-43.3%) for those with moderate ARDS, and 46.1% (95% CI, 41.9%-50.4%) for those with severe ARDS.[21] A systematic review found an overall pooled mortality estimate among 10,815 patients with ARDS due to COVID-19 to be 39% (95% CI: 23–56%).[22] Considering a mortality rate of 40% in patients with COVID-19 pneumonia and moderate to severe ARDS treated with usual care, we calculated that enrollment of 304 patients (152 in each group) would provide the study with 80% power to demonstrate an absolute difference of 15% in the primary outcome between the usual care group and helmet NIV group at a two-sided alpha level of 0.05. To account for 5% loss to follow-up, the total number of patients required for the trial is 320 patients.

Participant eligibility

The trial will enroll ICU patients with suspected[23] or confirmed COVID-19 pneumonia who have AHRF. Detailed inclusion and exclusion criteria can be found in **Table 1**.

Informed consent

Informed consent will be obtained from the potential trial participants or their surrogate decision makers. A hybrid model of consent will be used where a priori consent is obtained if possible, otherwise delayed consent model will be obtained as per local approvals. The first patient was enrolled in February 2021. As of June 29, 2021, a total of 199 patients were enrolled from 5 sites. There are several sites that are processing IRB and regulatory approvals.

Patient and public involvement

There was no patient or public involvement in the conception, design or conduct of the study, or the writing or editing of this paper. However, patient comfort and experience as well as compliance to the intervention were taken in to consideration and data on these are collected.

Trial interventions

Helmet group

A helmet (Subsalve, USA or its equivalent), which is made of transparent latex-free polyvinyl chloride, will be applied to patients randomized to the intervention group as per the study protocol which considers the manufacturer instructions. It will be immediately connected to an ICU ventilator in pressure support (PS) mode with positive end-expiratory pressure (PEEP) using a conventional respiratory circuit joining two port sites to allow inspiratory and expiratory flow. The starting settings is PS of 8-10 cm H2O, PEEP of 10 cmH2O with FiO_2 of 100%, targeting flow rate of ≥50 L/min with an inspiratory rise time of 50 msec and end flow/cycling off of 50% of maximal inspiratory flow. PEEP may be increased by 2 cm every 3 minutes to achieve oxygen saturation (SpO2) ≥90% on FIO_2 ≤ 60%, and PS can be increased by 2 cm every 3 minutes to achieve respiratory rate ≤ 25/min and disappearance of accessory muscle activity. The maximal allowed PS + PEEP is 30 cm H_2O. Interruptions of helmet should be avoided or kept at minimum at least in the first 48 hours.[20] More details of helmet NIV application, set up and weaning can be found in the **Supplementary File**. Some patients may not tolerate helmet NIV. In that case, the physician or the respiratory therapist explains the procedure to the patient. Dexmedetomidine infusion may be used to improve ccomfort with the helmet NIV. Other intravenous sedatives such as benzodiazepines or intravenous narcotics should generally not be used. If the patient continues to be intolerant to the helmet, the patient can be managed according to the usual care. Detailed data about helmet NIV tolerance are collected.

Control group

In the control group, patients receive usual care according to the clinical practices of each site. This may include oxygen provided using standard oxygen devices, high-flow nasal oxygen or NIV provided by nasal mask, face mask or total mask.

Endotracheal Intubation

The decision to intubate will be at the discretion of the treating team with no involvement from the research team. However, the protocol provides guidance on assessing patients for the need of endotracheal intubation throughout the study period (for both study groups: helmet NIV or usual care) according to the following general principles:

Enrolled patients should be assessed within 4 hours of enrollment (or sooner as required) and at frequent intervals for the following criteria, although the decision is usually not based on a single variable:

- Neurologic deterioration *(not attributed to sedation)*
- Persistent or worsening respiratory failure of NIV (manifesting as oxygen saturation <88%, respiratory rate >36/min, PaO_2/FiO_2 ratio <100 or persistent requirement of FiO_2 ≥70%)
- Intolerance of face mask or helmet
- Airway bleeding
- Copious respiratory secretions
- Respiratory acidosis with pH <7.25
- Hemodynamic instability
- Significant radiologic worsening

Co-Interventions

Patients who require endotracheal intubation are managed by the primary team with lung protective strategy with tidal volumes of 6 mL/kg of predicted body weight and titration of PEEP to achieve oxygen saturation of 88% to 95% at the lowest possible FiO_2. Daily interruption of sedation, awakening and breathing trials, and early mobilization are performed as per the ICU standards.[24] Management of COVID-19 is provided as per local protocols; physicians are advised to follow the clinical practice guidelines set by the Saudi Critical Care Society,[25] the Surviving Sepsis Campaign,[26 27] and the World Health Organization.[28] The study protocol does not mandate particular therapies; however, corticosteroids, immune modulators and antiviral therapy are all recorded. Conservative fluid management is recommended where neutral balance should be targeted and intravenous resuscitation should be reserved for shock treatment in both groups and fluid balance is recorded.

Blinding

Due to the nature of the study intervention, blinding is not be possible.

Recruitment schedule and enrollment procedures

Schedule of assessments is detailed in **Table 2**. All non-intubated subjects with suspected or confirmed COVID-19 are screened upon admission to the ICU. A screening log will be kept to monitor and report the size of the patient population from which eligible patients have been randomized. Co-enrollment in other RCTs is permissible as long as inclusion in the other RCT would not confound the results of this trial and after discussion with the steering committees of the other studies.

Data collection

Baseline data on demographics, admission diagnosis and clinical information are collected. Clinical information include Acute Physiology and Chronic Health Evaluation (APACHE) II score,[29] source of admission, ICU admission category (elective, emergency or non-surgical), ICU admission diagnosis and co-morbidities (as defined by the APACHE II severity of illness scoring system). Daily data will be recorded until discharge from ICU or 28 days after randomization. We will collect data on the use of helmet including the tolerance of helmet (>1-hour use).

Outcomes

The primary outcome is 28-day all-cause mortality. Secondary outcomes are intubation rate within 28 days**,** ICU mortality**,** hospital mortality (censored at day 180), ICU-free days at day 28**,** invasive ventilation-free days at day 28, renal replacement therapy-free days at day 28 and vasopressor-free days at day 28. Safety outcomes include skin pressure injuries, barotrauma and serious adverse events (including cardiovascular events and device complications).

Additionally, there will be a follow up of enrolled patients at day 180 about vital status, functional status (EuroQoL (EQ)-5D-5L) which is planned to be reported separately. For patients who have been discharged from hospital before day 180, follow up will be conducted by telephone.

Data analysis

A formal statistical analysis plan will be agreed upon and placed in the public domain before the study database is locked for the analysis of the primary outcome. The primary outcome

will be compared in the intention-to-treat and per-protocol cohorts (effectiveness analysis) using the chi-square test. Results will be reported as relative risk with 95% CI. Kaplan–Meier curves will be plotted to assess the time from enrollment to death and will be compared by means of the log-rank test. A two-tailed P value <0.05 will be considered to indicate statistical significance. SAS software, version 9.2 (SAS Institute) will be used for all the analyses.

A priori analysis will be done for the following subgroups:

I. Patients with moderate ARDS (PaO_2/FIO_2 ratio 100-200) and patients with severe ARDS ($PaO_2/FIO2$ ratio <100)
II. Obese patients (body mass index >30 kg/m^2) and patients with body mass index ≤30
III. Patients aged >65 years and ≤65 years
IV. APACHE II score higher or lower than the median of enrolled patients

For the occasional randomized patient who is withdrawn from the trial and allows use of data, the patient's data will be included in the group to which he/she was allocated as per the intention-to-treat principle and the reason of withdrawal will be documented.

Trial management and monitoring

The study Steering Committee members will be responsible for overseeing the conduct of the trial, for upholding or modifying study procedures as needed, addressing challenges with protocol implementation, formulating the analysis plan, reviewing and interpreting the data, and preparing the manuscript. This will be achieved through meetings (in-person or by conference calls) at least quarterly.

Several measures are taken to minimize, observe and document any potential safety concerns. First, any unexpected safety concerns will be reported immediately to the Steering

Committee and IRB. Second, an independent Data Safety Monitoring Board will be monitoring the safety of the trial. Lastly, interim analyses will be conducted after recruiting 1/3 and 2/3 of the total patients and the interim test statistics will be the primary outcome analysis for both safety and effectiveness. The Data Safety Monitoring Board will use formal stopping rules based on the primary endpoint of 28-day mortality. The trial may be stopped for safety ($p<0.01$) or effectiveness ($p<0.001$). There will be no plans to terminate the trial for futility. We will account for alpha spending by the O'Brien Fleming method and the final p value will be considered at 0.048. The principles used in the conduct of safety monitoring and reporting in this trial are those outlined by Cook et al.[30]

In this trial, reporting of serious adverse events will be restricted to events that are not captured as study outcome and are considered to be related to the helmet NIV (possibly, probably or definitely).[30] These may include cardiovascular events (i.e., cardiac arrest and hypotension with drop in blood pressure to systolic <90 mm Hg) and device complications (i.e., helmet deflation).

Ethics and dissemination

The study will be conducted according to the principles of the latest version of Good Clinical Practice (GCP) and in accordance with all relevant local ethical, regulatory, and legal requirements. A manuscript with the results of the primary study will be published in a peer-reviewed journal. Separate manuscripts will be written on secondary aims, and these will also be submitted for publication in peer reviewed journals as well.

Data availability

Once all planned analyses have been completed and published or presented, data will be shared upon reasonable request from the chief investigator.

Discussion

The importance of this study stems from the current pandemic situation as different treatment modalities are being sought to answer important clinical questions. Available literature on the evaluation of helmet NIV as a respiratory support modality in COVID-19 patients is limited. Table 3 provides the list of ongoing RCTs on helmet NIV. This study aims to contribute to the existing literature and in turn influence clinical practice.

We planned our pragmatic trial to address whether using helmet NIV as the primary non-invasive respiratory support in patients with severe COVID-19, in addition to the commonly used high-flow nasal oxygen and mask NIV improves outcome. By nature of this question, there is heterogeneity of the control group; as patients in this group could receive standard oxygen, high-flow nasal oxygen or mask NIV at the decision of the treating team. This approach is supported by a recent network meta-analysis of randomized controlled trials that showed only a modest effect of high-flow nasal oxygen and mask NIV on mortality or intubation rate compared to standard oxygen, while patients treated with helmet NIV had more than 50% reduction in mortality and intubation rate compared to the other three modalities.[18] In addition, this approach is likely to be more representative of usual practice in which patients may get oxygen therapy, high-flow nasal oxygen and NIV at different times during their acute illness. Given the fact that the use of helmet NIV has not been widespread across ICUs, we thought that the broader question addressed by our study might be more relevant to deciding whether to introduce this modality or not in a given ICU.

The main limitation to our study is inability to blind the given allocation due to the nature of the intervention.

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Acknowledgements

The authors would like to thank all the participating patients and their families, as well as the members of the Data Safety & Monitoring Board: Chair: Dr. Nicholas S. Hill (Professor of Medicine, Chief of Pulmonary, Critical Care and Sleep Division, Tufts Medical Center, Boston, Massachusetts, USA), DSM members: Dr. Stefano Nava (Professor of Respiratory Medicine University of Bologna, Chief of the Respiratory and Critical Care Sant' Orsola Hospital Bologna, Specialist in Respiratory Medicine and Intensive Care Medicine, University of Bologna, Italy), Dr. James Mojica (Vice Chief and Clinical Director of Pulmonary & Critical Care, Director, The Sleep Center at Spaulding, Massachusetts General Hospital, USA) and Dr. Michael Harhay (Assistant Professor of Epidemiology and Medicine-Pulmonary and Critical Care, Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania USA).

Contributors YA is the principal investigator and participated in the project concept, design, final approval, and manuscript preparation, review and submission. HT, SD, HD, SA, MH, HH, MM, OZ, EQ, WW, SQ, FH, JC, MS, AH, AM, AE, AB, ZA ZD, AK, RQ, AG, AT, KG, MA, HG, AA, FB, HS, MO, YI, AF participated in the critical revision, final approval of the protocol and manuscript preparation, review and submission. All authors agree to be accountable for the accuracy and integrity of the work.

Funding The study is funded by King Abdullah International Medical Research Center (RC 20/306/R). The study sponsor does not have any role in the study design, collection, management, analysis, and interpretation of data as well as writing of the report.

Competing interests None declared

Ethics approval

The study has been approved by the Institutional Review Board (IRB) of Ministry of National Guard Health Affairs (MNGHA) and the respective Institutional Review Boards of all the other centers.

Patient consent for publication Not required.

Provenance and peer review Not commissioned, externally peer reviewed.

Table 1. Eligibility Criteria

Inclusion Criteria	1. Suspected or confirmed COVID-19* 2. Aged ≥ 14 years old. ICUs that use other age cut-off for adult patients will adhere to their local standard (16 or 18 years) 3. Acute hypoxemic respiratory failure based on PaO2/FiO2 ratio < 200 despite supplemental oxygen with a partial or non-rebreathing mask at a flow rate >10 L/min or above 4. Able to follow instructions
Exclusion Criteria	1. Prior intubation during this hospital admission 2. Cardiopulmonary arrest 3. Glasgow coma scale <12 4. Tracheostomy 5. Upper airway obstruction 6. Active epistaxis 7. Requirement for more than one vasopressor to maintain mean arterial pressure >65 mm Hg. 8. Pregnancy 9. Imminent intubation 10. Patients with do-not-intubate orders (or equivalent) 11. Enrolled in another trial for which co-enrolment is not approved including trials on mechanical ventilation 12. Patients already treated with helmet

	13. Patients with chronic carbon dioxide retention (PaCO2>45)
Eligible non-randomized	1. Patient or substitute decision-maker declines consent 2. ICU physician or other treating clinician declines consent

*A suspected/probable COVID-19 case is defined as: At least two of the following symptoms: fever (measured or subjective), chills, rigors, myalgia, headache, sore throat, new olfactory and taste disorder(s) **OR** at least one of the following symptoms: cough, shortness of breath, or difficulty breathing **OR** severe respiratory illness with at least one of the following: Clinical or radiographic evidence of pneumonia, **OR** ARDS **AND** no alternative more likely diagnosis. A confirmed COVID-19 case is defined as: Detection of SARS-CoV-2 RNA in a respiratory specimen using a molecular amplification detection test such as rt-PCR (https://wwwn.cdc.gov/nndss/conditions/coronavirus-disease-2019-covid-19/case-definition/2020/).

Table 2. Schedule of assessments in the trial

Task	Screening	Randomization	Baseline	Day 1-28	180-Day Follow up
Assess eligibility to enter study	X				
Assess ability to gain consent & follow-up	X				
Consent	X				
Demographics and eligibility checklist	X	X	X		
Laboratory data			X	X	
Vital signs			X	X	
Vital status up to Day 28 in the ICU				X	X
Vital and functional status					X
Discharge date from ICU, from hospital				X	X
Adverse events				X	
Protocol violations				X	

Table 3. List of ongoing registered randomized controlled trials (RCTs) on helmet noninvasive ventilation

Trial	Registration	Interventions	Design	Countries	N
Helmet non-invasive ventilation for COVID-19 patients (Helmet-COVID)	NCT04477668	Helmet vs. usual care	Multicenter RCT	Saudi Arabia	320
Comparison of high-flow nasal oxygen, face-mask NIV and helmet NIV in COVID-19 ARDS patients (NIV COVID19)	NCT04715243	High-flow nasal oxygen vs. helmet NIV vs. mask NIV	Multicenter RCT	Oman	360
Helmet CPAP vs. high-flow nasal oxygen in COVID-19 (COVID HELMET)	NCT04395807	High-flow nasal oxygen vs. helmet CPAP	Single-center RCT	Sweden	120
High-flow nasal oxygen vs. CPAP Helmet in COVID-19 pneumonia (COVIDNOCHE)	NCT04381923	High-flow nasal oxygen vs. helmet CPAP	Single-center RCT	USA	200
Early CPAP in COVID-19 patients with respiratory failure (EC-COVID-RCT)	NCT04326075	Early helmet CPAP vs. usual care	Single-center RCT	Italy	900

Helmet-NIV Protocol

Setup and preparation

- Use unheated, low-compliance, dual limb breathing circuit.
- Insert a bacterial/viral filter at the expiratory port of the ventilator.
- Carry out the required preoperational check.
- To avoid patient-ventilator asynchrony, explain the application and the procedure of the helmet to the patient.
- Insert the earplugs into patient ears.
- Use the under-arm pads to avoid strap pressure.

Initial setup

- Can be used with a ventilator or NIV machines.
- Set up the ventilator on Pressure Support Ventilation (PSV).
- PSV 8-10 cm H2O pressure, positive end-expiratory pressure (PEEP) 10 cm H2O pressure, FiO2 100%.
- Flow rate >50 L/min, inspiratory rise time 50 msec, End Flow/Cycling off 50% of maximal inspiratory flow.

Titration

- Increase PEEP by 2 cm H2O every 3 minutes to achieve SpO2 ≥ 92% on FiO2 ≤ 60%
- Higher PEEP than what is used on face mask NIV is allowed and tolerated.
- Increase PS by 2 cm every 3 minutes to achieve respiratory rate (RR) ≤ 25/min or clear patient comfort.
- The maximal allowed PS + PEEP is 30 cm H_2O.
- Helmet interruptions should be avoided or kept at minimum at least for the first 48 hours.
- Titrate FiO2 to ≤60% as soon as possible.

Sedation

- Dexmedetomidine may be used to improve compliance with the helmet. Other intravenous sedatives such as benzodiazepines or intravenous narcotics should not be used.

Weaning when clinical condition allows

- Titrate PS by 2 cm H2O every 3 hours if RR ≤ 25/min.
- Titrate PEEP by 2 cm H2O every 3 hours if SpO2 >92% on <60% FiO2.
- If RR ≤25/min on PSV ≤8 cm and SpO2 >92% on FiO2 ≤50% and PEEP ≤8 cm H2O, the helmet can be discontinued and patient switched to high-flow nasal cannula, or oxygen supply at O2 at 6L/min or higher.
- Helmet NIV could be resumed at any time if the respiratory rate was greater than 25 breaths/min and/or SpO2 was lower than 92% on FiO2 of ≥60%.

Nursing Care

- Perform oral care/suction before helmet application.
- Nutrition can be provided through a straw. Place a nasogastric tube before helmet application if felt necessary by treating physician (not commonly needed).
- A suction Yankauer for suctioning and a straw for drinking can be introduced through the patient port without removing the helmet.
- Intravenous sedation (Dexmedetomidine or others) can be used at the discretion of the treating physician to assure patient comfort.

Equipment required

- Mechanical ventilator (BP 840, PB 980, Servo-I, Drager V 500, Astral and V680)
- Unheated double lumen circuit
- Bacterial/viral filter
- Subsalve helmet or equivalent
- Under arm pads
- Ear plugs

General recommendations to consider intubation for patients on NIV (assessed within 4 hours and at frequent intervals throughout NIV treatment):

- Neurologic deterioration (not attributed to sedation)
- Persistent or worsening respiratory failure of NIV:
    - oxygen saturation <88%
    - respiratory rate >36/min
    - P/F ratio <100
    - a persistent requirement of FiO2 ≥70%
- Intolerance of face mask or helmet
- Airway bleeding
- Copious respiratory secretions
- Respiratory acidosis with pH <7.25
- Hemodynamic instability
- Significant radiologic worsening

Humidification

Appropriate level of humidification can be achieved via bubble humidifier with external oxygen flow of 5 L/min entrained into the ventilator circuit proximal to the patient helmet.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	6
	2b	All items from the World Health Organization Trial Registration Data Set	6
Protocol version	3	Date and version identifier	6
Funding	4	Sources and types of financial, material, and other support	24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	24
	5b	Name and contact information for the trial sponsor	24
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	24
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	24

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	8-12
	6b	Explanation for choice of comparators	8-12
Objectives	7	Specific objectives or hypotheses	8-12
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8-12
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8-12
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-12
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14, 16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13-14
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	16-17
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	14
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14-15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14-15

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14-17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15-16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16-17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16-17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16-17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable, no samples collected
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16-17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	22
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable; the protocol manuscript was written by the authors
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	11
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable, no samples collected

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Helmet noninvasive ventilation for COVID-19 patients "Helmet-COVID": study protocol for a multicenter randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-052169.R2
Article Type:	Protocol
Date Submitted by the Author:	28-Jul-2021
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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Intensive care, Respiratory medicine, Infectious diseases
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, RESPIRATORY MEDICINE (see Thoracic Medicine), COVID-19

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Helmet noninvasive ventilation for COVID-19 patients "Helmet-COVID": study protocol for a multicenter randomized controlled trial

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Abstract

Introduction

Noninvasive ventilation delivered by helmet is has been used for respiratory support of patients with acute hypoxemic respiratory failure due to COVID-19 pneumonia. The aim of this study is to compare helmet noninvasive ventilation with usual care versus usual care alone to reduce the mortality.

Methods and analysis

This is a multicenter, pragmatic, parallel, randomized controlled trial that compares helmet noninvasive ventilation with usual care to usual care alone in 1:1 ratio. A total of 320 patients will be enrolled in this study. The primary outcome is 28-day all-cause mortality. The primary outcome will be compared between the two study groups in the intention-to-treat and per-protocol cohorts. An interim analysis will be conducted for both safety and effectiveness.

Ethics and dissemination

Approvals are obtained from the Institutional Review Boards (IRBs) of each participating institution. Our findings will be published in peer-review journals and presented at relevant conferences and meetings.

Trial registration number NCT04477668 registered on July 20, 2020

Article Summary

Strengths and limitations of this study

- This trial compares helmet NIV to usual care for respiratory support of patients with acute hypoxemic respiratory failure due to COVID-19 pneumonia.
- The trial is a multi-center, pragmatic, parallel randomized controlled trial.
- The main limitation is the unblinded design due to the nature of the intervention.

Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a pandemic resulting in over 181 million cases and approximately 3.9 million fatalities as of June 29, 2021.[1] The resulting Coronavirus Disease 2019 (COVID-19) leads to severe pneumonia and acute respiratory distress syndrome (ARDS) among other organ injury.[2] ARDS may occur in up to 5% of infected patients.[3-5] Early in the pandemic, invasive mechanical ventilation was widely used because of concerns about noninvasive ventilation safety and efficacy. However, noninvasive ventilation (NIV) use increased with time, including mask NIV and helmet NIV.

NIV has been shown to be physiologic benefits in patients with acute hypoxemic respiratory failure (AHRF) secondary to pulmonary edema, atelectasis, or pneumonia.[6] It has been shown to improve arterial oxygenation by increasing functional residual capacity, shifting the tidal volume to a more compliant part of the pressure-volume curve, thus reducing both the work of breathing and the risk of tidal opening and closure of the airways.[7] NIV is commonly provided through nasal or oro-nasal interfaces. The resulting aerosol generation may increase the risk of transmission of pathogens to healthcare providers, raising concerns about the use of NIV in patients with viral pneumonia.[8] Helmet NIV has been used for AHRF including patients with COVID-19 pneumonia. The helmet surrounds the patient's entire head to provide positive pressure and supply oxygen and is sealed with a soft, airtight collar that wraps around the neck. Due to this design, it has advantages over the nasal and oro-nasal interfaces. These include less air leaks, no skin or nasal bridge skin injuries, no eye irritation, fitting for different facial contours,[9] and hypothetically less dissemination of aerosols in the environment. However, helmet interface may be associated with increase in dead space (especially if the settings are not used appropriately), claustrophobia, discomfort, and difficulty in access for suction and feeding.

Evaluation of helmet NIV as a respiratory support modality started more than two decades ago.[10] Helmet NIV has been investigated as a treatment for different forms of AHRF in adults in various settings, such as pre-hospital ambulance, emergency department and ICU.[7 11-15] However, earlier clinical studies are relatively scarce and mostly small in size, and often used improvement in oxygenation and intubation rate as primary outcomes.[6]

However, the evidence on helmet NIV for AHRF is growing. A systematic review of randomized controlled trials (RCTs) and observational studies published before June 2016 found 11 studies involving 621 patients.[16] Compared with controls, the use of the helmet was associated with lower hospital mortality, intubation rate, and complications.[16] Moreover, there was no significant difference in gas exchange and ICU stay.[16] A meta-analysis of four RCTs (377 patients) showed that helmet NIV significantly increased the ratio of arterial oxygen partial pressure to fraction of inspired oxygen (PaO_2/FiO_2) and decreased arterial carbon dioxide levels, intubation rate and in-hospital mortality compared to standard oxygen therapy.[17] In a more recent systematic review and network meta-analysis that included 25 studies (published up to April 2020) and 3804 patients with AHRF, mortality and intubation rate were lower with helmet NIV compared to standard oxygen by more than 50%, while the effect of mask NIV and high-flow nasal oxygen were modest compared to standard oxygen.[18] Helmet NIV was superior to both mask NIV and high-flow nasal oxygen, while mask NIV and high-flow nasal oxygen were not different in their effects on mortality and intubation rate.[18] One study reported the cost-effectiveness of helmet NIV compared to mask NIV.[19]

Data on helmet NIV in AHRF related to COVID-19 are emerging. A recent RCT conducted in 4 Italian ICUs on patients with COVID-19 and moderate to severe AHRF found that treatment with helmet NIV did not result in significantly fewer days of respiratory support at 28 days from randomization (primary outcome) as compared with high-flow nasal oxygen alone (mean difference 2 days, 95% CI, -2 to 6, p=0.26).[20] Nevertheless, the intubation rate

was significantly lower in the helmet NIV group compared to the high-flow nasal oxygen group (30% vs 51%; p=0.03).[20] Additionally, the median number of days free of invasive mechanical ventilation within 28 days was significantly higher in the helmet NIV group than in the high-flow nasal oxygen group (28 versus 25 days; mean difference, 3 days; 95% CI, 0-7; P = 0.04).[20] The hospital mortality was 24% in the helmet NIV group and 25% in the high-flow nasal oxygen group.[20]

As the efficacy of helmet NIV to improve outcomes in severe AHRF due to COVID-19 pneumonia has not been clearly established, the aim of this study is to compare helmet NIV with usual care versus usual care alone to reduce 28-day all-cause mortality. We hypothesize that helmet NIV will reduce 28-day all-cause mortality in patients with suspected or confirmed severe COVID-19 pneumonia and AHRF.

Methods and analysis

Trial design

This is an investigator-initiated, pragmatic parallel RCT that will compare helmet NIV with usual care to usual care alone in 1:1 ratio in patients with suspected or confirmed COVID-19 pneumonia and AHRF. Randomization is performed using a computer-generated schedule using variable block sizes (4 or 6) and is stratified by site. The trial is sponsored by King Abdullah International Medical Research Center, Riyadh, Saudi Arabia, has been registered with ClinicalTrials.gov (NCT04477668) and is conducted across multiple centers in Saudi Arabia. Training and in-service education on helmet NIV use as well as on protocol implementation are provided to all participating centers. The competency of the bedside respiratory therapists is supervised by experienced respiratory care supervisors and intensivists.

Sample size

In a large observation study of patients with AHRF and ARDS, hospital mortality was 34.9% (95% CI, 31.4-38.5%) for patients with mild ARDS, 40.3% (95% CI, 37.4%-43.3%) for those with moderate ARDS, and 46.1% (95% CI, 41.9%-50.4%) for those with severe ARDS.[21] A systematic review found an overall pooled mortality estimate among 10,815 patients with ARDS due to COVID-19 to be 39% (95% CI: 23–56%).[22] Considering a mortality rate of 40% in patients with COVID-19 pneumonia and moderate to severe ARDS treated with usual care, we calculated that enrollment of 304 patients (152 in each group) would provide the study with 80% power to demonstrate an absolute difference of 15% in the primary outcome between the usual care group and helmet NIV group at a two-sided alpha level of 0.05. To account for 5% loss to follow-up, the total number of patients required for the trial is 320 patients.

Participant eligibility

The trial will enroll ICU patients with suspected[23] or confirmed COVID-19 pneumonia who have AHRF. Detailed inclusion and exclusion criteria can be found in **Table 1**.

Informed consent

Informed consent will be obtained from the potential trial participants or their surrogate decision makers. A hybrid model of consent will be used where a priori consent is obtained if possible, otherwise delayed consent model will be obtained as per local approvals. The first patient was enrolled in February 2021. As of June 29, 2021, a total of 199 patients were enrolled from 5 sites. There are several sites that are processing IRB and regulatory approvals.

Patient and public involvement

There was no patient or public involvement in the conception, design or conduct of the study, or the writing or editing of this paper. However, patient comfort and experience as well as compliance to the intervention were taken in to consideration and data on these are collected.

Trial interventions

Helmet group

A helmet (Subsalve, USA or its equivalent), which is made of transparent latex-free polyvinyl chloride, will be applied to patients randomized to the intervention group as per the study protocol which considers the manufacturer instructions. It will be immediately connected to an ICU ventilator in pressure support (PS) mode with positive end-expiratory pressure (PEEP) using a conventional respiratory circuit joining two port sites to allow inspiratory and expiratory flow. The starting settings is PS of 8-10 cm H2O, PEEP of 10 cmH2O with FiO_2 of 100%, targeting flow rate of ≥50 L/min with an inspiratory rise time of 50 msec and end flow/cycling off of 50% of maximal inspiratory flow. PEEP may be increased by 2 cm every 3 minutes to achieve oxygen saturation (SpO2) ≥90% on FIO_2 ≤ 60%, and PS can be increased by 2 cm every 3 minutes to achieve respiratory rate ≤ 25/min and disappearance of accessory muscle activity. The maximal allowed PS + PEEP is 30 cm H_2O. Interruptions of helmet should be avoided or kept at minimum at least in the first 48 hours.[20] More details of helmet NIV application, set up and weaning can be found in the **Supplementary File**. Some patients may not tolerate helmet NIV. In that case, the physician or the respiratory therapist explains the procedure to the patient. Dexmedetomidine infusion may be used to improve ccomfort with the helmet NIV. Other intravenous sedatives such as benzodiazepines or intravenous narcotics should generally not be used. If the patient continues to be intolerant to the helmet, the patient can be managed according to the usual care. Detailed data about helmet NIV tolerance are collected.

Control group

In the control group, patients receive usual care according to the clinical practices of each site. This may include oxygen provided using standard oxygen devices, high-flow nasal oxygen or NIV provided by nasal mask, face mask or total mask.

Endotracheal Intubation

The decision to intubate will be at the discretion of the treating team with no involvement from the research team. However, the protocol provides guidance on assessing patients for the need of endotracheal intubation throughout the study period (for both study groups: helmet NIV or usual care) according to the following general principles:

Enrolled patients should be assessed within 4 hours of enrollment (or sooner as required) and at frequent intervals for the following criteria, although the decision is usually not based on a single variable:

- Neurologic deterioration *(not attributed to sedation)*
- Persistent or worsening respiratory failure of NIV (manifesting as oxygen saturation <88%, respiratory rate >36/min, PaO_2/FiO_2 ratio <100 or persistent requirement of FiO_2 ≥70%)
- Intolerance of face mask or helmet
- Airway bleeding
- Copious respiratory secretions
- Respiratory acidosis with pH <7.25
- Hemodynamic instability
- Significant radiologic worsening

Co-Interventions

Patients who require endotracheal intubation are managed by the primary team with lung protective strategy with tidal volumes of 6 mL/kg of predicted body weight and titration of PEEP to achieve oxygen saturation of 88% to 95% at the lowest possible FiO_2. Daily interruption of sedation, awakening and breathing trials, and early mobilization are performed as per the ICU standards.[24] Management of COVID-19 is provided as per local protocols; physicians are advised to follow the clinical practice guidelines set by the Saudi Critical Care Society,[25] the Surviving Sepsis Campaign,[26 27] and the World Health Organization.[28] The study protocol does not mandate particular therapies; however, corticosteroids, immune modulators and antiviral therapy are all recorded. Conservative fluid management is recommended where neutral balance should be targeted and intravenous resuscitation should be reserved for shock treatment in both groups and fluid balance is recorded.

Blinding

Due to the nature of the study intervention, blinding is not be possible.

Recruitment schedule and enrollment procedures

Schedule of assessments is detailed in **Table 2**. All non-intubated subjects with suspected or confirmed COVID-19 are screened upon admission to the ICU. A screening log will be kept to monitor and report the size of the patient population from which eligible patients have been randomized. Co-enrollment in other RCTs is permissible as long as inclusion in the other RCT would not confound the results of this trial and after discussion with the steering committees of the other studies.

Data collection

Baseline data on demographics, admission diagnosis and clinical information are collected. Clinical information include Acute Physiology and Chronic Health Evaluation (APACHE) II score,[29] source of admission, ICU admission category (elective, emergency or non-surgical), ICU admission diagnosis and co-morbidities (as defined by the APACHE II severity of illness scoring system). Daily data will be recorded until discharge from ICU or 28 days after randomization. We will collect data on the use of helmet including the tolerance of helmet (>1-hour use).

Outcomes

The primary outcome is 28-day all-cause mortality. Secondary outcomes are intubation rate within 28 days**,** ICU mortality**,** hospital mortality (censored at day 180), ICU-free days at day 28**,** invasive ventilation-free days at day 28, renal replacement therapy-free days at day 28 and vasopressor-free days at day 28. Safety outcomes include skin pressure injuries, barotrauma and serious adverse events (including cardiovascular events and device complications).

Additionally, there will be a follow up of enrolled patients at day 180 about vital status, functional status (EuroQoL (EQ)-5D-5L) which is planned to be reported separately. For patients who have been discharged from hospital before day 180, follow up will be conducted by telephone.

Data analysis

A formal statistical analysis plan will be agreed upon and placed in the public domain before the study database is locked for the analysis of the primary outcome. The primary outcome

will be compared in the intention-to-treat and per-protocol cohorts (effectiveness analysis) using the chi-square test. Results will be reported as relative risk with 95% CI. Kaplan–Meier curves will be plotted to assess the time from enrollment to death and will be compared by means of the log-rank test. A two-tailed P value <0.05 will be considered to indicate statistical significance. SAS software, version 9.2 (SAS Institute) will be used for all the analyses.

A priori analysis will be done for the following subgroups:

I. Patients with moderate ARDS (PaO_2/FIO_2 ratio 100-200) and patients with severe ARDS ($PaO_2/FIO2$ ratio <100)
II. Obese patients (body mass index >30 kg/m^2) and patients with body mass index ≤30
III. Patients aged >65 years and ≤65 years
IV. APACHE II score higher or lower than the median of enrolled patients

For the occasional randomized patient who is withdrawn from the trial and allows use of data, the patient's data will be included in the group to which he/she was allocated as per the intention-to-treat principle and the reason of withdrawal will be documented.

Trial management and monitoring

The study Steering Committee members will be responsible for overseeing the conduct of the trial, for upholding or modifying study procedures as needed, addressing challenges with protocol implementation, formulating the analysis plan, reviewing and interpreting the data, and preparing the manuscript. This will be achieved through meetings (in-person or by conference calls) at least quarterly.

Several measures are taken to minimize, observe and document any potential safety concerns. First, any unexpected safety concerns will be reported immediately to the Steering

Committee and IRB. Second, an independent Data Safety Monitoring Board will be monitoring the safety of the trial. Lastly, interim analyses will be conducted after recruiting 1/3 and 2/3 of the total patients and the interim test statistics will be the primary outcome analysis for both safety and effectiveness. The Data Safety Monitoring Board will use formal stopping rules based on the primary endpoint of 28-day mortality. The trial may be stopped for safety ($p<0.01$) or effectiveness ($p<0.001$). There will be no plans to terminate the trial for futility. We will account for alpha spending by the O'Brien Fleming method and the final p value will be considered at 0.048. The principles used in the conduct of safety monitoring and reporting in this trial are those outlined by Cook et al.[30]

In this trial, reporting of serious adverse events will be restricted to events that are not captured as study outcome and are considered to be related to the helmet NIV (possibly, probably or definitely).[30] These may include cardiovascular events (i.e., cardiac arrest and hypotension with drop in blood pressure to systolic <90 mm Hg) and device complications (i.e., helmet deflation).

Ethics and dissemination

The study will be conducted according to the principles of the latest version of Good Clinical Practice (GCP) and in accordance with all relevant local ethical, regulatory, and legal requirements. A manuscript with the results of the primary study will be published in a peer-reviewed journal. Separate manuscripts will be written on secondary aims, and these will also be submitted for publication in peer reviewed journals as well.

Discussion

The importance of this study stems from the current pandemic situation as different treatment modalities are being sought to answer important clinical questions. Available

literature on the evaluation of helmet NIV as a respiratory support modality in COVID-19 patients is limited. Table 3 provides the list of ongoing RCTs on helmet NIV. This study aims to contribute to the existing literature and in turn influence clinical practice.

We planned our pragmatic trial to address whether using helmet NIV as the primary non-invasive respiratory support in patients with severe COVID-19, in addition to the commonly used high-flow nasal oxygen and mask NIV improves outcome. By nature of this question, there is heterogeneity of the control group; as patients in this group could receive standard oxygen, high-flow nasal oxygen or mask NIV at the decision of the treating team. This approach is supported by a recent network meta-analysis of randomized controlled trials that showed only a modest effect of high-flow nasal oxygen and mask NIV on mortality or intubation rate compared to standard oxygen, while patients treated with helmet NIV had more than 50% reduction in mortality and intubation rate compared to the other three modalities.[18] In addition, this approach is likely to be more representative of usual practice in which patients may get oxygen therapy, high-flow nasal oxygen and NIV at different times during their acute illness. Given the fact that the use of helmet NIV has not been widespread across ICUs, we thought that the broader question addressed by our study might be more relevant to deciding whether to introduce this modality or not in a given ICU.

The main limitation to our study is inability to blind the given allocation due to the nature of the intervention.

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Acknowledgements

The authors would like to thank all the participating patients and their families, as well as the members of the Data Safety & Monitoring Board: Chair: Dr. Nicholas S. Hill (Professor of Medicine, Chief of Pulmonary, Critical Care and Sleep Division, Tufts Medical Center, Boston, Massachusetts, USA), DSM members: Dr. Stefano Nava (Professor of Respiratory Medicine University of Bologna, Chief of the Respiratory and Critical Care Sant' Orsola Hospital Bologna, Specialist in Respiratory Medicine and Intensive Care Medicine, University of Bologna, Italy), Dr. James Mojica (Vice Chief and Clinical Director of Pulmonary & Critical Care, Director, The Sleep Center at Spaulding, Massachusetts General Hospital, USA) and Dr. Michael Harhay (Assistant Professor of Epidemiology and Medicine-Pulmonary and Critical Care, Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania USA).

Contributors YA is the principal investigator and participated in the project concept, design, final approval, and manuscript preparation, review and submission. HT, SD, HD, SA, MH, HH, MM, OZ, EQ, WW, SQ, FH, JC, MS, AH, AM, AE, AB, ZA ZD, AK, RQ, AG, AT, KG, HG, AA, FB, HS, MO, YI, AF participated in the critical revision, final approval of the protocol and manuscript preparation, review and submission. All authors agree to be accountable for the accuracy and integrity of the work.

Funding The study is funded by King Abdullah International Medical Research Center (RC 20/306/R). The study sponsor does not have any role in the study design, collection, management, analysis, and interpretation of data as well as writing of the report.

Competing interests None declared

Ethics approval

The study has been approved by the Institutional Review Board (IRB) of Ministry of National Guard Health Affairs (MNGHA) and the respective Institutional Review Boards of all the other centers.

Patient consent for publication Not required.

Provenance and peer review Not commissioned, externally peer reviewed.

Table 1. Eligibility Criteria

Inclusion Criteria	1. Suspected or confirmed COVID-19* 2. Aged ≥ 14 years old. ICUs that use other age cut-off for adult patients will adhere to their local standard (16 or 18 years) 3. Acute hypoxemic respiratory failure based on PaO2/FiO2 ratio < 200 despite supplemental oxygen with a partial or non-rebreathing mask at a flow rate >10 L/min or above 4. Intact airway protective gag reflex 5. Able to follow instructions
Exclusion Criteria	1. Prior intubation during this hospital admission 2. Cardiopulmonary arrest 3. Glasgow coma scale <12 4. Tracheostomy 5. Upper airway obstruction 6. Active epistaxis 7. Requirement for more than one vasopressor to maintain mean arterial pressure >65 mm Hg. 8. Pregnancy 9. Imminent intubation 10. Patients with do-not-intubate orders (or equivalent) 11. Enrolled in another trial for which co-enrolment is not approved including trials on mechanical ventilation 12. Patients already treated with helmet 13. Patients with chronic carbon dioxide retention (PaCO2>45) 14. Previous enrolment in this trial 15. The primary cause of respiratory failure is not heart failure as judged by the treating team
Eligible non-randomized	1. Patient or substitute decision-maker declines consent 2. ICU physician or other treating clinician declines consent

*A suspected/probable COVID-19 case is defined as: At least two of the following symptoms: fever (measured or subjective), chills, rigors, myalgia, headache, sore throat, new olfactory and taste disorder(s) **OR** at least one of the following symptoms: cough, shortness of breath, or difficulty breathing **OR** severe respiratory illness with at least one of the following: Clinical or radiographic evidence of pneumonia, **OR** ARDS **AND** no alternative more likely diagnosis. A confirmed COVID-19 case is defined as: Detection of SARS-CoV-2 RNA in a respiratory specimen using a molecular amplification detection test such as rt-PCR (https://wwwn.cdc.gov/nndss/conditions/coronavirus-disease-2019-covid-19/case-definition/2020/).

Table 2. Schedule of assessments in the trial

Task	Screening	Randomization	Baseline	Day 1-28	180-Day Follow up
Assess eligibility to enter study	X				
Assess ability to gain consent & follow-up	X				
Consent	X				
Demographics and eligibility checklist	X	X	X		
Laboratory data			X	X	
Vital signs			X	X	
Vital status up to Day 28 in the ICU				X	X
Vital and functional status					X
Discharge date from ICU, from hospital				X	X
Adverse events				X	
Protocol violations				X	

Table 3. List of ongoing registered randomized controlled trials (RCTs) on helmet noninvasive ventilation

Trial	Registration	Interventions	Design	Countries	N
Helmet non-invasive ventilation for COVID-19 patients (Helmet-COVID)	NCT04477668	Helmet vs. usual care	Multicenter RCT	Saudi Arabia	320
Comparison of high-flow nasal oxygen, face-mask NIV and helmet NIV in COVID-19 ARDS patients (NIV COVID19)	NCT04715243	High-flow nasal oxygen vs. helmet NIV vs. mask NIV	Multicenter RCT	Oman	360
Helmet CPAP vs. high-flow nasal oxygen in COVID-19 (COVID HELMET)	NCT04395807	High-flow nasal oxygen vs. helmet CPAP	Single-center RCT	Sweden	120
high-flow nasal oxygen vs. CPAP Helmet in COVID-19 pneumonia (COVIDNOCHE)	NCT04381923	High-flow nasal oxygen vs. helmet CPAP	Single-center RCT	USA	200
Early CPAP in COVID-19 patients with respiratory failure (EC-COVID-RCT)	NCT04326075	Early helmet CPAP vs. usual care	Single-center RCT	Italy	900

Helmet-NIV Protocol

Setup and preparation

- Use unheated, low-compliance, dual limb breathing circuit.
- Insert a bacterial/viral filter at the expiratory port of the ventilator.
- Carry out the required preoperational check.
- To avoid patient-ventilator asynchrony, explain the application and the procedure of the helmet to the patient.
- Insert the earplugs into patient ears.
- Use the under-arm pads to avoid strap pressure.

Initial setup

- Can be used with a ventilator or NIV machines.
- Set up the ventilator on Pressure Support Ventilation (PSV).
- PSV 8-10 cm H2O pressure, positive end-expiratory pressure (PEEP) 10 cm H2O pressure, FiO2 100%.
- Flow rate >50 L/min, inspiratory rise time 50 msec, End Flow/Cycling off 50% of maximal inspiratory flow.

Titration

- Increase PEEP by 2 cm H2O every 3 minutes to achieve SpO2 ≥ 92% on FiO2 ≤ 60%
- Higher PEEP than what is used on face mask NIV is allowed and tolerated.
- Increase PS by 2 cm every 3 minutes to achieve respiratory rate (RR) ≤ 25/min or clear patient comfort.
- The maximal allowed PS + PEEP is 30 cm H_2O.
- Helmet interruptions should be avoided or kept at minimum at least for the first 48 hours.
- Titrate FiO2 to ≤60% as soon as possible.

Sedation

- Dexmedetomidine may be used to improve compliance with the helmet. Other intravenous sedatives such as benzodiazepines or intravenous narcotics should not be used.

Weaning when clinical condition allows

- Titrate PS by 2 cm H2O every 3 hours if RR ≤ 25/min.
- Titrate PEEP by 2 cm H2O every 3 hours if SpO2 >92% on <60% FiO2.
- If RR ≤25/min on PSV ≤8 cm and SpO2 >92% on FiO2 ≤50% and PEEP ≤8 cm H2O, the helmet can be discontinued and patient switched to high-flow nasal cannula, or oxygen supply at O2 at 6L/min or higher.
- Helmet NIV could be resumed at any time if the respiratory rate was greater than 25 breaths/min and/or SpO2 was lower than 92% on FiO2 of ≥60%.

Nursing Care

- Perform oral care/suction before helmet application.
- Nutrition can be provided through a straw. Place a nasogastric tube before helmet application if felt necessary by treating physician (not commonly needed).
- A suction Yankauer for suctioning and a straw for drinking can be introduced through the patient port without removing the helmet.
- Intravenous sedation (Dexmedetomidine or others) can be used at the discretion of the treating physician to assure patient comfort.

Equipment required

- Mechanical ventilator (BP 840, PB 980, Servo-I, Drager V 500, Astral and V680)
- Unheated double lumen circuit
- Bacterial/viral filter
- Subsalve helmet or equivalent
- Under arm pads
- Ear plugs

General recommendations to consider intubation for patients on NIV (assessed within 4 hours and at frequent intervals throughout NIV treatment):

- Neurologic deterioration (not attributed to sedation)
- Persistent or worsening respiratory failure of NIV:
    - oxygen saturation <88%
    - respiratory rate >36/min
    - P/F ratio <100
    - a persistent requirement of FiO2 ≥70%
- Intolerance of face mask or helmet
- Airway bleeding
- Copious respiratory secretions
- Respiratory acidosis with pH <7.25
- Hemodynamic instability
- Significant radiologic worsening

Humidification

Appropriate level of humidification can be achieved via bubble humidifier with external oxygen flow of 5 L/min entrained into the ventilator circuit proximal to the patient helmet.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	6
	2b	All items from the World Health Organization Trial Registration Data Set	6
Protocol version	3	Date and version identifier	6
Funding	4	Sources and types of financial, material, and other support	24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	24
	5b	Name and contact information for the trial sponsor	24
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	24
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	24

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	8-12
	6b	Explanation for choice of comparators	8-12
Objectives	7	Specific objectives or hypotheses	8-12
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8-12
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8-12
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-12
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14, 16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13-14
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	16-17
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	14
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14-15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14-15

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14-17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15-16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16-17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16-17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16-17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable, no samples collected
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16-17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	22
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable; the protocol manuscript was written by the authors
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	11
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable, no samples collected

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.