QUEEN'S UNIVERSITY BELFAST

WARWICK CLINICAL TRIALS UNIT

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
IRAS number:	251756
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

intensive care society 50 YEARS proud to be the voice of critical care since 1970

FUNDED BY NIHR | National Institute for Health Research

NHS University Hospitals Birmingham NHS Foundation Trust

TABLE OF CONTENTS

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

List of authors and reviewers

Authors

Professor Ranjit Lall, Lead Trial Statistician, Warwick Clinical Trials Unit, University of Warwick

Professor Nigel Stallard, Lead Trial Statistician, Warwick Clinical Trials Unit, University of Warwick

Dr Chen Ji, Trial Statistician, Warwick Clinical Trials Unit, University of Warwick

Reviewers

Professor Gavin Perkins, Chief Investigator, Warwick Clinical Trials Unit, University of Warwick

Professor Danny McAuley, Co-Chief Investigator, Wellcome Wolfson Institute for Experimental Medicine, Queen's University Belfast

Professor Kathy Rowan, TSC Chair, CTU Director, Intensive Care National Audit & Research Centre (ICNARC)

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 *T*rials) 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.

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

			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

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.

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]

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.

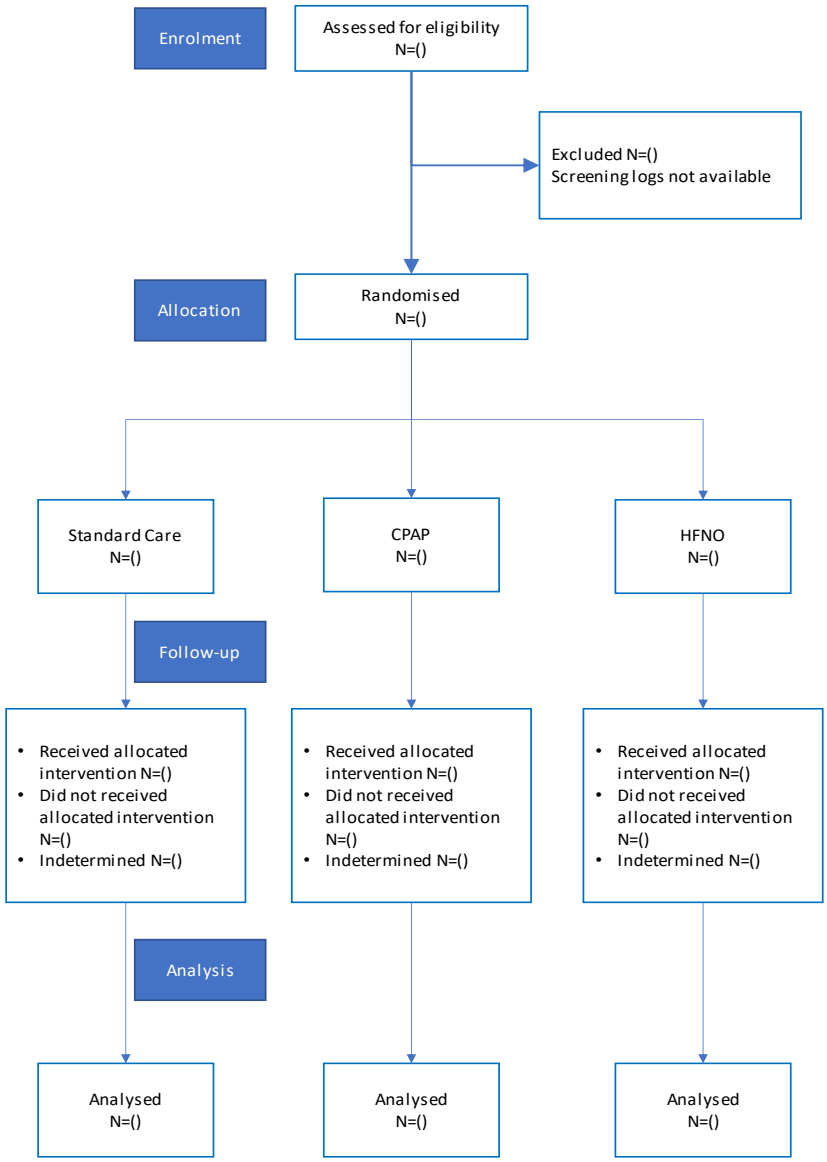
We will not define the criterion for success. Instead, we will report the posterior probability (with 95% credible intervals) of treatment effect on the primary outcome (intubation or mortality within 30 days) and its sub-components (intubation rate and mortality within 30 days). We will report the probability 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.

SECTION 7 REFERENCES

1. Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G. Real estimates of mortality following COVID-19 infection. Lancet Infect Dis. 2020;20:773.
2. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet. 2001;357:1191-4.
3. Graham JW, Olchowski AE, Gilreath TD. How many imputations are really needed? Some practical clarifications of multiple imputation theory. Prev Sci. 2007;8:206-13.
4. Jennison C, Turnbull BW. Group Sequential Methods with Applications to Clinical Trials: Boca Raton: Chapman & Hall/CRC; 2000.
5. Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021;384:693-704.
6. Horby PW, Pessoa-Amorim G, Peto L, Brightling CE, Sarkar R, Thomas K, Jeebun V, Ashish A, Tully R, Chadwick D, Sharafat M, Stewart R, Rudran B, Baillie JK, Buch MH, Chappell LC, Day JN, Furst SN, Jaki T, Jeffery K, Juszczak E, Lim WS, Montgomery A, Mumford A, Rowan K, Thwaites G, Mafham M, Haynes R, Landray MJ. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. medRxiv. 2021:2021.02.11.21249258.
7. Schoenfeld D. Partial Residuals for the Proportional Hazards Regression Model. Biometrika. 1982;69:239 -41.
8. Angrist JD, Imbens GW, Rubin DB. Identification of Causal Effects Using Instrumental Variables. Journal of the American Statistical Association. 1996;91:444-55.
9. Connell AM. Employing complier average causal effect analytic methods to examine effects of randomized encouragement trials. Am J Drug Alcohol Abuse. 2009;35:253-9.
10. Mansournia MA, Altman DG. Inverse probability weighting. BMJ. 2016;352:i189.
11. Lewis SR, Baker PE, Parker R, Smith AF. High-flow nasal cannulae for respiratory support in adult intensive care patients. Cochrane Database Syst Rev. 2021;3:CD010172.

SECTION 8 APPENDIX A: Figures

8.1.1 Figure 1: CONSORT diagram



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.

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				

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					

	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					

	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					

	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					

	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					

	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.

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					

	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					

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.

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

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.

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

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.