PROTOCOL

RECOVERY-RS Respiratory Support: Respiratory Strategies in COVID-19; CPAP, High-flow, and standard care

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TRIAL SUMMARY

Trial Title	RECOVERY-RS Respiratory Support: Respiratory Strategies in COVID-19; CPAP, High-flow, and standard care
Internal ref. number (or short title)	RECOVERY-Respiratory Support
Clinical Phase	Phase III
Trial Design	Adaptive (group-sequential), pragmatic, randomised controlled, open-label, multi-centre, effectiveness trial
Trial Participants	Adult, critically ill patients, with suspected or confirmed, COVID-19
Planned sample size	4002
Treatment Duration	30 days
Follow-up Duration	30 days or hospital discharge, whichever comes latest
Planned Trial Period	18 months

	Objectives	Outcome Measures
Primary	To determine if CPAP or HFNO is clinically effective compared to standard care (excluding CPAP or HFNO)	Intubation and mortality
Secondary	To assess in-hospital patient data in terms of their stay	Intubation rates; time to intubation; time to death (mortality); mortality in critical care (Level 2/3); mortality in hospital stay; mortality at 30 days; admission to ICU; length of stay in critical care (Level 2/3); length of stay in hospital

LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
AE	Adverse event
ARF	Acute respiratory failure
BiPAP	Bilevel positive airway pressure (BiPAP)
CI	Chief Investigator
CONSORT	*Con*solidated *S*tandards *o*f *R*eporting *Tr*ials
COVID-19	Coronavirus Disease 2019
CPAP	Continuous positive airway pressure
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
HFNO	High flow nasal oxygen
ICF	Informed Consent Form
ICNARC	Intensive Care National Audit and Research Centre
ICU	Intensive Care Unit
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
MRC	Medical Research Council
NIV	Non-invasive ventilation
NNT	Number needed to treat
PI	Principal Investigator
PPI	Patient & Public Involvement
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development
SAE	Serious Adverse Event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOP	Standard Operating Procedure
TSC	Trial Steering Committee
WCTU	Warwick Clinical Trials Unit

1.   BACKGROUND

1.1   Epidemiology and burden of the condition

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged at the end of 2019 as a novel coronavirus, resulting in a current global pandemic of respiratory illness, Coronavirus Disease 2019 (COVID-19). Using very recent World Health Organization (WHO) data on the cumulative number of deaths up to 1 March 2020, mortality rates of 5·6% (95% CI: 5·4%–5·8%) for China and 15·2% (12·5%–17·9%) outside of China have been reported[1]. Indeed, as of 29 March 2020, there have been 575,444 confirmed cases, with 26,654 confirmed deaths, across 202 countries (available at   https://www.who.int/emergencies/diseases/novel-coronavirus-2019).   National statistics detailed by the Centre of Evidence Based Medicine, University of Oxford, report all-cause mortality by respiratory disease, across England and Wales, during 3 January 2020 to 13 March (i.e. during the COVID-19 outbreak) have averaged approximately 15%[2], albeit peak pandemic phase has not yet occurred in the UK. A recent (27 March 2020) report from the Intensive Care National Audit and Research Centre (ICNARC), reported 846 admissions to critical care units in England, Wales, and Northern Ireland with confirmed COVID-19; where 24 hour outcome data were available in 775 patients, 79 had died, 86 were discharged alive, and 609 patients remained in critical care[3].

COVID-19 has a wide spectrum of clinical severity, ranging from asymptomatic to critically ill, and ultimately death.   A common and prominent complication of advanced COVID-19 is acute hypoxemic respiratory insufficiency requiring oxygen and ventilation therapies. Often deterioration may be rapid. A recent report showed that 14% of patients developed dyspnea, tachypnea with a respiratory rate greater than or equal to 30 per minute, desaturation with peripheral oxygen saturation (SpO_2) less than or equal to 93%, poor oxygenation with a ratio of partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FIO_2) less than 300 mmHg, or lung infiltrates greater than 50%, within 48 h[4].

Ventilatory support is the cornerstone of management for COVID-19 patients presenting with respiratory impairment. Reports from China, the source of the pandemic, suggest a prevalence of hypoxic respiratory failure in patients with COVID-19 of 19%[5], although true global figures are unclear. That said, there is evidence that patients have received as standard care management in the form of supplemental oxygen therapy, high-flow nasal oxygen (HFNO), continuous positive airways pressure (CPAP), non-invasive positive pressure ventilation (NIV), and invasive mechanical ventilation[6]. Standard care treatment for patients requiring ventilatory support may involve more than one method and a cross over between non-invasive and invasive devices.

Already the potential impact of the respiratory symptomology associated with COVID-19 on UK critical care units can be appreciated; nearly 80% of the patients in the aforementioned ICNARC report required invasive mechanical ventilation, compared with just over 40% in a non-COVID-19 cohort of viral pneumonia between 2017-2019[3]. However the ability to deliver this treatment at this scale (and potentially greater) across UK critical care settings places huge pressures on existing services with finite resources. This scenario of excess demand on limited ventilator availability and critical care bed capacity is currently being witnessed worldwide, in particular in neighbouring European countries.

Determining the most effective form of ventilatory support for patients with COVID-19 is therefore paramount to ensure optimum therapy is delivered to patients, and to protect UK vital critical care resources and infrastructure. Findings from this trial will also have the potential to inform global ventilation practice for patients with COVID-19.

1.2   Existing knowledge

High flow nasal oxygen

There is currently no direct evidence to support the use of HFNO in patients with COVD-19[6]; instead evidence around the possible application of this therapy in COVID-19 is derived from the acute respiratory failure (ARF) population where it appears inconsistent overall. The most recent relevant Cochrane systematic review and meta-analysis from 2017 demonstrated that the evidence to support the use of HFNO for acute respiratory failure was insufficient to conclude, whether HFNO provided safe and effective respiratory support to these patients[7]. The majority of trials (10 out of 11) included in this review compared HFNC versus low-flow oxygen. This review was unable to demonstrate whether HFNO was more effective or safe than other oxygen delivery devices. For the primary outcomes of treatment failure, defined as need for non-invasive or invasive ventilation (1066 participants; six studies) and mortality (755 participants; three studies), investigators found no differences between HFNO and low-flow oxygen therapies (risk ratio (RR), Mantel-Haenszel (MH), random-effects 0.79, 95% confidence interval (CI) 0.49 to 1.27; and RR, MH, random-effects 0.63, 95% CI 0.38 to 1.06, respectively). There was no evidence that HFNO reduced the rate of treatment failure or risk of death compared with low-flow oxygen devices, and also no evidence of any advantage for HFNO in terms of adverse event rates, ICU length of stay, or duration of respiratory support. In this review the data comparing HFNO to CPAP or Bilevel positive airway pressure(BiPAP) was very limited.

In another recent systematic review and meta-analysis comparing HFNO with usual care, there was no difference in mortality (HFNO, 60/1,006 [6%] vs usual care, 90/1,106 [8.1%]) (n = 2,112; p = 0.29;

I2, 25%; fixed effect model: odds ratio, 0.83; 95% CI, 0.58–1.17) or rate of intubation (HFNC, 119/1,207 [9.9%] vs usual care, 204/1,300 [15.7%]) (n = 2,507; p = 0.08; I2, 53%; random effect model: odds ratio, 0.63; 95% CI, 0.37–1.06)[8]. A qualitative analysis of 13 studies on tolerability and comfort suggested that HFNO was associated with improved patient comfort and dyspnea scores[8]. In contrast, other recent systematic reviews and meta-analyses have demonstrated a benefit of HFNO in reducing intubation compared with conventional oxygen (RR 0.85, 95% CI 0.74 to 0.99), but similarly no effect on risk of death or ICU length of stay[9-11]. Reducing the need for intubation is a clinically meaningful outcome, with additional important benefits for healthcare resource utilisation.

Current Surviving Sepsis Campaign (SSC) COVID-19 guidelines make a weak recommendation, based on low quality evidence, for using HFNO over conventional oxygen therapy[6]. A similar strength of recommendation is made for using HFNO over NIV[6], based on contrasting evidence around the effectiveness for HFNO to reduce mortality, need for intubation, and ICU length of stay[9 12] and potential for greater patient tolerability for HFNO [12]. Guidelines from the Australia and New Zealand Intensive Care Society (ANZICS) similarly recommend HFNO for patients presenting with hypoxia[13]. Both sets of guidelines do however, advise close monitoring of patients receiving either HFNO in a setting of sufficient acuity to enable controlled intubation in the event of deterioration given the high risk of failure[6 13].

Continuous positive airway pressure
There are currently no data available on the use of CPAP directly in patients with COVID-19. A number of trials have explored the effectiveness of CPAP in ARF. These trials provide some evidence that CPAP has a role in improving important outcomes such as progression to intubation, length of stay in ICU and/or hospital. In a 2015 Cochrane systematic review and meta-analysis, Faria *et al*[14] compared the effectiveness of NIV i.e. continuous positive airway pressure (CPAP) or bi-level NIV, in reducing mortality and the rate of tracheal intubation in adults with acute respiratory failure after upper abdominal surgery, compared to standard therapy (oxygen therapy). Two trials involving 269 participants were included and CPAP or bi-level NIV reduced the rate of tracheal intubation (risk ratio (RR) 0.25; 95% confidence interval (CI) 0.08 to 0.83 with a number needed to treat (NNT) for additional benefit of 11. There was very low quality evidence that the intervention may also reduce ICU length of stay (mean difference (MD) -1.84 days; 95% CI -3.53 to -0.15) however there were no differences for mortality (low quality evidence) and hospital length of stay.

Bakke *et al*[15] explored the effectiveness of CPAP and NIV versus standard medical treatment in prehospital treatment of patients with acute respiratory failure in terms of mortality, hospital

length of stay, intensive care unit length of stay or intubation rate. Four studies in this review were high quality studies comparing CPAP to standard care, with only 1 trial showing a reduction in both mortality and intubation rate. The remaining 3 high quality studies showed no significant differences in any of the outcomes of interest albeit showing a trend toward lower intubation rate with supplementary CPAP. Four studies in this review compared NIV to standard medical treatment, and found no difference in mortality or intubation rate, and two studies demonstrated a reduction in ICU stay. Williams *et al*[16] included studies comparing CPAP (and usual care) with no CPAP for ARF in the prehospital setting; a meta-analysis included 5 studies (3 RCTs, 1 non-randomised comparative study, and 1 retrospective comparative study) totalling 1002 patients and showed pooled estimates demonstrated significantly fewer intubations ([OR] 0.31; 95% confidence interval [CI] 0.19-0.51) and lower mortality (OR 0.41; 95% CI 0.19-0.87) in the CPAP group.

Current international guidelines do not address the use of CPAP in COVID-19 patients, focusing instead on HFNO, NIV, and invasive mechanical ventilation once patients are intubated. In contrast, national guidance from NHS England state that CPAP is the preferred form of non-invasive ventilator support; HFNO is not advocated due to lack of efficacy[17].

Non-invasive ventilation

There is no direct evidence to support the use of NIV in patients with hypoxic respiratory failure, with some reports of increased risk to healthcare workers of exposure to infection[6]. Previous meta-analyses where reductions in intubation and mortality have been demonstrated with NIV have been in patient populations less relevant to COVID-19[6]. Failure rates are generally high with use of NIV outside of cardiogenic pulmonary oedema. Should other pathophysiology be present e.g. acute hypercapnic respiratory failure, NIV may be considered[13 17-19]. Surviving Sepsis Campaign guidelines recommend HFNO over NIV[6], based on contrasting evidence around the effectiveness for HFNO to reduce mortality, need for intubation, and ICU length of stay[9 12] and potential for greater patient tolerability for HFNO[12]. In patients with COVID-19, where HFNO is not available and there is no urgent need for intubation, a trial of NIV with close monitoring and short-interval assessment for deterioration may be considered (weak recommendation, very low quality evidence)[6].

1.3   Hypothesis

In adult patients, with suspected or confirmed COVID-19, CPAP or HFNO are more effective than standard care for reducing the rate of intubation and / or mortality.

We will aim to recruit a maximum of 4002 patients to explore this hypothesis. However, as this is an adaptive trial (group-sequential) in design, we will review the data at each stage using formal

interim analyses and continue with all arms or drop an intervention arm if required. The trial will therefore stop early and not require this total sample size if an intervention appears to be effective at an interim analysis.

1.4   Need for a trial

This review of the literature highlights that whilst there is some evidence to support current ventilation options for patients with COVID-19, there is little evidence to guide the relative efficacy of these interventions especially HFNO versus CPAP versus standard care oxygen therapy prior to intubation. Importantly, evidence is derived from the general ARF population; there are no COVID-19-specific data. Evidence on the relative effectiveness of these interventions is paramount to ensuring that critically ill patients with COVID-19 are optimally managed in terms of oxygen requirements and that progression to intubation is minimised. There is clear clinical uncertainty as evidenced in the contrasting recommendations amongst existing sets of recommendations[6 13 17].

In selecting the interventions for investigation in this trial, we have elected to compare the effects of HFNO and CPAP against standard care. We have elected not to examine NIV due to the uncertainty around its applicability to the COVID-19 population and the clinical nature of respiratory impairment in these patients. This trial will provide important data to clarify current national recommendations on the preferred mode of non-invasive respiratory support[17].

We have also reviewed the experiences to date from other countries and relevant literature to support treatment options in patients admitted with suspected or confirmed COVID-19 and developing hypoxia. Yang *et al*[20] have recently published the first series of 52 patients from the China COVID-19 crisis. They highlight that HFNO and mechanical ventilation (either non-invasive or invasive) was the main supportive treatment for these critically ill patients. Many practical drivers have been highlighted that influence the use of these options. It is a deep concern in some areas that the demand for oxygen therapy will outweigh the ability to provide it to patients. For those interventions that require equipment there is huge dearth of equipment available and for some interventions (such as NIV) there is substantial specialist training required to deliver the intervention optimally. This is balanced against the absolute need to reduce the number of patients requiring intubation given the imbalance between ventilator provision and likely demand.

1.5   Ethical considerations

The trial will recruit patients in UK-based hospitals and centres to provide care to COVID-19 patients in England, Wales, Scotland and Northern Ireland, many of whom will lack capacity to consent due

to the nature of the underlying disease process. It is likely that patients eligible for the trial will lack capacity, primarily due to acute confusion secondary to hypoxia and infection.

Patients will be assessed for capacity in the first instance. Those with capacity will be provided with information about the trial and asked to give verbal consent prior to enrolment. Given the urgent need to initiate treatment and the context in which the trial will operate (e.g. restricted visiting and infection control risks) , if the patient does not have capacity, it is not reasonably practicable to consult a relative / guardian / consultee or a medical practitioner independent of the research team. In England, Wales and Northern Ireland, legislation permits the Research Ethics Committee to authorise enrolment where action needs to be taken as a matter of urgency and to subsequently seek consent. This approach is guided by a published framework, developed in collaboration with the National Research Ethics Service for use in research in an emergency setting[21]. For sites in Scotland, if a patient does not have capacity, the legislation does not allow enrolment without consent from the patient or guardian.

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and to Good Clinical Practice (GCP) guidelines. It will also comply with all applicable UK legislation, the Emergency framework for deferred consent (for England, Wales and Northern Ireland), developed by Davies *et al*[21] in conjunction with the National Research Ethics Service, and Warwick Standard Operating Procedures (SOPs). Adults without capacity will not be recruited from Scotland. All data will be stored securely and held in accordance with the Data Protection Act 2018.

1.6   CONSORT

The trial will be reported in line with the CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) statement (Lancet 2001, 357: 1191-1194, www.consort-statement.org).

2.   TRIAL DESIGN

2.1   Study setting

The main trial will take place in NHS hospitals (in England, Wales, Scotland and Northern Ireland) or purpose built-hospitals with wards and critical care areas that have access to a population of patients with confirmed or suspected COVID-19, and where consultants and staff managing the patient have clinical equipoise for the use of trial interventions and agree to maintain trial allocation in randomised patients.

2.2 Trial summary and flow diagram

The trial will be an adaptive (group-sequential), pragmatic, randomised controlled, open-label, multi-centre, effectiveness trial to determine if the use of CPAP or HFNO reduces intubation or death (mortality), within 30 days. We will test each of the intervention against standard care, and if required, drop one of the interventions if there is evidence of harm or ineffectiveness.

Patients with suspected or confirmed COVID-19 will be eligible for randomisation when $FiO_2 \geq 0.4$ and $SpO_2 \leq 94\%$, in a 1:1:1 ration to receive either CPAP, HFNO, or standard care (excluding either of the two treatments). Data will be recorded by participating ICUs until hospital discharge, and all surviving patients will be followed up to 30 days.

Figure 1. **Trial flow diagram**

Hospital inpatient with suspected or confirmed COVID-19

Clinical status
FiO$_2 \geq 0.4$ and SpO$_2 \leq 94\%$

Screening

Not eligible (Reasons)

Opportunity to opt out discussion (if appropriate)

Randomisation

Total sample = 4002

Consent

Intervention delivery

CPAP according to local practice

N=1334

HFNO according to local practice

N= 1334

Standard Care

N=1334

All other co-interventions as part of COVID management as per local guidelines

Primary outcome

Composite Outcome – Intubation or death (mortality) (up to 30 days)

Secondary outcomes

Intubation rates; Time to intubation; Time to death (mortality); Mortality in critical care (Level 2/3); Mortality in hospital stay; Mortality at 30 days; Admission to ICU; Length of stay in critical care (Level 2/3); Length of stay in hospital

2.3   Aims and objectives

2.3.1   Primary objective

The primary objective of this trial is to determine if CPAP or HFNO is clinically effective compared to standard care in relation to intubation and mortality in patients with confirmed or suspected COVID-19.

2.3.2   Secondary objective

The secondary objectives for this study are to assess in-hospital patient data in terms of their stay.

2.4   Outcome measures

2.4.1   Efficacy

- *Primary*

  The primary outcome is a composite outcome comprising intubation or mortality within 30 days. If necessary, patients will be followed up to ascertain all-cause mortality rates at 30 days, using NHS Digital, the Intensive Care National Audit and Research Centre (ICNARC) and equivalent NHS data linkage in the devolved nations. Intubation will be obtained from hospital data.

- *Secondary outcomes*

  Secondary outcomes relating to effectiveness include:
  - Intubation rates
  - Time to intubation
  - Duration of invasive ventilation
  - Time to death (mortality)
  - Mortality in critical care (level 2/3)
  - Mortality in hospital stay
  - Mortality at 30 days
  - Admission to ICU
  - Length of stay in critical care (level 2/3)
  - Length of stay in hospital

  All secondary outcomes will be obtained from hospital records and data linkage where appropriate.

2.4.2 Safety

We will collect data on:

- Adverse events
- Serious adverse events

2.5 Eligibility criteria

The eligibility criteria are designed to include those who reflect the general population of patients with confirmed or suspected COVID-19 and who may benefit from the therapeutic interventions. Patients are eligible to be included in the trial if they meet the following criteria:

2.5.1 Inclusion criteria

1. Adults ≥ 18 years
2. Hospital inpatient with suspected or proven COVID-19
3. $FiO_2 \geq 0.4$ and $SpO_2 \leq 94\%$
4. Plan for escalation to intubation if needed

2.5.2 Exclusion criteria

1. Planned intubation and mechanical ventilation imminent within 1 hour
2. Known or clinically apparent pregnancy
3. Any absolute contraindication to CPAP or HFNO
4. Decision not to intubate due to ceiling of treatment or withdrawal of treatment anticipated
5. Equipment for both CPAP and HFNO not available

2.6 Participant identification / Screening

During the study recruitment period, hospital research teams will, on a regular basis, attend or contact hospital clinical areas caring for patients with known or suspected COVID-19. Teams will liaise with clinical staff to identify individuals with acute hypoxaemic respiratory failure that may be eligible for enrolment. Based on this referral, a member of the team delivering the trial at the hospital (e.g. doctor, nurse, research practitioner) with appropriate knowledge will formally assess eligibility of the patient against trial inclusion and exclusion criteria. No additional tests or investigations will be required for assessing eligibility.

2.7   Site Staff Training

We will be using the emergency research consent process. The PI will retain overall responsibility for conduct of the trial at their site.

2.8   Informed consent

England, Wales and Northern Ireland

Patients will be assessed for capacity. Patients with capacity will be provided with verbal information about the trial and given a copy of the written participant information sheet. They will be given adequate time to review the information sheet and ask questions. Due to ongoing concerns regarding risk of infection transmission, verbal consent only will be sought and documented on a study form and in the patient hospital records. Where a patient objects at this point they will not be entered into the study.

For patients who lack capacity, it is not practical to consult a personal consultee or independent registered medical practitioner prior to enrolment without placing the potential participant at risk of harm from delaying treatment. These processes will also not be feasible or safe to undertake in order to minimise risk of viral transmission to those involved. Significant limitations have been placed on the visitation of COVID-19 patients and therefore a personal consultee is unlikely to immediately be available, and to attempt contact via telephone will delay treatment. Pressures on clinical services will make it impractical to identify an appropriate independent medical practitioner. In accordance with the legislation in England, Wales and Northern Ireland, as action needs to be taken as a matter of urgency, the Research Ethics Committee has authorised enrolment prior to obtaining informed consent. Once the urgency of the situation has passed, consent to continue will be sought from the patient (if capacity returns) or consultee. This approach is guided by a published framework, developed in collaboration with the National Research Ethics Service for use in research in an emergency setting[21]. For sites in Scotland, if a patient does not have capacity, the legislation does not allow enrolment without consent from the patient or guardian.

It is also important to highlight that all of the interventions proposed in the trial (CPAP, HFNO, and standard care) are existing standards of care currently employed in clinical practice; we are not investigating any experimental interventions in this trial.

Further details of the rationale for our approach are detailed in Table 2 and can be seen in figure 2, and our steps for obtaining consent following initial enrolment are described in Section 2.8.1.

Table 1: Mental Capacity Act Emergency Consent framework (for England, Wales and Northern Ireland only)

1. Is this research needed?	
	There is an urgent need to determine the optimum strategy to manage COVID-19 patients with worsening respiratory failure. This proposal has been commissioned to answer a research question that is considered to be of high priority by the UK clinical community.
2. Is there uncertainty about treatment?	
	There are perceived benefits to each study intervention, and each is in widespread use across the NHS. However, there is ongoing uncertainty as to the optimal approach
3. Is there a need to recruit subjects who lack capacity?	
	Eligible participants will be critically unwell and are likely to lack capacity as part of their underlying condition (e.g. acute hypoxia, sepsis). These individuals are an important COVID-19 group that are potentially at greater risk of deterioration.
4. In the context of the research is consent or consultation feasible?	
	We have carefully considered the feasibility of seeking agreement from a personal or professional consultee in the context of this research. - Personal consultee- throughout the NHS, significant limitations have been placed on the visitation of COVID-19 patients. On this basis, a personal consultee will not be immediately physical available for consultation. Waiting for a personal consultee to attend the hospital would place the consultee at risk of infection and cause treatment delays. - Professional consultee- due to COVID-19, there will be extreme pressure on UK health services. In this context, we consider it impractical for hospital research teams to identify an appropriate medical practitioner to act as a professional consultee without delaying treatment.
5) Does treatment need to be given quickly? 6) Might delay change the effect of treatment or the results?	
	It is essential that treatment (as per the study arms) is initiated as soon as possible. Delays in treatment initiation may place the patient at risk, and increase the likelihood of the need for tracheal intubation and increase the risk of death. Delays may therefore make study interventions appear less effective by reducing any observed treatment effect.
7. Will procedures accommodate variations in capacity?	
	Patients will be assessed for capacity in the first instance and provided with the patient information sheet detailing the trial, the patient will be given adequate time to consider the trial before providing verbal consent.

8. Would the legal representative/consultee be likely to have capacity?	
	A consultee may have capacity, but consultation is impractical due to the urgent need to commence treatment and research context.
9. Is it practical to consult a professional legal representative unconnected to the research?	
	As per question four, the research context makes it impractical to consult a professional consultee.
10. What should the patient, consultee or legal representative be asked later?	
	We will subsequently ask for patient consent or consultee agreement for ongoing delivery of the intervention (if applicable) and ongoing data collection.

Figure 2. Consent processes for England, Wales and Northern Ireland
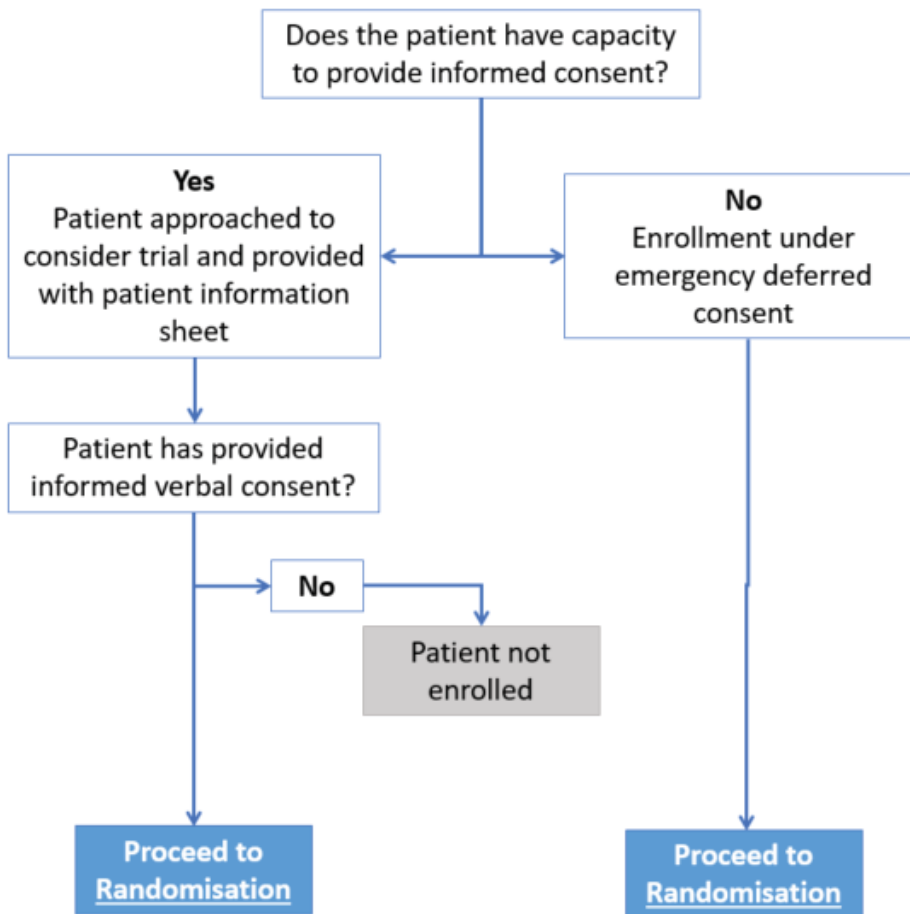
Scotland

Patients will be assessed for capacity. Patients with capacity will be provided with verbal information about the trial and given a copy of the written participant information sheet. They will be given adequate time to review the information and ask questions. Due to ongoing concerns regarding risk of infection transmission, verbal consent only will be sought and documented on a study form and in the patient hospital records. Where a patient declines participation at this point they will not be entered into the study.

For patients that lack capacity, it is not practical or appropriate to consult a guardian/welfare attorney prior to enrolment without placing the potential participant at risk of harm from delaying treatment. These processes will also not be feasible or safe to undertake in order to minimise risk of viral transmission to those involved. Significant limitations have been placed on the visitation of COVID-19 patients and therefore a guardian is unlikely to be immediately be available, and to attempt contact via telephone will delay treatment. Therefore these patients will not be entered into the study, see figure 3.

Figure 3. Consent processes for Scotland
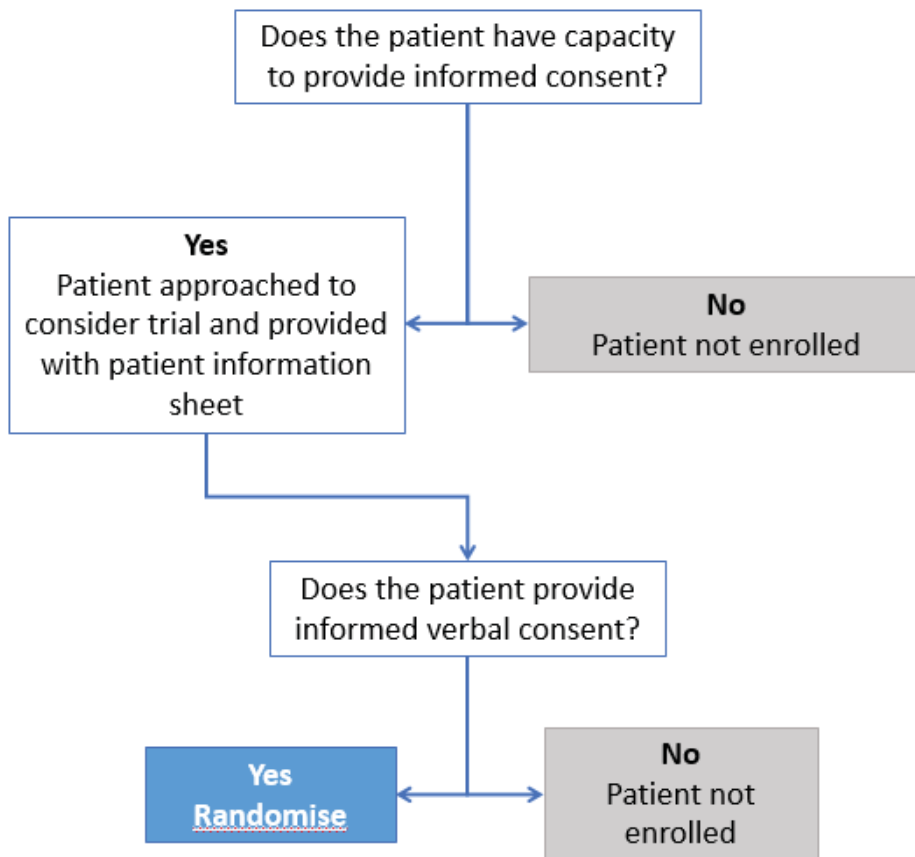
2.8.1 Consent following initial enrolment (for England, Wales and Northern Ireland only)

Following enrolment, the participant will be followed up regularly by the hospital research team. In participants that regain capacity, the site research team will approach the participant and provide verbal information about the trial. They will also be provided with the written participant information sheet, and given adequate time to review the information sheet and ask questions. Due to ongoing concerns regarding risk of infection transmission, verbal consent only will be sought and documented on a study form and in the patient hospital records.

In participants that do not regain capacity by hospital discharge, an approach will be made to a personal consultee or professional consultee. The initial approach should ideally be made to a personal consultee. However, this will likely be precluded due to visiting restrictions, in which case the opinion of a professional consultee will be sought. The professional consultee will be a registered medical practitioner that is independent of the trial. The consultee will be provided with a verbal explanation of the trial and a copy of the written participant information sheet and cover note. If the consultee does not know of any objection to research participation expressed by the participant, they will be asked to verbally confirm this. This will be recorded on a study record form. Procedures for consent following enrolment are different in the three jurisdictions (England & Wales, Scotland, Northern Ireland). Consent processes in Northern Ireland will follow the Exception for Urgent treatment in Part 8 of the Mental Capacity Act (Northern Ireland) 2016. For this trial, the consent processes used in England & Wales will be used in Northern Ireland, with the exception that Nominated Person assent will be taken and no Nominated Consultees will be appointed. These procedures will be updated in line with updated legislation.

Under the emergency regulations that have been introduced for COVID-19 related research, in the event that the participant dies prior to regaining capacity and before consent or consultee agreement can be sought, patient identifiable information may be retained by the WCTU to complete trial analysis as per the protocol and statistical analysis plan, for sites in England, Wales and Scotland. Patient identifiable information will not be transferred or retained by the WCTU for participants in Northern Ireland that do not provide consent.

On occasion, participant consent or personal/professional consultee agreement may not be obtained prior to hospital transfer or discharge. In this circumstance, the site research team will attempt to contact the participant or their consultee (if it is known that the participant lacks mental

capacity) at their place of residence to seek agreement. Up to three attempts to contact the participant will be made. Given the urgent need to answer this research question, for sites in England, Wales and Scotland, minimal personal identifiable data (NHS or CHI number, date of birth, postcode) will be submitted contemporaneously to Warwick Clinical Trials Unit. Patient identifiable information will not be transferred or retained by the WCTU for participants in Northern Ireland that do not provide consent. In the event that a trial participant declines consent to continue in the trial, personal identifiable data will be deleted. Information collected about the participant up to the point of withdrawal will be retained for analysis.

2.9 Randomisation

2.9.1 Randomisation

In this trial, there may well be the possibility that the devices will not be available as a result of the challenging environment the clinical staff are presented with. For this reason, we will set up two randomisation systems, which will be integrated to maintain balance.

Prior to randomisation, the clinician/nurse will check the availability of the devices. If no device is available then there will be no randomisation. If one of the devices is available (either CPAP or HFNO), then the clinician/nurse will choose the randomisation procedure which allocates standard care and CPAP or HFNO (system 1). If both devices are available, then system 2 will allow for an allocation using the three arms (standard care, CPAP or HFNO). These two systems will be integrated and constantly updated to ensure that the allocation ratio (1:1:1 for standard care: CPAP: HFNO) is maintained if possible. There is a possibility that this ratio will not be maintained and this has been compensated for in our sample size, which has been inflated accordingly.

A simple and secure, interactive voice response (IVR) randomisation system has been established by the programming team at Warwick Clinical Trials Unit. A computer-generated randomisation sequence has been generated by the minimisation method. Patients will be stratified by site, gender (M/F), and age (<50, >=50 years). If a patient has been randomised and found to be ineligible or the device is not available, they will be included in the analysis on an intention-to-treat basis. Any data already collected will be retained and included in the analysis unless otherwise indicated.

A back-up emergency randomisation system is currently being developed and full details will be made available and maintained on the trial website.

2.9.2 Post-randomisation withdrawals, exclusions and Moves out of Region

Participants may be discontinued from the trial treatment and/or the trial at any time without prejudice. Unless a participant explicitly withdraws their consent, they should be followed-up wherever possible and data collected as per the protocol until the end of the trial.

2.10 Trial treatments / intervention

Patients in all three treatment groups will be intubated and receive invasive mechanical ventilation if clinically required.

2.10.1 Continuous Positive Airway Pressure arm

Continuous positive airway pressure will be administered according to local protocol/guidelines. Details of initial settings (CPAP Pressure and FiO$_2$) will be recorded on the CRF. Administration of CPAP will not be protocolised and left to clinical discretion for management.

2.10.2 High Flow Nasal Oxygen

High flow nasal oxygen will be administered according to local protocol/guidelines. Details of initial settings (Flow and FiO$_2$) will be recorded on the CRF. Administration of HFNO will not be protocolised and left to clinical discretion for management.

2.10.3 Standard care

Standard care will comprise regular ward level oxygen therapy according to local protocol/guidelines, and excludes escalation to CPAP and HFNO. Administration of regular oxygen therapy will not be protocolised and left to clinical discretion for management.

2.11 Blinding and contamination

2.11.1 Methods for ensuring blinding

This is an open-label study. However, while the study is in progress, access to tabular results by treatment allocation will not be available to the research team, patients, or members of the Trial Steering Committee (unless the Data Safety Committee advises otherwise).

In addition, the clinical staff delivering the interventions will not be blinded or masked, and therefore there is possibility that bias could be introduced by knowledge of treatment allocation through administration of interventions. Due to the exceptional circumstance of this study, it is not possible to protocolise the interventions or provide training for clinical staff to ensure that delivery of the treatment is standardised across the trial sites. We will assess this bias in the interim stages of the trial and present the trial data by each site and intervention to the Data Monitoring

Committee and Trial Steering Committee. Both our primary and secondary outcomes are objective and this will ensure that detection bias is reduced.

2.11.2 Contamination

It is likely that the intervention the patient is randomised to may not be the one that is allocated or the patient may have crossed over to one of the other interventions. In this case, we will still include the patient in the trial on an intention-to-treat bias. However, we will do additional statistical analyses which will accommodate for patients who did not conform to the allocated intervention by means of a compliers analysis (as detailed in the statistical analysis section).

2.12 End of trial

The study will end when 4002 participants have been randomised and the last participant has completed final follow-up. The study will be stopped prematurely if:

- Mandated by the Ethics Committee
- Following recommendations from the Data Monitoring Committee (DMC)
- Funding for the trial ceases

The Ethics Committee that originally gave a favourable opinion of the study will be notified in writing if the study has been concluded or terminated early.

3 METHODS AND ASSESSMENTS

3.1 Schedule of delivery of intervention and data collection

Table 2. Trial assessments

Visit	1	2	3	4
Visit Window (No. Weeks $\pm$ No. Days)	**Day 0** Baseline	**Regular in-hospital reviews** (at least weekly)	**Day 30** (+/- 2 days)†	**Hospital** **discharge†**
Baseline data collection	✓			
Randomisation	✓			
Intervention	✓*	✓*		
Adverse events		✓	✓	✓
Survival status		✓	✓	✓
Outcome assessment			✓	✓

*- Intervention will be delivered up to point of death, tracheal intubation, or clinical determination that no ongoing need (palliation or improvement).

†- Participants to be followed-up to day 30 or hospital discharge, whichever comes later

4   ADVERSE EVENT MANAGEMENT

4.1 Definitions

4.1.1 Adverse Events (AE)

An Adverse Event (AE) is defined as any untoward medical occurrence in a trial participant and which does not necessarily have a causal relationship with the treatment/intervention. Only AEs clearly related to the use of CPAP or HFNO or expected will be recorded.

The following are expected adverse events and will be recorded in the CRF; they predominantly relate to the use of CPAP, as there are minimal AEs reported for HFNO:

- Interface intolerance due to excessive air leaks

- Pain

- Cutaneous pressure sore or pressure area

- Claustrophobia

- Oro-nasal dryness

- Respiratory acidosis with pH <7.25 prior to intubation

- Haemodynamic instability

- Vomiting

- Aspiration of gastric contents

4.1.2   Serious Adverse Events (SAEs)

A Serious Adverse Event (SAE) is an AE that fulfils one or more of the following criteria:

- Results in death

- Is immediately life-threatening

- Requires hospitalisation or prolongation of existing hospitalisation

- Results in persistent or significant disability or incapacity

- Is a congenital abnormality or birth defect

- Immediate intervention was required to prevent one of the above or is an important medical condition.

4.1.3 Assessing and Reporting AEs, SAEs and related SAEs

Adverse events

These events will be included as part of the safety analysis for the trial and do not need to be reported separately to the Trial Coordinating Centre. The local PI will be responsible for confirming the relatedness of any AE to the trial intervention. If an AE occurs, the clinician responsible for the patient should decide whether it is safe to continue CPAP, with or without modification, or whether CPAP should be discontinued. AEs will be reviewed/monitored by the TMG for trends.

Serious adverse events

Serious adverse events (SAE), occurring from the time of randomisation until 30 days post cessation of the trial intervention must be recorded on the Serious Adverse Event reporting form in the participant's CRF and emailed to WCTU (WCTUQA@warwick.ac.uk) within 24 hours of the research staff becoming aware of them. Events that do not need reporting as SAEs are listed below.

For each SAE the following information will be collected from the investigator site:

- full details in medical terms and case description

- event duration (start and end dates, if applicable)

- action taken

- outcome

- seriousness criteria

- causality (i.e. relatedness to intervention), in the opinion of the investigator (Table 3)

Once received, an independent causality assessment will be undertaken by the CI or clinical delegate. For any SAEs which are suspected to be caused by the trial intervention by either the CI or site clinician, expectedness will be confirmed by the CI or a delegate at WCTU. SAEs that are deemed to be unexpected and related to the study will be notified to the Research Ethics Committee (REC) within 15 days. All such events will be reported to the Sponsor, Trial Steering Committee and Data Monitoring Committee at their next meetings. All participants experiencing SAEs will be followed-up until the event has been resolved or a final outcome has been reached as per protocol until the end of the trial.

Table 3. Relationship of SAEs to trial intervention

Relationship to trial intervention	Description
Unrelated	There is no evidence of any causal relationship
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g.

	the event did not occur within a reasonable time after administration of the trial intervention or device). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible relationship	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial intervention or device). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments). This event will be reported as related.
Probable relationship	There is evidence to suggest a causal relationship and the influence of other factors is unlikely. This event will be reported as related.
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. This event will be reported as related.

4.1.4 SAEs Exempt from reporting

Because the trial is recruiting a population that is already in a life-threatening situation, it is expected that many of the participants will experience SAEs. Events that commonly occur in this population and those that are collected as outcomes of the trial should not be reported as SAEs. Common events, not for reporting include:

- Death
- Organ failure
- Pneumonia
- Intubation
- Tracheostomy

4.2 Responsibilities

Principal Investigator (PI):

Checking for AEs

1. Using medical judgement in assigning seriousness and causality
2. Ensuring that all SAEs are recorded and reported to WCTU (to receive on behalf of the Sponsor) within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with WCTU if a record of receipt is not received within 2 working days of initial reporting.

3. Ensuring that AEs are recorded and reported to WCTU (to receive on behalf of the Sponsor) in line with the requirements of the protocol.

Chief Investigator (CI)/delegate or independent clinical reviewer:
1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning causality review of any specific SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
3. Production and submission of annual reports to the REC.

Sponsor or delegate:
1. Central data collection and verification of AEs and SAEs, according to the trial protocol.
2. Expectedness assessment of related SAEs.
3. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk/benefit according to the Trial Monitoring Plan.
4. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and/or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
5. Expedited reporting of related and unexpected SAEs to the REC within required timelines.
6. Notifying Investigators of related and unexpected SAEs that occur within the trial.

Trial Steering Committee (TSC):
In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC):
In accordance with the Trial Terms of Reference for the DMC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

4.3 Notification of deaths

Death is collected as a study outcome. No separate notification of death is required.

4.4 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

5 DATA MANAGEMENT

5.1 Data collection and management

We will use the standard CTU study web-based application for study management and to record participant data (including case report forms) in accordance with the protocol. Clinical data will be collected during the ICU stay up to 30 days after randomisation or hospital discharge, whichever is later. Baseline characteristics collected include patient demographics, comorbidities, pre-admission function, inclusion/exclusion criteria, consent, time and date of randomisation, temperature at hospital admission, and COVID-19 diagnosis status. Data captured following randomisation will include initial device settings, duration of ventilation, prone therapy, ICU/hospital admission status, patient observations, AEs (treatment failure, need for other treatments, renal function, renal replacement therapy), survival status. Confirmation of COVID-19 diagnosis at any point will be recorded. Ethnicity, socioeconomic status and mortality will be reported from hospital records up until discharge and tracked after discharge using NHS Digital, the ICNARC and Research Centre and equivalent NHS data linkage in the devolved nations. ICU and hospital length of stay will be obtained from local centres or data linkage if appropriate.

The case report form (CRF) has been developed by the CTU and made available to the participating sites as a paper and electronic CRF (eCRF) for ease of data collection; supporting materials will be available to staff. All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by a unique trial-specific number/patient identifier/code in any database, not by name. The trial will be conducted in accordance with the current approved protocol, Good Clinical Practice (GCP), relevant data protection regulations and standard operating procedures (SOPs). A monitoring plan and risk assessment will be devised to protect participant safety and integrity of trial data.

5.2 Database

The database has been developed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) agreed between the programmer and appropriate trial staff.

5.3 Data storage

All essential documentation and trial records will be stored by WCTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel.

5.4 Data access and quality assurance

All data access will be controlled by generic usernames and passwords, and any changes to data will require the user to enter their username and password as an electronic signature in accordance with regulatory requirements. Staff will have access restricted to the functionality and data that are appropriate for their role in the study.

5.5 Archiving

Trial documentation and data will be archived for at least ten years after completion of the trial. Trial Master File and associated data will be archived by WCTU; trial data generated at study sites will be archived according to local policy.

6 STATISTICAL ANALYSIS

6.1 Power and sample size

The maximum total sample size will be 4002 patients over the three intervention arms (1334 per arm).

The primary end point will be a binary composite outcome of intubation or mortality within 30 days. An event (1) will be defined as intubation or death and an event (0) will be defined as no requirement for intubation and alive.

In a systematic review and meta-analysis to evaluate the evidence for the use of HFNO against usual care in ARF[8], the rate of mortality was 8.1% (90/1106) on the usual care arm and the rate of intubation was 15.7% (204/1300). A large UK based multi-centre open-labelled randomised control trial (3CPO) of 1069 patients presented with severe acute cardiogenic pulmonary oedema at 26 emergency department, compared standard oxygen therapy, CPAP and NIV, found a 7 day mortality rate of 9.8% and a mean intubation rate of 2.9% on the standard care arm. This is similar to the intubation rates of 2.7% reported in the British Thoracic Society's *National Respiratory Audit Programme Annual Report 2011/12*[22]. In a large systematic review and cost-effectiveness evaluation[23] of pre-hospital NIV for ARF, the intubation rate on usual rate ranged from 4.6%-17.7% and mortality at 30 days was found to be 9.3%-12.8%. In relation to COVID-19 infection, a very

recent publication in the Lancet using WHO data on the cumulative number of deaths to March 1, 2020, mortality rates were reported to be 5·6% (95% CI 5·4–5·8) for China and 15·2% (12·5–17·9) outside of China[1].   Furthermore, in another study relating to the COVID-19, which assessed, lopinavir- ritonovir and standard care, in hospitalised adults with confirmed SARS-Cov-2 infection and with an oxygen saturation of <=94%, the mortality rate on standard care at day 28 was 25% [24].

In our sample size calculation, we have assessed both outcome measures and taken the largest in terms of the incidence, to ensure we have maximum power and sample size for our study. Therefore taking the data from Baud *et al*[1] to be representative of usual care and assuming a conservative incidence of 15% for the composite outcome of intubation or mortality on the usual care arm, then using a two-sided 5% significance level, a total 3000 patients (1000 per arm across 3 arms) would give approximately 90% power to detect an odds ratio of 0.625, corresponding to a reduction from 15% to 10% in the composite event rate. allowing for the 11 interim analyses. Our comparisons will be based on CPAP versus standard care and HFNO versus standard care and allow for the formal interim analyses as agreed with the DMC.

However, there remain many uncertainties regards the sample size parameters and also whether an equal randomisation allocation ratio will be maintained. For this reason we have inflated our sample size to 4000 patients (4002 across the three arms) to maintain the study power and detect small effect sizes, if they exist. It may allow us to also assess the difference between CPAP and HFNO, if difference between these interventions are small enough to be detected with this larger sample size. Furthermore, it may be likely that we will not need all these patients if the trial stops at a formal interim analysis or if the DMC recommends that an arm is dropped.

The formal stopping rules will be set out in the statistical analysis plan, following discussions with the DMC. These criteria will be used to accept or drop an intervention arm, based on the assessment of the primary outcome at each interim point.

6.2 Statistical analysis of efficacy and harms

6.2.4   Statistics and data analysis

The statistical analysis will be based on intention to treat and will be conducted in line with the CONSORT statement[25]. For the overall analyses, numbers of events will be assessed using the logistic regression unadjusted and adjusted for important predictors, such as previous morbidities, age and gender) and results will be presented using odds ratios (with 95% confidence intervals). At the interim stages, the numbers of events will be analysed using the latter methods and compared

to the p-value critical values. A final p-value and treatment effect estimate will be calculated adjusting for the interim analyses using the methods described by Jennison and Turnbull[26], Fairbanks and Madsen[27] and, Emmerson and Fleming[28]. Intubation rates and mortality at 30 days will be assessed using the logistic regression models (both for adjusted and unadjusted analyses) and summarised using odds ratio (with 95% confidence intervals). Continuous secondary data will be presented using summary statistics and analysed using parametric or non-parametric methods depending on the distribution of the data.

If possible, we will conduct a compliers average cause effect (CACE) analysis to assess the effect on the non-compliance to the allocation interventions (for all three interventions or two, if one is dropped)[29].

We anticipate no or very little missing data. However, in the case of missingness, we will use multiple imputation techniques (ICE procedures) to assess the missingness mechanisms.

6.2.5 Planned recruitment rate

Recruitment will take place in 40 adult ICUs and centres to treat COVID-19 patients across the UK (England, Wales, Scotland and Northern Ireland) with a track record of delivery on critical care research, in order to facilitate enrolment of the required number of patients and ensure relevance to the wider NHS. Assuming a maximum sample size of 4002 patients, each site would enrol approximately 100 patients over the planned 12 months duration for recruitment.

Due to the rapidly evolving clinical landscape in the context of COVID-19, estimating a monthly recruitment rate is challenging; we anticipate the majority of patients would be recruited in the first 6 months but there is the possibility that seasonal fluctuations could result in further presentations in the winter months. We have therefore elected to focus on an overall recruitment number per site to accommodate any variations in monthly recruitment.

In 2018-19, 83% of ICUs in England actively recruited to the NIHR Portfolio of critical care research studies. In addition, the Chief Investigators have extensive experience of leading and participating in successful large-scale, UK multi-centre trials, including the devolved nations. We will employ the NIHR Critical Care National Specialty Group database, the UK Critical Care Research Group membership, and sites previously involved in critical care research studies, to identify sites.

6.3 Health Economic Evaluation

There will be no health economic evaluation within this trial.

7 TRIAL ORGANISATION AND OVERSIGHT

7.1 Sponsor and governance arrangements

The University of Warwick will sponsor the study.

Sub-contracts delegating responsibilities to research sites will be established using our standard contracting processes with NHS organisations.

7.2 Ethical approval

All required ethical approval(s) for the trial will be sought using the Integrated Research Application System. The trial will be conducted in accordance with all relevant regulations. Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has agreement of the relevant NHS Trust Research & Development (R&D) department. Sites will not be permitted to enrol patients into the trial until all required agreements are in place.

Annual reports will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The REC will be notified of the end of the trial (whether at planned time or prematurely). The CI will submit a final report to the required authorities with the results, including any publications within one year of the end of the trial.

Peer review for this protocol will initially be provided by the Department of Health and Social Care and the NIHR Urgent Public Health prioritisation group. Additional peer review will be obtained as required.

7.3 Trial Registration

The trial is registered in advance of recruitment commencing, on the ISRCTN database (https://www.isrctn.com/).
Registration confirmed: ISRCTN16912075

7.4 Notification of serious breaches to GCP and/or trial protocol

Trial protocol deviation and violations

Deviations from clinical trial protocols and GCP occur commonly in clinical studies. The majority of these instances are technical deviations that do not result in harm to the trial subjects or significantly affect the scientific value of the reported results of the trial. Violation is a failure to

comply with or variance from GCP and/or the final approved protocol. This results from error, fraud or misconduct. These cases should be documented in the protocol deviation and violation section of the case report form for the trial and appropriate corrective and preventative actions taken. Deviations will be included and considered when the clinical study report is produced, as they may have an impact on the analysis of the data.

Serious breach

A "serious breach" is a breach which is likely to effect to a significant degree –

      (a) the safety or physical or mental integrity of the subjects of the trial; or

      (b) the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase, and will notify the licensing authority in writing of any serious breach of

      (a) the conditions and principles of GCP in connection with that trial; or

      (b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

7.5 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. The University of Warwick provides indemnity for any harm caused to participants by the design of the research protocol.

7.6 Trial timetable and milestones

These milestones are estimated and subject to change given the rapidly evolving circumstances under which this trial will be conducted.

	Month	Recruitment
Set-up	1	n/a
Recruitment	2-13	4002
Follow up	14	n/a
Analysis	15-18	n/a

7.7 Administration

Trial coordination will be based at WMS/WCTU, University of Warwick. All day-to-day coordination of the study will be the responsibility of the Trial Manager. All clinical coordination of the study will be the responsibility of Professor Gavin Perkins. The study is managed by a multi-disciplinary team.

The study office team will assist and facilitate the setting up of centres wishing to collaborate in the study. In addition the study office team will:

- Distribute the standardised data collection forms to collaborators
- Organise the telephone randomisation service for formal study entry
- Monitor the collection of data, process data and seek missing data
- Train local staff with regards to data collection remotely
- Ensure the confidentiality and security of all study forms and data
- Conduct extensive data checking and cleaning
- Organise any interim and main analyses
- Organise Steering Committee, DMC and Collaborators meetings

The study office will receive completed data forms, via the online web application or email. Upon receipt, data forms will be checked for completeness and entered into a study specific dedicated computer programme which will check the data validity.

7.8 Trial Management Group (TMG)

The Trial Management Group, consisting of the project staff and co-investigators involved in the day-to-day running of the trial, will meet regularly throughout the project. Significant issues arising from management meetings will be referred to the Trial Steering Committee or Investigators, as appropriate.

7.9 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced personnel and trialists as well as at least one 'lay' representative. The TSC will have an independent Chairperson. Meetings will be held via teleconference or video conference at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The Steering Committee, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason

- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMC
- Informing and advising on all aspects of the trial

Membership of the TSC it to be confirmed. The full remit and responsibilities of the TSC will be documented in the Committee Charter which will be signed by all members.

7.10 Data Monitoring Committee (DMC)

A DMC will be appointed comprising of two independent clinicians with experience in clinical trials and an independent statistician. They will be provided with interim reports with outcome measures, when data are available on 1000 patients, at 4 time points in the study. One of the independent clinicians will have experience in undertaking clinical trials in emergency or acute care. The DMC charter will be based on the DAMOCLES study group template.[35] Its roles will include: monitoring the data and making recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue; making recommendations as to whether to drop any arm from the study for futility, either relative to standard care or to other arms; advising the TSC regarding the release of data and/or information; considering data emerging from other related studies.

Membership of the DMC will be confirmed. DMC meetings will also be attended by the Chief Investigator and Trial Manager (for non-confidential parts of the meeting) and the trial statistician. The full remit and responsibilities of the DMC will be documented in the Committee Charter which will be signed by all members.

7.11 Essential Documentation

A Trial Master File will be set up according to Warwick University SOP and held securely at the coordinating centre. The coordinating centre will provide Investigator Site Files to all recruiting centres involved in the trial.

7.12 Financial Support

A full breakdown of costs, specifically 'Research' and 'NHS Service Support' costs, will be provided in due course. The study will be included on the NIHR Portfolio and is eligible for NHS Service Support costs.

8   MONITORING, AUDIT AND INSPECTION

Local monitoring of protocol compliance

In this pragmatic trial, the precise delivery of study interventions will be at the discretion of the treating clinical team. We will record the delivery of interventions on the case report form, including unanticipated crossover between study arms.

Monitoring

On-site monitoring will not be feasible in this trial, due to restrictions on non-essential staff visiting hospitals with COVID-19 patients. A risk-based proportionate approach outlined in the monitoring plan for off-site monitoring will be developed through discussion with the trial sponsor, that takes account of the challenging circumstances in which this trial will operate and the extreme pressure that will be placed on hospital staff.

Reporting

Protocol deviations or violations (and actions taken to prevent recurrence) will be recorded in the case report form. Serious breaches of the study protocol or GCP should be immediately reported to the Chief Investigator. The Chief Investigator in consultation with the PI will take whatever immediate action is required to safeguard the wellbeing of participant. The Chief Investigator will notify the Sponsor immediately and Ethics committee within 7 days of becoming aware of the serious breach.

9   CO-ENROLMENT

Co-enrolment with other trials will be reviewed on a case-by-case basis in accordance with national NIHR-supported co-enrolment guidelines[30]. There are many current examples of successful co-enrolment between UK critical care studies, facilitated by these guidelines.

10 PATIENT AND PUBLIC INVOLVEMENT (PPI)

Three members of Royal College of Anaesthetist Patient Carer Public Involvement Engagement (PCPIE) were approached to give their opinion on research question, study design, appropriateness of emergency consent and patient facing documents. PCPIE members were unanimous in their support for the research question and considered the study to be highly relevant to patients and public. They opined that it is critical and urgent to find the optimal breathing support for patients to avoid invasive ventilation and improve patient survival. They were also particularly supportive of the adaptive pragmatic study design and planned rapid dissemination of study results. Emergency

consent was considered both appropriate in a very difficult and time critical situation and sensitive in limiting burden to patient and family.

Furthermore, we also consulted with an independent member of the Clinical Research Ambassador Group, University Hospitals Birmingham NHS Foundation Trust with extensive experience of contributing to emergency care trials. This PPI colleague was supportive and confirmed our approach of emergency consent given the challenging clinical circumstances and urgency with which treatment of potential benefit should be delivered to patients, advising that they felt it would be considered acceptable to patients and members of the public. Planned use of data without consent was also agreed as being necessary, and acceptable.

In addition, investigating optimum ventilation practice was prioritised in a 2014 James Lind Alliance Priority Setting Partnership for intensive care research involving patients and family representatives[31], and subsequently in a NIHR critical care research priority setting survey[32]. We will continue to engage patients and family members at later stages of the trial conduct where possible, such as dissemination of findings.

11 CONFIDENTIALITY

The University of Warwick (Research Impact Services, University of Warwick, Coventry CV4 7AL) is the Sponsor for the study. The study is being conducted in full adherence with the principles of the Declaration of Helsinki and MRC Good Clinical Practice principles and guidelines. It also complies with all applicable UK legislation and Warwick Standard Operating Procedures. All data are being stored securely and held in accordance with the Data Protection Act 2018. All identifiable data are pseudonymised and treated as confidential. All CRFs, questionnaires, study reports and communication regarding the study will identify the patients by the assigned unique trial identifier and initials only. Patient confidentiality will be maintained at every stage and identifiable information will not be made publicly available to the extent permitted by the applicable laws and regulations. The trial consent process ensures that patients have the choice of whether or not to continue to participate in data collection and are given all relevant information about the study to make an informed decision. Participants are informed that they are free to withdraw from the trial at any time during any phase without providing a reason and without prejudice, if they so wish.

12 DISSEMINATION AND PUBLICATION

The approach will be informed by WCTU SOP 22 'Publication & Dissemination'.

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial coordinating team, and the final version will be agreed by the Trial Steering Committee before submission for publication, on behalf of the collaboration. The success of the trial depends on the collaboration of doctors, nurses and researchers from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the trial.

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).

The results of the trial will be shared widely, and participants are able to request a copy of the results through contacting the local study team. Following the conclusion of the trial, summary information will be sent to surviving participants who recorded a desire to receive this information.

13 RESILIENCE

Given the circumstances under which this trial will be conducted, we have specifically built in resilience to support all relevant personnel involved. There are two Chief Investigators, two statisticians, five further respiratory/critical care physicians, two respiratory physiotherapists, and key WCTU representation, with additional access to the full team of trial managers, coordinators and other staff within the CTU. In addition, we adopt the same approach when identifying members of the TSC and DMC.

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RECOVERY-RS
RESPIRATORY SUPPORT

STATISTICAL ANALYSIS PLAN (SAP)
Ventilation strategies in COVID-19:
CPAP, high-flow, and standard care
The RECOVERY-Supportive Care trial

EudraCT Number:	
ISRCTN Number:	ISRCTN16912075
Funding Body:	NIHR
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REC:	London - Brighton & Sussex Research Ethics Committee
REC Approval date:	3rd April 2020
Sponsor	University of Warwick
Protocol Version	4.0, 29th May 2020
SAP Version	1.0
Date	24th May 2021
Stage	Formal

SAP Amendments:

Amendment No.	Date of Amendment	Date of Approval

TABLE OF CONTENTS

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Abbreviations and Definitions

AE	Adverse Event
BMI	Body Mass Index
CACE	Compliers Average Causal Effect
CFS	Clinical Frailty Scale
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CONSORT	Consolidated Standards of Reporting Trials
CPAP	Continuous positive airway pressure
CURB-65	A score calculated based on the Confusion, Urea, Respiratory rate, Blood pressure and Age values
DMC	Data Monitoring Committee
FiO_2	Fraction of inspired oxygen
HFNO	High flow nasal oxygen
ICE	Imputation by chained equations
IMD	Index of Multiple Deprivation
IPW	Inverse Probability Weighting
IQR	Interquartile range
ITT	Intention-to-treat
MCMC	Monte Carlo Markov Chain
NIV	Non-invasive ventilation
$PaCO_2$	Partial pressure of carbon dioxide
PaO_2	Partial pressure of oxygen
SAE	Serious Adverse Event
SD	Standard deviation
SpO_2	Oxygen saturation
TSC	Trial Steering Committee
UCL	University College London

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SECTION 1   AIMS AND DESIGN OF THE TRIAL

1.1   Introduction

This document details the proposed presentation and analysis for the main paper(s) reporting results from the multi-centre randomised controlled trial RECOVERY-RS Respiratory Support (ISRCTN16912075) to investigate multiple forms of ventilatory support for hospitalised patients with COVID-19 with regard to the intubation and/or mortality rate.

The results reported in these papers will follow the strategy set out here. Any subsequent analysis of a more exploratory nature will not be bound by this strategy, and will be detailed in a separate statistical analysis plan (SAP). Suggestions for subsequent analyses by oversight committees, journal editors or referees, will be considered carefully in line with the principles of this SAP.

Any deviations from the SAP will be described and justified in the final report to the funder. The analysis will be conducted out by an identified, appropriately qualified and experienced statistician, who will ensure the integrity of the data during their processing.

1.2   Trial design

The RECEOVERY-RESPIRATORY SUPPORT trial is an adaptive (group-sequential), pragmatic, randomised controlled, open-label, multi-centre, effectiveness trial.

Hypothesis: In adult patients, with suspected or confirmed COVID-19, Continuous positive airway pressure (CPAP) or High flow nasal oxygen (HFNO) are more effective than standard care for reducing the rate of intubation and / or mortality.

Type of intervention: CPAP and HFNO

Type of control: Standard care

Randomisation method: Minimisation using site, age and sex.

This SAP is based on the latest version of the protocol (version 4.0, 29th May 2020).

1.3 Objectives

1.3.1 *Primary objective*

The primary objective of this trial is to determine if CPAP or HFNO is clinically effective compared with standard care in relation to intubation and mortality rates in patients with suspected or proven COVID-19.

1.3.2 *Secondary objective*

The secondary objective of the trial is to assess in-hospital patient data in terms of their stay.

1.4 Eligibility criteria

1.4.1 *Inclusion criteria*

Patients are eligible if the following criteria below are met:

1. Adults ≥ 18 years

2. Admitted to hospital with suspected or proven COVID-19

3. FiO2 ≥0.4 and SpO2 ≤94%

4. Plan for escalation to intubation if needed

1.4.2 *Exclusion criteria*

Patients will be ineligible if any of the following criteria are met:

1. Planned intubation and mechanical ventilation imminent within 1 hour

2. Known or clinically apparent pregnancy

3. Any absolute contraindication to CPAP or HFNO

4. Decision not to intubate due to ceiling of treatment or withdrawal of treatment anticipated

5. Equipment for both CPAP and HFNO not available

1.5   Outcome measures

1.5.1   *Primary outcome*

The primary outcome is a composite outcome comprising intubation or mortality within 30 days.

1.5.2   *Secondary outcomes*

Secondary outcomes relating to effectiveness include:

- Intubation rate

- Time to intubation

- Duration of invasive ventilation

- Time to death (mortality)

- Admission to critical care

- Mortality in critical care (level 2/3)

- Mortality in hospital

- Mortality at 30 days

- Length of stay in critical care (level 2/3)

- Length of stay in hospital

All secondary outcomes will be obtained from hospital records and routine data.

1.5.3   *Tertiary outcomes*

- Treatment crossover

All tertiary outcomes will be obtained from hospital records.

1.5.4   *Safety outcomes*

Adverse events (AEs) and serious adverse events (SAEs) will be reported.

1.6   Sample size

In our sample size calculation, we have assessed both outcome measures and taken the largest in terms of the incidence, to ensure we have maximum power and sample size for our study. Therefore taking the data from Baud et al[1] to be representative of usual standard care and assuming a conservative incidence of 15% for the composite outcome of intubation or mortality on the Standard Care arm, then using a two-sided 5% significance level, a total 3,000 patients (1,000 per arm across 3 arms) would give 90% power to detect an odds ratio of 0.625, corresponding to a reduction from 15% to 10% in the composite event rate, allowing for the 11 interim analyses as detailed in section 4.2. Our comparisons will be based on CPAP versus standard care and HFNO versus standard care.

However, there remain many uncertainties regards the sample size parameters and also whether patients will be randomised between all three arms. For this reason we have inflated our sample size to 4,000 patients (4,002 across the three arms) to maintain 90% power and detect small effect sizes, if they exist. It may allow us to also assess the difference between CPAP and HFNO, if difference between these interventions are small enough to be detected with this larger sample size. Furthermore, it may be likely that we will not need all these patients if the trial stops at a formal interim analysis or if the DMC recommends that an arm is dropped.

1.7   Randomisation

In this trial, there may well be the possibility that the devices will not be available as a result of the challenging environment the clinical staff are presented with. For this reason, we will set up two randomisation systems, which will be integrated to maintain balance.

Prior to randomisation, the clinician/nurse will check the availability of the devices. If no device is available then there will be no randomisation. If one of the devices is available (either CPAP or HFNO), then the clinician/nurse will choose the randomisation procedure which allocates standard care and CPAP or HFNO (system 1). If both devices are available, then system 2 will allow for an allocation using the three arms (standard care, CPAP or HFNO). These two systems will be integrated and constantly updated to ensure that the allocation ratio (1:1:1 for standard care: CPAP: HFNO) is maintained if possible. There is a possibility that this ratio will not be maintained and this has been compensated for in our sample size, which has been inflated accordingly.

A simple and secure, interactive voice response (IVR) randomisation system has been established by the programming team at Warwick Clinical Trials Unit. A computer-generated randomisation sequence has been generated by the minimisation method. Patients will be stratified by site, gender (M/F), and age (<50, >=50 years). If a patient has been randomised and found to be ineligible or the

device is not available, they will be included in the analysis on an intention-to-treat basis. Any data already collected will be retained and included in the analysis unless otherwise indicated.

A back-up emergency randomisation system is currently being developed and full details will be made available and maintained on the trial website.

1.8 Trial reporting

The trial will be reported in line with the CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *Tr*ials) statement[2].

SECTION 2   MONITORING OF THE TRIAL (OPERATIONAL AND STATISTICAL)

Monitoring of the trial is a continuous process, from the start to the end of the trial. At the end of the trial, two aspects related to monitoring will be examined:

1.   Operational (logistical) and Process Management monitoring;

2.   Statistical monitoring (assessment of bias – as stated in the protocol).

2.1   Operational (logistical) and Trial Management monitoring of patients

2.1.1   *Recruitment of patients*

A number of sites have been selected to randomise patients into the trial. Due to the limited availability of interventional devices for CPAP and HFNO at each site, patients may be randomised between two arms (CPAP and Standard Care or HFNO and Standard Care) or three arms (CPAP, HFNO and Standard Care).

- A CONSORT diagram showing the flow chart of patients recruited in the study will be illustrated in Figure 1.

- Randomisation balance by treatment arm and device availability will be presented in Table 1.

2.1.2   *Protocol violation and deviation*

Protocol violation and deviation will be tabulated in Table 2.

2.1.3   *Withdrawals*

Trial withdrawals may occur from the first hospital contact of patients. Patients who withdraw their consent will be logged on the database from the point that they communicate their intention to the trial team and no further contact will be made, unless they allow passive follow-up by the team. All withdrawals will be summarised by treatment arm in Table 2. All data up to the time of complete withdrawal (i.e. non-passive withdrawal) will be retained in the analysis.

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2.1.4 *Status of patients in the trial from prior to hospitalisation to follow-up*

The status of patients in the trial, from randomisation to the end of the study, will be summarised by treatment arm in Table 3.

2.1.5 *Safety data*

Treatment related AEs and SAEs will be listed and summarised by treatment arm in Table 4.

2.1.6 *Unblinding*

This is an open-label trial. However, while the study is in progress, access to tabular results by treatment allocation will not be available to the research team, patients, or members of the Trial Steering Committee (TSC) (unless the Data Monitoring Committee (DMC) advises otherwise).

2.2 Statistical monitoring during the trial

2.2.1 *Statistical monitoring (assessment of bias)*

- The characteristics of patients are reported to the DMC in each interim analysis. The DMC assesses these data for any variables that may exceed potential thresholds (as judged by the clinical experts).

- Eleven interim analyses were planned during the trial. The analyses will be conducted as detailed in section 4.2. If the trial is not stopped early, the final analysis will be based on a maximum number of 4,002 patients.

- If the trial is stopped early because of funding, the number of interim analyses will be modified based on the DMC's recommendation.

- Details of the sample size calculation is shown in section 1.6.

SECTION 3   CLINICAL OUTCOMES AND ANALYSIS DATA

3.1   Outcome variables

OUTCOMES	TIME POINT	SUBJECTS	DEFINITION/SCORING
Primary outcome			
Intubation or mortality within 30 days	30 days post randomisation	All patients	Patients who are intubated or deceased.
Secondary outcomes			
Intubation rate	Up to hospital discharge	All patients	Proportion of patients who are intubated.
Time to intubation	Up to hospital discharge	Intubated patients	Days between randomisation and intubation.
Duration of invasive ventilation	Up to hospital discharge	Intubated patients	Days between the start and end dates of invasive ventilation or number of advanced respiratory support days.
Time to death	30 days or hospital discharge, whichever is later	All patients	Days between randomisation and death.
Admission to critical care*	Up to hospital discharge	All patients	Proportion of patients admitted to critical care
Mortality in critical care*	Up to the first intensive care units (ICU) discharge	ICU admitted patients	Proportion of deceased patients.
Mortality in hospital stay	Up to hospital discharge	All patients	Proportion of in-hospital deaths.
Mortality at 30 days	30 days post randomisation	All patients	Proportion of deceased patients.
Length of stay in critical care*	From randomisation to the first ICU discharge or death; Recurrent ICU admissions are not counted	ICU admitted patients	Days between randomisation and ICU discharge/death.
Length of stay in hospital	From randomisation to hospital discharge	All patients	Days between randomisation and hospital discharge/death.
Tertiary outcomes			
Treatment crossover	Up to hospital discharge	All patients	Proportion of patients crossed over to the other intervention arm(s) for more than 6 hours, unless it occurs after

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			intubation or as a part of palliative care.

Note: If a participant received critical care outside of a physical ICU/HDU location, the admission and discharge dates are when clinician defined need for support was in keeping with critical care and when clinician defined need for critical care has stopped, respectively.

3.2   Safety variables

OUTCOMES	TIME POINT	SUBJECTS	SCORING
Process variables			
Serious adverse event	From randomisation to 30 days post cessation of the trial intervention	All patients	An adverse event is considered serious if it: • Results in death • Is immediately life-threatening • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Is a congenital anomaly or birth defect • Is an important medical condition
Adverse events	From randomisation to 30 days post cessation of the trial intervention	All patients	• Interface intolerance due to excessive air leaks • Pain linked to the intervention • Cutaneous pressure sore or pressure area • Claustrophobia • Oro-nasal dryness • Respiratory acidosis with pH <7.25 prior to intubation • Haemodynamic instability defined as systolic <90, MAP<60 or new onset arrhythmia. • Vomiting • Aspiration of gastric contents • Pneumothorax • Pneumomediastinum • Other

3.3   Type of populations

3.3.1   *Intention to treat (ITT) Population*

The primary and secondary analyses will be performed for the Intention to treat (ITT) population. That is, patients will be analysed according to the treatment arm to which they have been randomised. They will form the populations for two pairwise comparisons: CPAP vs Standard Care and HFNO vs Standard Care. In particular, not all interventional arms are available for each individual patient at randomisation. Therefore, each comparison population will include the Standard Care

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patients when the comparative arm is available at randomisation for them. One of the main reasons for advocating ITT analysis is that it gives an estimate as would be in the 'real world' and it also maintains the baseline comparability achieved by the randomisation process. If the initial random assignment is undermined, then confounding can be introduced and the internal validity of the results is consequently questionable.

3.4   Analysis Datasets

Usually there are two datasets used for the statistical analysis: (a) Observed and (b) Imputed.

The observed dataset will be used for the ITT analysis of primary and secondary outcomes as well as tertiary data where applicable.

An imputed dataset, where possible, will be made for completeness for the primary outcome in the ITT analysis.

3.4.1   *Observed dataset*

This will comprise of all the data observed (including follow-up) with missing values.

3.4.2   *Imputed dataset*

Missing data for the primary outcome are likely to be minor. However, if the missing primary outcome data exceeds 20% by the time of final analysis, we will assess the missing mechanism. Multiple imputation techniques (e.g. imputation by chained equations or ICE procedures), if applicable, will be employed and the imputed data will be used as a sensitivity analysis. The number of imputed datasets will be determined by the proportion of missing data. usually 10-20 datasets would be sufficient for 10-30% missing data.[3]

SECTION 4   INTERIM ANALYSIS

4.1   Purpose of interim analysis

This is an adaptive (group sequential) trial so that if there is strong evidence of the effectiveness of one or both interventional arms during the trial, the trial can be stopped early based on the DMC decision. Arms may also be dropped early for harm or safety concerns, if the DMC feel necessary after reviewing the interim results.

4.2   Schedule of interim analysis

At the beginning of the trial, we planned to conduct 11, almost monthly, interim analyses and one final analysis after the end of recruitment (March 2021).

We would envisage that the first interim will be when 200 patients in total are recruited (end of May according to the projections below), when we should have approximately 40 patients with the primary outcome and this is the earliest we can provide an interim analysis. Otherwise, the events will be too small in number for any meaningful analysis.

Then following the 200 patients recruited, our interims will follow depending on recruitment rate, as projected in the table below.

Date	Total recruitment
Apr-20	40
May-20	208
Jun-20	528
Jul-20	888
Aug-20	1288
Sep-20	1688
Oct-20	2088
Nov-20	2488
Dec-20	2888
Jan-21	3288
Feb-21	3688
Mar-21	4002

However, the schedule was changed as it has been difficult to reach the recruitment target due to the rapidly changing pandemic across regions and along the time. From the third interim analysis,

we will carry out the interim analysis based on the DMC's suggestion. The number of interim analysis will be adjusted accordingly depending on the recruitment progress, funding, and the DMC's advice.

4.3 Stopping rules and analysis method

Effectiveness monitoring of each pairwise comparison with control is based on an alpha spending function approach with one-sided familywise type I error rate of 0.025 spent over the 11 interim analyses. This will allow the trial to stop early if one or both interventions are more effective than standard care. Critical values are adjusted for the fractional information (i.e. primary outcome data) observed at each interim analysis with the type I error spent linearly proportional to the information. If a decision is made to stop the trial early due to trial funding, the final critical value will be corrected for the interim analyses performed. No adjustment will be made to allow for the multiple comparisons with control. Interim boundary will be calculated using a user written programme in R.

Our composite primary outcome of mortality or intubation by 30 days will allow us to capture the full spectrum of early and late deaths. However, this does not provide the DMC with the immediate information that is needed for this trial, when much of the patients will have the short immediate outcome of intubation. Therefore, we will present the analyses based on three sets of patients at each of the interim analysis:

(i) All those who have intubation data.

(ii) All those who have reached 30 days and should have the primary outcome.

(iii) ii plus those who were discharged from hospital before reaching 30 days.

Note that the number of patients in the analysis (ii) is likely to be less than those in analysis (i). We assumed those who were discharged before 30 days and had no confirmed 30 days survival status are alive at 30 days.

In each analysis, the intubation rate and primary outcome will be summarised using frequency and percentage by treatment arm. Unadjusted logistic regression will be used to analyse the primary outcome and intubation rate. DMC decision on efficacy will only be made based on the unadjusted results of the primary outcome.

If there is any indication of harm or futility, this is not determined by the stopping rules; the decision to stop the trial for harm or futility will be left to the clinical judgement of the DMC and will be isolated from the efficacy information. No binding harm or futility rules have been assumed.

The cumulative results of the interim analyses are listed in Figure 2.

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4.4 Bias control

Although this is open label trial, the unblinded outcome data will be accessed and analysed by trial statisticians only. No other team members at Warwick Clinical Trials Unit and trial sites will have access to the unblinded (by treatment) analysis to avoid uncontrollable biases. The unblinded results will be presented to the DMC in the Closed session. The baseline summary of the trial patients, as well as the trial operational characteristics, will be presented by pooled treatment in the report to TSC and the funder.

SECTION 5   MAIN STATISTICAL ANALYSIS

5.1   General considerations

In general, continuous baseline and outcome data will be summarised with descriptive statistics, including n, mean, standard deviation (SD), median, and interquartile range (IQR). Categorical baseline and outcome data will be summarised with frequency count and percentage. Missingness will be reported for both types of data.

In addition, we will compare outcome data between interventional arms and standard care according to device availability at randomisation. Odds ratio with 95% confidence interval (CI) will be reported for categorical outcomes and mean difference with 95% CI will be reported for continuous outcomes, unless stated otherwise. For time to event analysis, hazard ratio with 95% CI will be reported. The final p value for the primary analysis will be corrected for the interim analyses performed using the method described by Jennison and Turnbull.[4] A two-sided p value <0.05 is considered statistically significant for secondary, tertiary and subgroup analyses.

5.2   Statistical software

All analyses will be conducted using SAS, Stata or R, where appropriate.

5.3   Characteristics of patients

The following baseline characteristics of randomised patients will be summarised by treatment arm in Table 5:

- Age at randomisation (continuous and categorical: <50, >=50 years)
- Sex (categorical: Male, Female)
- Ethnicity (categorical: White, Black, Asian and other Minority group, unknown)
- Index of Multiple Deprivation (IMD) (categorical)
- Time from symptom onset to hospital admission (continuous)
- Time from symptom onset to randomisation (continuous)
- COVID-19 status (categorical: confirmed, suspected)
- Comorbidities (categorical: Yes, No; including: renal failure, cardiac failure, lung disease, heart disease, dementia, diabetes, hypertension, malignancy, morbid obesity)
- Pre-admission function (Clinical Frailty Scale) (categorical: level 1-9)
- Core body temperature at hospital admission (continuous)
- Heart rate (continuous)

- Systolic blood pressure (continuous)
- Diastolic blood pressure (continuous)
- Respiratory rate (continuous)
- CURB-65 score (categorical: 1-5)
- Fraction of inspired oxygen (FiO2) (continuous)
- Oxygen saturation (SpO2) (continuous)
- SpO2 to FiO2 ratio (continuous)
- Partial pressure of oxygen (PaO2) (continuous)
- PaO2 to FiO2 ratio (continuous)
- Partial pressure of carbon dioxide (PaCO2) (continuous)
- Awake prone positioning (categorical: Yes, No)
- CPAP device type (categorical: Non-invasive (NIV) device, CPAP device (University College London (UCL)), CPAP device (non-UCL))

5.4   Covariates for model adjustment

Some secondary analyses will be adjusted for important covariates to take into account important confounders, potential baseline imbalance, or to improve precision. The covariates include the minimisation variables (site, age, and sex), baseline variables (morbid obesity, ethnicity, FiO2, respiratory rate, IMD and treatment phases). Treatment phases is defined as 1st (<=June 2020, July 2020 to Jan 2021, Feb 2021 onwards). This classification is driven by the scientific discovery of the effect of Dexamethasone and Tocilizumab in June 2020 and January 2021.[5, 6]

5.5   Primary analysis

5.5.1   *Primary outcome: Intubation or mortality within 30 days (ITT)*

The primary analysis will compare the primary outcome by treatment arm on an ITT basis using logistic regression without adjustment for covariates. The final p value for the primary analysis will allow for the interim analyses performed. Results will be presented in Table 6.

5.6 Secondary analyses

5.6.1 Intubation or mortality within 30 days (ITT)

The primary outcome will also be analysed on an ITT basis using logistic regression with adjustment for covariates. Results will be presented in Table 6.

5.6.2 Intubation or mortality within 30 days (ITT, imputed)

Where applicable, the missing primary outcome data will be imputed. The imputed datasets will be analysed on an ITT basis using logistic regression with and without adjustment for covariates. Results will be presented in Table 6.

5.6.3 Intubation rate (ITT)

Patients' intubation before hospital discharge will be recorded. Data will be analysed on an ITT basis using logistic regression with and without adjustment for covariates. Results will be presented in Table 7.

5.6.4 Time to intubation (ITT)

Time to intubation from randomisation will be summarised by treatment arm. Data will be analysed on an ITT basis using Cox regression with and without adjustment for covariates. Patients who are discharged without intubation are considered as right censored. We will present the observed data by treatment using Kaplan-Meier plot. The proportional hazards assumption will be checked by test or graphs (e.g. plots of log (-log (survival function)) versus time or plots of Schoenfeld residuals versus time).[7] Results will be presented in Table 8 and Figure 3.

5.6.5 Duration of invasive ventilation (ITT)

Duration of invasive ventilation is defined as the time interval between the start and end of invasive ventilation.

Data will be analysed on an ITT basis using the methods described in section 5.6.4, with patients still intubated at the time of death considered as right censored.

Results will be presented in Table 9 and Figure 3.

5.6.6 Time to death (ITT)

Time to death up to 30 days post randomisation will be summarised by treatment arm.

Data will be analysed on an ITT basis using the methods described in section 5.6.4.

Results will be presented in Table 10 and Figure 4.

5.6.7 Admission to critical care (ITT)

Critical care admission will be analysed on an ITT basis using logistic regression with and without adjustment for covariates. Results will be presented in Table 11.

5.6.8 Mortality in critical care (level 2/3) (ITT)

Mortality in critical care will be analysed on an ITT basis using logistic regression with and without adjustment for covariates. Results will be presented in Table 12.

5.6.9 Mortality in hospital stay (ITT)

Mortality in hospital stay will be analysed on an ITT basis using logistic regression with and without adjustment for covariates. Results will be presented in Table 13.

5.6.10 Mortality at 30 days (ITT)

Mortality at 30 days will be analysed on an ITT basis using logistic regression with and without adjustment for covariates. Results will be presented in Table 14.

5.6.11 Length of stay in critical care (level 2/3) (ITT)

Length of stay in critical care will be analysed on an ITT basis using linear regression with and without adjustment for covariates. Results will be presented by survival status and overall in Table 15.

5.6.12 Length of stay in hospital (ITT)

Length of stay in hospital will be analysed on an ITT basis using linear regression with and without adjustment for covariates. Results will be presented by survival status and overall in Table 16.

5.6.13 Adverse event and serious adverse event

AEs and SAEs will be listed and summarised by treatment arm in Table 4.

5.7   Tertiary outcomes

5.7.1   Treatment crossover

Treatment crossover will be summarised by treatment arm. Results will be presented in Table 17.

5.8   Subgroup analyses

Pre-specified sub-group analyses will be conducted:

1.   Age (<50 vs >=50)

2.   Sex (Male vs Female)

3.   Ethnicity (White vs BAME vs Unknown)

4.   Time from symptom onset to randomisation (<=7 days vs >7 days)

5. FiO_2 (≤0.6 vs >0.6)

6.   Index of Multiple Deprivation

7.   BMI (<=35 vs >35)

These sub-group analyses will be conducted in the observed dataset on the basis of ITT population. They will involve modelling the primary outcome as the dependent variable and interaction with treatment. Thus the analyses will use logistic regression model with and without adjustment for covariates detailed in section 5.3. The following results will be presented by subgroup in Figure 5a (unadjusted) and 5b (adjusted): Frequency count and percentage in each comparative group, odds ratio with 95% CI, Forest plot and a p value indicating the overall significance.

SECTION 6   ADDITIONAL STATISTICAL ANALYSIS

All additional analyses are exploratory in nature. This SAP specifies two analyses below. Any further analyses will be specified in a separate SAP.

6.1   Inverse Probability Weighting Analysis

Patients may switch to a different interventional treatment after being allocated to one of the trial arms. The switch is considered non-compliant to the protocol and defined as crossover if the switched treatment duration is longer than 6 hours. Exceptions to this definition include 1) the primary outcome is confirmed before the crossover; 2) the treatment is used as part of palliative care.

One common choice to correct for this type of non-compliance is Complier Average Causal Effect (CACE) analysis. However, the compliance rate is likely to vary across the treatment arms, suggesting that the monotonic and random assignment assumptions of the CACE analysis might be violated.[8, 9] In addition, the crossover is likely to be not random and triggered by worsening clinical condition after randomisation.

Therefore, we will use inverse probability weighting (IPW) method to take into account the crossovers.[10] The IPW method corrects for the bias caused by treatment crossover. The patients remaining in their allocated treatment will be weighted to compensate the information of the crossover patients. Logistic regression with crossover predictors will be included to calculate the weights. Odds ratio with 95% CI will be reported. Results will be presented in Table 18.

6.2   Bayesian analysis

Our target sample size was set as 4002 (1334 in each arm). Since the beginning of the trial, the UK has gone through multiple waves of the coronavirus pandemic. The trial recruitment has been closely associated with the waves and was limited mainly due to the low tide periods. Therefore, the recruitment is not likely to achieve 4002, which may impose a risk of lack of power to detect any pre-specified effect size. To gain more understanding of the data, we propose a Bayesian logistic regression analysis of the primary outcome, on an ITT basis.

We will use a non-informative prior for treatment difference. An enthusiastic prior and sceptical prior will also be used for sensitivity analysis. The enthusiastic prior reflects a strong belief of the treatment effect and is centred on the optimistic estimate based on the recent clinical evidence[11]

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that is reviewed by the clinical experts in the trial team. The sceptical prior reflects a weak belief of this treatment effect and is centred at the null hypothesis of no effect with a very small probability (5%) to be greater than the optimistic treatment effect estimate.

We will not define the criterion for success. Instead, we will report the posterior probability (with 95% credible intervals) of treatment effect on the primary outcome (intubation or mortality within 30 days) and its sub-components (intubation rate and mortality within 30 days). We will report the probability of reduced the composite outcome risk by 1%, 2.5% and 5%. We will also report the convergence of Markov Chain Monte Carlo (MCMC) sampler in Figure 6 and posterior distribution of risk difference in Figure 7. Results will be presented in Table 19.

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SECTION 8   APPENDIX A: Figures

8.1.1   Figure 1: CONSORT diagram

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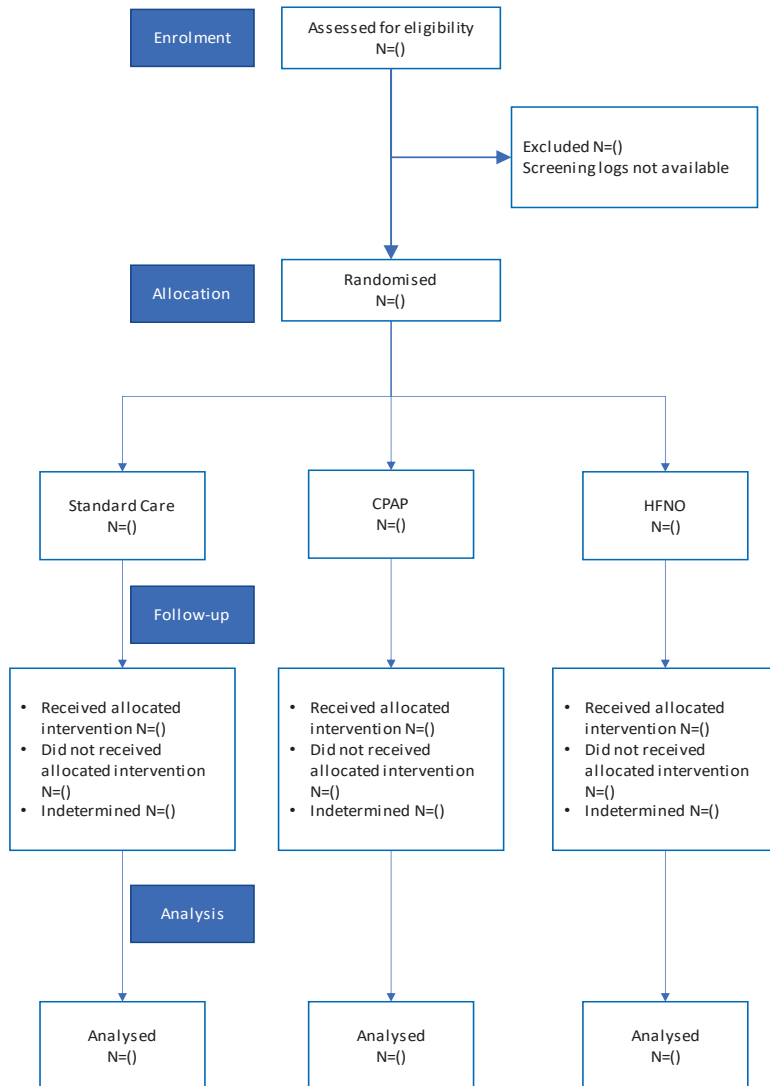
8.1.2   Figure 2: Cumulative results of the interim analyses

8.1.3   Figure 3: Kaplan Meier curve for intubated patients by treatment arm (top: time to intubation; bottom: time to the end of intubation)

8.1.4   Figure 4: Kaplan Meier curve for patient survival status by treatment arm (top: mortality; bottom: discharged alive)

8.1.5   Figure 5a: Subgroup analysis (unadjusted)

8.1.6   Figure 5b: Subgroup analysis (adjusted)

8.1.7   Figure 6: Convergence diagnostic plots for Bayesian analysis

8.1.8   Figure 7: Posterior distribution of risk difference

SECTION 9   APPENDIX B: Tables

9.1   Trial operational and patient baseline characteristics

9.1.1   *Table 1: Randomisation balance by device availability*

Randomisation	Treatment arm		
	STANDARD CARE	CPAP	HFNO
Device availability			
CPAP and STANDARD CARE			NA
HFNO and STANDARD CARE		NA	
CPAP, HFNO and STANDARD CARE			
Total			
Pairwise comparison	Treatment arm		
	STANDARD CARE	CPAP	HFNO
CPAP vs STANDARD CARE			NA
HFNO vs STANDARD CARE		NA	

Note: NA, not applicable.

9.1.2   *Table 2: Protocol deviations, violations and withdrawal by treatment arm*

		STANDARD CARE	CPAP	HFNO	Total
Deviations	Reason 1				
	Reason 1				
	Reason 2				
	Total				
Violations	Reason 1				
	Reason 1				
	Reason 2				
	Total				
Withdrawal	Withdrawal from trial, data collection continued				
	Withdrawal from trial and data collection				
	Total				

Note: P-value is calculated using Chi-squared test of Fisher's exact test.

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9.1.3 *Table 3: Patient status from prior to hospitalisation to the end of study*

		STANDARD CARE	CPAP	HFNO	Total
Status at randomisation	All eligible patients				
Status at critical care	Admitted to critical care				
	Intubated at critical care				
	Deceased in critical care				
	Discharged alive from critical care				
Status at hospital	Not admitted to critical care				
	Still in hospital				
	Deceased in hospital				
	Alive at hospital discharge				
	- Discharged alive before 30 days				
	Patient withdrew from trial				
Status at 30 days if discharged early than 30 days post randomisation	Deceased within 30 days				
	Alive at 30 days				
	Patient withdrew from trial				
	Patient LOST TO FOLLOW-UP				

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9.1.4 *Table 4: Adverse events and serious adverse events by treatment arm*

		STANDARD CARE	CPAP	HFNO	Total
Adverse events	Reason 1				
	Reason 2				
	…				
	Total				
Serious adverse events	Reason 1				
	Reason 2				
	…				
	Total				

9.1.5 *Table 5: Patient characteristics by treatment arm*

		STANDARD CARE	CPAP	HFNO	TOTAL	p value
Age (years)	N					
	Mean					
	Std. Deviation					
	Median					
	IQR					
	Missing					
Age group	<50 years					
	>=50 years					
Sex	Male					
	Female					
	Missing					
Index of Multiple Deprivation	N					
	Mean					
	Std. Deviation					
	Median					
	IQR					
	Missing					
Ethnicity	White					
	Black, Asian and Minority group					
	Black					
	Asian					
	Other					

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	Unknown					
Time from symptom onset to hospital admission (days)	N					
	Mean					
	Std. Deviation					
	Median					
	IQR					
	Missing					
Time from symptom onset to randomisation (days)	N					
	Mean					
	Std. Deviation					
	Median					
	IQR					
	Missing					
COVID-19 status	Confirmed					
	Suspected					
	Missing					
Comorbidities	None					
	End stage renal failure requiring renal replacement therapy					
	Congestive cardiac failure					
	Chronic lung disease					
	Coronary heart disease					
	Dementia					
	Diabetes requiring medication					
	Hypertension					
	Uncontrolled or active malignancy					
	Morbid obesity (BMI >35)					
Pre-admission function (Clinical Frailty Scale)	CFS1 - Very Fit					
	CFS2 - Well					
	CFS3 - Managing Well					

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	CFS4 - Vulnerable					
	CFS5 - Mildly Frail					
	CFS6 - Moderately Frail					
	CFS7 - Severely Frail					
	CFS8 - Very Severely Frail					
	CFS9 - Terminally Ill					
Core body temperature at hospital admission (°C)	N					
	Mean					
	Std. Deviation					
	Median					
	IQR					
	Missing					
Heart rate (beats per minute)	N					
	Mean					
	Std. Deviation					
	Median					
	IQR					
	Missing					
Systolic blood pressure (mmHg)	N					
	Mean					
	Std. Deviation					
	Median					
	IQR					
	Missing					
Diastolic blood pressure (mmHg)	N					
	Mean					
	Std. Deviation					
	Median					
	IQR					
	Missing					
Respiratory rate (breaths per minute)	N					
	Mean					
	Std. Deviation					
	Median					
	IQR					

	Missing					
Confusion	Yes					
	No					
	Not applicable - sedated					
	Missing					
CURB-65 score	N					
	Mean					
	Std. Deviation					
	Median					
	IQR					
	Missing					
Urea (mmol/L)	N					
	Mean					
	Std. Deviation					
	Median					
	IQR					
	Missing					
FiO_2, fraction of inspired oxygen	N					
	Mean					
	Std. Deviation					
	Median					
	IQR					
	Missing					
SpO_2, Oxygen saturation (%)	N					
	Mean					
	Std. Deviation					
	Median					
	IQR					
	Missing					
SpO_2:FiO_2 ratio	N					
	Mean					
	Std. Deviation					
	Median					
	IQR					
	Missing					
PaO_2, partial pressure of oxygen (kPa)	N					
	Mean					
	Std. Deviation					

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	Median					
	IQR					
	Test not available					
	Missing					
PaO$_2$:FiO$_2$ ratio	N					
	Mean					
	Std. Deviation					
	Median					
	IQR					
	Test no available					
	Missing					
PaCO$_2$, partial pressure of carbon dioxide (kPa)	N					
	Mean					
	Std. Deviation					
	Median					
	IQR					
	Test not available					
	Missing					
Awake prone positioning	Yes					
	No					
	Missing					
CPAP device type	NIV device					
	UCL device					
	Non-UCL device					
	Missing					

9.2 Intention to treat

9.2.1 Table 6: Unadjusted and adjusted analysis of Intubation or mortality within 30 days (Intention to treat, Observed and Imputed data)

		Pairwise treatment comparisons					
		CPAP v HFNO*		CPAP vs STANDARD CARE[†]		HFNO vs STANDARD CARE[‡]	
Observed data		CPAP	HFNO	CPAP	Standard Care	HFNO	Standard Care
Intubation or mortality within 30 days	Intubated or died						
	No event						
	Missing						
Unadjusted analysis	Risk difference (95% CI)	NA					
	Odds ratio (95% CI)	NA					
	P-value	NA					
Adjusted analysis	Risk difference (95% CI)	NA					
	Odds ratio (95% CI)	NA					
	P-value	NA					
Imputed data							
Intubation or mortality within 30 days	Intubated or died						
	No event						
Unadjusted analysis	Risk difference (95% CI)	NA					
	Odds ratio (95% CI)	NA					

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	P-value	NA			
Adjusted analysis	Risk difference (95% CI)	NA			
	Odds ratio (95% CI)	NA			
	P-value	NA			

Note: *, only patients randomised at sites when both CPAP and HFNO were available; No unadjusted or adjusted analysis is carried out. †, includes patients randomised at sites when CPAP or both CPAP and HFNO available. ‡, includes patients randomised at sites when HFNO or both CPAP and HFNO available. NA, not applicable.

9.2.2 *Table 7: Unadjusted and adjusted analysis of Intubation rate (Intention to treat)*

		Pairwise treatment comparisons					
		CPAP v HFNO*		CPAP vs STANDARD CARE†		HFNO vs STANDARD CARE‡	
		CPAP	HFNO	CPAP	Standard Care	HFNO	Standard Care
Intubation rate	Yes						
	No						
	Missing						
Unadjusted analysis	Risk difference (95% CI)	NA					
	Odds ratio (95% CI)	NA					
	P-value	NA					
Adjusted analysis	Risk difference (95% CI)	NA					
	Odds ratio (95% CI)	NA					

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P-value	NA			

Note: *, only patients randomised at sites when both CPAP and HFNO were available; No unadjusted or adjusted analysis is carried out. †, includes patients randomised at sites when CPAP or both CPAP and HFNO available. ‡, includes patients randomised at sites when HFNO or both CPAP and HFNO available. NA, not applicable.

9.2.3 *Table 8: Unadjusted and adjusted analysis of Time to intubation (Intention to treat)*

		Pairwise treatment comparisons					
		CPAP v HFNO*		CPAP vs STANDARD CARE†		HFNO vs STANDARD CARE‡	
		CPAP	HFNO	CPAP	Standard Care	HFNO	Standard Care
Time to intubation	N						
	Mean (SD)						
	Median (IQR)						
	Missing						
Unadjusted analysis (Cox regression)	Hazard ratio (95% CI)	NA					
	P-value	NA					
Adjusted analysis (Cox regression)	Hazard ratio (95% CI)	NA					
	P-value	NA					

Note: SD, standard deviation. IQR, interquartile range. *, only patients randomised at sites when both CPAP and HFNO were available; No unadjusted or adjusted analysis is carried out. †, includes patients randomised at sites when CPAP or both CPAP and HFNO available. ‡, includes patients randomised at sites when HFNO or both CPAP and HFNO available. NA, not applicable.

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9.2.4 *Table 9: Unadjusted and adjusted analysis of Duration of invasive ventilation (Intention to treat)*

		Pairwise treatment comparisons					
		CPAP v HFNO*		CPAP vs STANDARD CARE[†]		HFNO vs STANDARD CARE[‡]	
		CPAP	HFNO	CPAP	Standard Care	HFNO	Standard Care
Duration of invasive ventilation	N						
	Mean (SD)						
	Median (IQR)						
	Missing						
Unadjusted analysis	Hazard ratio (95% CI)	NA					
	P-value	NA					
Adjusted analysis	Hazard ratio (95% CI)	NA					
	P-value	NA					

Note: SD, standard deviation. IQR, interquartile range. *, only patients randomised at sites when both CPAP and HFNO were available; No unadjusted or adjusted analysis is carried out. †, includes patients randomised at sites when CPAP or both CPAP and HFNO available. ‡, includes patients randomised at sites when HFNO or both CPAP and HFNO available. NA, not applicable.

9.2.5 *Table 10: Unadjusted and adjusted analysis of Time to death (Intention to treat)*

		Pairwise treatment comparisons					
		CPAP v HFNO*		CPAP vs STANDARD CARE[†]		HFNO vs STANDARD CARE[‡]	
		CPAP	HFNO	CPAP	Standard Care	HFNO	Standard Care
Time to death	N						
	Mean (SD)						
	Median (IQR)						

	Missing					
Unadjusted analysis (Cox regression)	Hazard ratio (95% CI)	NA				
	P-value	NA				
Adjusted analysis (Cox regression)	Hazard ratio (95% CI)	NA				
	P-value	NA				

Note: SD, standard deviation. IQR, interquartile range. *, only patients randomised at sites when both CPAP and HFNO were available; No unadjusted or adjusted analysis is carried out. †, includes patients randomised at sites when CPAP or both CPAP and HFNO available. ‡, includes patients randomised at sites when HFNO or both CPAP and HFNO available. NA, not applicable.

9.2.6 *Table 11: Unadjusted and adjusted analysis of critical care admission (Intention to treat)*

		Pairwise treatment comparisons					
		CPAP v HFNO*		CPAP vs STANDARD CARE[†]		HFNO vs STANDARD CARE[‡]	
		CPAP	HFNO	CPAP	Standard Care	HFNO	Standard Care
Admission to critical care	Yes						
	No						
	Missing						
Unadjusted analysis	Risk difference (95% CI)	NA					
	Odds ratio (95% CI)	NA					
	P-value	NA					
Adjusted analysis	Risk difference (95% CI)	NA					

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	Odds ratio (95% CI)	NA		
	P-value	NA		

Note: *, only patients randomised at sites when both CPAP and HFNO were available; No unadjusted or adjusted analysis is carried out. †, includes patients randomised at sites when CPAP or both CPAP and HFNO available. ‡, includes patients randomised at sites when HFNO or both CPAP and HFNO available. NA, not applicable.

9.2.7 *Table 12: Unadjusted and adjusted analysis of Mortality in critical care (Intention to treat)*

		Pairwise treatment comparisons					
		CPAP v HFNO*		CPAP vs STANDARD CARE†		HFNO vs STANDARD CARE‡	
		CPAP	HFNO	CPAP	Standard Care	HFNO	Standard Care
Mortality in critical care	Survived						
	Died						
	Missing						
Unadjusted analysis	Risk difference (95% CI)	NA					
	Odds ratio (95% CI)	NA					
	P-value	NA					
Adjusted analysis	Risk difference (95% CI)	NA					
	Odds ratio (95% CI)	NA					
	P-value	NA					

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Note: *, only patients randomised at sites when both CPAP and HFNO were available; No unadjusted or adjusted analysis is carried out. †, includes patients randomised at sites when CPAP or both CPAP and HFNO available. ‡, includes patients randomised at sites when HFNO or both CPAP and HFNO available. NA, not applicable.

9.2.8 *Table 13: Unadjusted and adjusted analysis of Mortality in hospital (Intention to treat)*

		Pairwise treatment comparisons					
		CPAP v HFNO*		CPAP vs STANDARD CARE†		HFNO vs STANDARD CARE‡	
		CPAP	HFNO	CPAP	Standard Care	HFNO	Standard Care
Mortality in hospital	Survived						
	Died						
	Missing						
Unadjusted analysis	Risk difference (95% CI)	NA					
	Odds ratio (95% CI)	NA					
	P-value	NA					
Adjusted analysis	Risk difference (95% CI)	NA					
	Odds ratio (95% CI)	NA					
	P-value	NA					

Note: *, only patients randomised at sites when both CPAP and HFNO were available; No unadjusted or adjusted analysis is carried out. †, includes patients randomised at sites when CPAP or both CPAP and HFNO available. ‡, includes patients randomised at sites when HFNO or both CPAP and HFNO available. NA, not applicable.

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9.2.9   *Table 14: Unadjusted and adjusted analysis of Mortality at 30 days (Intention to treat)*

		Pairwise treatment comparisons					
		CPAP v HFNO*		CPAP vs STANDARD CARE[†]		HFNO vs STANDARD CARE[‡]	
		CPAP	HFNO	CPAP	Standard Care	HFNO	Standard Care
Mortality at 30 days	Survived						
	Died						
	Missing						
Unadjusted analysis	Risk difference (95% CI)	NA					
	Odds ratio (95% CI)	NA					
	P-value	NA					
Adjusted analysis	Risk difference (95% CI)	NA					
	Odds ratio (95% CI)	NA					
	P-value	NA					

Note: *, only patients randomised at sites when both CPAP and HFNO were available; No unadjusted or adjusted analysis is carried out. †, includes patients randomised at sites when CPAP or both CPAP and HFNO available. ‡, includes patients randomised at sites when HFNO or both CPAP and HFNO available. NA, not applicable.

9.2.10   *Table 15: Unadjusted and adjusted analysis of Critical care length of stay (Intention to treat)*

		Pairwise treatment comparisons					
		CPAP v HFNO*		CPAP vs STANDARD CARE[†]		HFNO vs STANDARD CARE[‡]	
		CPAP	HFNO	CPAP	Standard Care	HFNO	Standard Care

		CPAP v HFNO*		CPAP vs STANDARD CARE†		HFNO vs STANDARD CARE‡	
		CPAP	HFNO	CPAP	Standard Care	HFNO	Standard Care
Length of stay in critical care (Survivors)	N						
	Mean (SD)						
	Median (IQR)						
	Missing						
Unadjusted analysis	Mean difference (95% CI)	NA					
	P-value	NA					
Adjusted analysis	Mean difference (95% CI)	NA					
	P-value	NA					
		Pairwise treatment comparisons					
		CPAP v HFNO*		CPAP vs STANDARD CARE†		HFNO vs STANDARD CARE‡	
		CPAP	HFNO	CPAP	Standard Care	HFNO	Standard Care
Length of stay in critical care (Non-survivors)	N						
	Mean (SD)						
	Median (IQR)						
	Missing						
Unadjusted analysis	Mean difference (95% CI)	NA					
	P-value	NA					
Adjusted analysis	Mean difference (95% CI)	NA					
	P-value	NA					

Note: SD, standard deviation. IQR, interquartile range. *, only patients randomised at sites when both CPAP and HFNO were available; No unadjusted or adjusted analysis is carried out. †, includes patients randomised at sites when CPAP or both CPAP and HFNO available. ‡, includes patients randomised at sites when HFNO or both CPAP and HFNO available. NA, not applicable.

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9.2.11 _**Table 16: Unadjusted and adjusted analysis of Hospital length of stay (Intention to treat)**_

		Pairwise treatment comparisons					
		CPAP v HFNO*		CPAP vs STANDARD CARE[†]		HFNO vs STANDARD CARE[‡]	
		CPAP	HFNO	CPAP	Standard Care	HFNO	Standard Care
Length of stay in hospital (Survivors)	N						
	Mean (SD)						
	Median (IQR)						
	Missing						
Unadjusted analysis	Mean difference (95% CI)	NA					
	P-value	NA					
Adjusted analysis	Mean difference (95% CI)	NA					
	P-value	NA					
		Pairwise treatment comparisons					
		CPAP v HFNO*		CPAP vs STANDARD CARE[†]		HFNO vs STANDARD CARE[‡]	
		CPAP	HFNO	CPAP	Standard Care	HFNO	Standard Care
Length of stay in hospital (Non-survivors)	N						
	Mean (SD)						
	Median (IQR)						
	Missing						
Unadjusted analysis	Mean difference (95% CI)	NA					
	P-value	NA					
Adjusted analysis	Mean difference (95% CI)	NA					
	P-value	NA					

Note: SD, standard deviation. IQR, interquartile range. *, only patients randomised at sites when both CPAP and HFNO were available; No unadjusted or adjusted analysis is carried out. †, includes patients randomised at sites when CPAP or both CPAP and HFNO available. ‡, includes patients randomised at sites when HFNO or both CPAP and HFNO available. NA, not applicable.

9.2.12   *Table 17: Unadjusted analysis of Treatment crossover*

		Standard Care	CPAP	HFNO
Treatment crossover	Yes			
	No			
	CPAP vs Standard Care χ^2, p value			
	HFNO vs Standard Care χ^2, p value			

9.3   Additional analysis

9.3.1   Table 18: Analysis of Intubated or mortality within 30 days using the inverse-probability-weighting method

		Pairwise treatment comparisons			
		CPAP vs STANDARD CARE[†]		HFNO vs STANDARD CARE[‡]	
		CPAP	Standard Care	HFNO	Standard Care
Intubated or mortality within 30 days	Intubated or died				
	No event				
	Missing				
	Odds ratio (95% CI)				
	P-value				

Note: †, includes patients randomised at sites when CPAP or both CPAP and HFNO available. ‡, includes patients randomised at sites when HFNO or both CPAP and HFNO available. NA, not applicable.

9.3.2 *Table 19: Bayesian analysis of the primary composite outcome and sub-components*

(a) Non-informative prior			Pairwise treatment comparisons			
			CPAP vs STANDARD CARE[†]		HFNO vs STANDARD CARE[‡]	
			CPAP	Standard Care	HFNO	Standard Care
Primary composite outcome	Intubated or mortality within 30 days	Posterior event probability (95% credible interval)				
Sub-components	Intubation rate within 30 days	Posterior event probability (95% credible interval)				
	Mortality at 30 days	Posterior event probability (95% credible interval)				
(b) Sceptical prior			Pairwise treatment comparisons			
			CPAP vs STANDARD CARE[†]		HFNO vs STANDARD CARE[‡]	
			CPAP	Standard Care	HFNO	Standard Care
Primary composite outcome	Intubated or mortality within 30 days	Posterior event probability (95% credible interval)				
Sub-components	Intubation rate within 30 days	Posterior event probability (95% credible interval)				
	Mortality at 30 days	Posterior event probability (95% credible interval)				
(c) Enthusiastic prior			Pairwise treatment comparisons			
			CPAP vs STANDARD CARE[†]		HFNO vs STANDARD CARE[‡]	
			CPAP	Standard Care	HFNO	Standard Care

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Primary composite outcome	Intubated or mortality within 30 days	Posterior event probability (95% credible interval)		
Sub-components	Intubation rate within 30 days	Posterior event probability (95% credible interval)		
	Mortality at 30 days	Posterior event probability (95% credible interval)		

Note: †, includes patients randomised at sites when CPAP or both CPAP and HFNO available. ‡, includes patients randomised at sites when HFNO or both CPAP and HFNO available.