MARCH

The MARCH Trial

Mucoactives in Acute Respiratory failure: Carbocisteine and Hypertonic saline

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STATISTICAL ANALYSIS PLAN

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This document and all preceding versions will be stored in the Trial Master File for this trial

CONTENTS

ABBREVIATIONS

ABBREVIATION	DEFINITION
ABG	Arterial Blood Gas
AE	Adverse Event
ARF	Acute Respiratory Failure
CI	Confidence Interval
COVenT	Core Outcomes for Ventilation Trials
Cox-PH	Cox proportional hazards
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
CSR	Clinical Study Report
DMEC	Data Monitoring and Ethics Committee
EQ-5D-5L	EuroQol-5 Dimension-5 Level
GCP	Good Clinical Practice
GLM	Generalised Linear Model
HEAP	Health Economics Analysis Plan
HRQol	Health Related Quality of Life
ICNARC	Intensive Care National Audit & Research Centre
ICU	Intensive Care Unit
ITT	Intent-To-Treat
NICTU	Northern Ireland Clinical Trials Unit
PI	Principal Investigator
PICO	Population, Intervention, Comparator, Outcomes
PP	Per-Protocol
PPIE	Patient and Public Involvement and Engagement
RD	Risk Difference
RR	Risk ratio
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source data verification
SHR	Subhazard Ratio
SOP	Standard Operating Procedures
TMF	Trial Master File
TSC	Trial Steering Committee
UACM	Usual Airway Clearance Management
QoL	Quality of Life

1. BACKGROUND AND DESIGN

This is a 2x2 factorial, randomised, controlled, allocation concealed, open-label, phase 3 pragmatic clinical- and cost-effectiveness trial, with an internal pilot, of two medicinal products (i.e. a CTIMP). Specifically, in PICO terms, as an overview:

Population: Adult, critically ill patients admitted to the ICU with ARF and requiring invasive mechanical ventilation, with secretions that are difficult to clear with usual airway clearance management (as assessed by the treating clinical team)

Intervention: Mucoactives (carbocisteine, or hypertonic saline, or both) in conjunction with usual airway clearance management, including suctioning, heated humidification, and respiratory physiotherapy; isotonic saline may also be used depending on clinician preference

Comparator: Usual airway clearance management alone, including suctioning, heated humidification (either active heated humidification devices, or passive heat and moisture exchangers), and respiratory physiotherapy; isotonic saline may also be used depending on clinician preference

Outcomes: Primary – Duration of mechanical ventilation
Secondary – Range of clinical and safety outcomes at 60 days and 6 months, cost effectiveness at 6 months

Full details of the background to the trial and its design are presented in the protocol v4.0 02/12/2024 which can be accessed via the NICTU website (https://nictu.hscni.net)

2. OUTCOME MEASURES

2.1 Primary outcome measure

The primary outcome is duration of mechanical ventilation (in hours).

This is defined (measured) as time from randomisation until first successful unassisted breathing (defined as maintaining unassisted breathing at 48 hours) or death. This outcome is one of the 'COVenT' core outcomes for trials of interventions intended to modify the duration of mechanical ventilation[1].

To clarify:

i) Unassisted breathing is defined as no inspiratory support or extracorporeal lung support
ii) Success is defined as maintaining unassisted breathing at 48 hours
iii) Duration includes time receiving extracorporeal lung support, invasive mechanical ventilation and non-invasive ventilation delivering volume or pressure support ventilation
iv) Duration excludes time receiving high-flow oxygen therapy and continuous positive airway pressure
v) Patients with a tracheostomy in situ may still achieve successful unassisted breathing

vi) Follow-up to 60 days from randomisation

2.2 Secondary outcome measures

Secondary clinical and safety outcomes, timing of their assessment, and measurement tools, are summarised in Table 1. The secondary outcomes of extubation, re-intubation, duration of ICU and hospital stay, all-cause mortality, and health-related quality of life represent the remaining outcomes in the COVenT core outcome set[1]. Data contributing to the economic evaluations also represent those items recently recommended as a priority for this purpose[2].

Clinical and safety outcomes will be measured at baseline and daily up to and including Day 28 (or the primary outcome is reached), or ICU discharge, or death, whichever comes first.

Participants will be followed-up to 60 days post-randomisation for the outcomes of duration of mechanical ventilation, extubation and reintubation. Health-related quality of life and all-cause mortality will be measured at 60 days, and at 6 months.

Table 1. Detail of secondary outcomes

Outcome	Measurement tool, definition, method
In hospital	
Extubation	Time from randomisation to first successful extubation (success defined as remaining free from endotracheal or tracheostomy tubes at 48 hours) Censored at 60 days
Re-intubation	Event of reintubation of endotracheal tube after a planned extubation; excludes temporary reinsertion of endotracheal tube for procedures only Censored at 60 days
Respiratory physiotherapy input	Occurrence and frequency of airway clearance sessions Censored at Day 28 (or the primary outcome is reached), or ICU discharge, or death, whichever comes first. (Where unassisted breathing begins on Day 27 or Day 28, respiratory physiotherapy input will be recorded up to Day 29 and Day 30 respectively).
Antibiotic usage	Dose of individual agents Censored at Day 28 (or the primary outcome is reached), or ICU discharge, or death, whichever comes first. (Where unassisted breathing begins on Day 27 or Day 28, antibiotic usage will be recorded up to Day 29 and Day 30 respectively).
Duration of ICU and hospital stay	Time from randomisation until patient first leaves the relevant facility or dies Censored at 6 months
All-cause mortality	Confirmation and cause of death
Safety (please see below for additional explanation of safety outcome definitions)	i) Clinically important upper gastrointestinal (GI) bleeding due to peptic ulceration confirmed on upper GI endoscopy ii) Bronchoconstriction requiring nebulised bronchodilators iii) Ventilator or circuit dysfunction with respiratory deterioration iv) Hypoxaemia during nebulisation Censored at Day 28 (or the primary outcome is reached), or ICU discharge, or death, whichever comes first. (Where unassisted breathing begins on Day 27 or Day 28, safety outcomes will be recorded up to Day 29 and Day 30 respectively).
Hospital resource use	Number of days at Level of Care 0/1/2/3 Censored at 6 months
Time of consent to continue	
Health-related quality of life	EQ-5D-5L.
60 days	
Health-related quality of life	EQ-5D-5L.
All-cause mortality	Confirmation and cause of death.
6 months	

Health-related quality of life	EQ-5D-5L.
All-cause mortality	Confirmation and cause of death.
Health service use since hospital discharge	Categories: care at hospital, emergency, GP surgery, health clinic, or other community setting, health care at home, medication.

2.3 Safety Outcomes

i) Clinically important upper gastrointestinal (GI) bleeding due to peptic ulceration confirmed on upper GI endoscopy

-Defined as overt bleeding on upper GI endoscopy, developing as a complication in the ICU and accompanied by 1 or more of the following features within 24 hours:

1. spontaneous drop of systolic, mean arterial pressure or diastolic blood pressure of 20 mmHg or more
2. start of vasopressor or a 20% increase in vasopressor dose
3. decrease in haemoglobin of at least 2 g/dl
4. transfusion of 2 units of packed RBC or more[3]

ii) Bronchoconstriction requiring nebulised bronchodilators

- During or up to 30 minutes following nebulisation[4]

iii) Ventilator or circuit dysfunction with respiratory deterioration

-This may include hypoventilation, hypoxaemia, or other signs of respiratory deterioration temporally associated with ventilator or ventilator circuit dysfunction[5]

iv) Hypoxaemia during nebulisation

-A drop in SpO_2 to below 90% during or up to 30 minutes following nebulisation[4] requiring an increase in FiO_2

Full details of the background to the trial and its design are presented in the protocol v4.0 02/12/2024 which can be accessed via the NICTU website (https://nictu.hscni.net)

3. DATA

3.1 CRF Forms and variables

Full details of the data to be collected and the timing of data collection are described in sections 12 and 13 of the protocol v4.0 02/12/2024 which can be accessed via the NICTU website (https://nictu.hscni.net)

All data for an individual patient will be collected and recorded in source documents and transferred onto a bespoke, web-based, electronic case report from (CRF) for the study. A data dictionary, record of automatic and manual data queries, and a full audit trail, will ensure data captured are consistent, reliable, and fully compliant with Good Clinical Practice (GCP) and any other relevant regulatory requirements. For routinely collected clinical data the NHS record will be the source document. Patient identification on the CRF will be through their unique participant study number, allocated at the time of randomisation. Data will be collected and recorded on the electronic CRF by the PI or designee as per the CRF submission guidelines.

If the participant is transferred to another MARCH site the PI or designated member of the site study team will liaise with the receiving hospital to ensure complete data capture as per CRF instruction. If this is not possible, the primary outcome must be collected as a minimum.

For the economic evaluation, HRQoL will be measured using the EQ-5D-5L administered at the time of consent to continue, 60 days, and 6 months. Resource utilisation data will be collected via questionnaires administered at 6 months. Where the patient has been discharged from hospital, questionnaires will be administered by post/telephone/email by the CTU. The participating site will provide the CTU with the contact details for the patient (including name, address and email) to enable the collection of follow up data.

A copy of the CRFs and questionnaires (e.g. Health Related Quality of Life (HRQoL) questionnaires) are presented in the protocol and/or the Trial Master File.

3.2 Management of datasets

As the NICTU is providing the Data Management for the study then the Data Manager in collaboration with the Study Statistician will extract data from MACRO following procedures as detailed in the Standard Operation Procedure (SOP) DM09 Database Closure/Lock and the corresponding study Data Management Plan (DMP).

3.3 Data completion schedule

All patients recruited to the trial must be evaluated according to the schedule of assessments described. Data will be collected at each time point detailed.

Day 0 (Baseline)

Baseline data are collected in the 24 hours preceding randomisation (Day 0). If more than one value is available for this 24 hour period the value closest but prior to the time of randomisation will be recorded. Baseline data collected will include, but not be limited to, the following:

- Date of birth
- Sex
- Ethnicity
- Postcode (as a surrogate for socioeconomic status), obtained via ICNARC data linkage (or equivalent) or via site
- Medical history including chronic comorbidities
- ICNARC Case Mix Programme (CMP) or equivalent (if applicable)
- NHS Number, or Community Health Index (CHI) number, or H&C Number
- Date and time of Hospital admission
- Date and time of ICU admission
- Date and time of onset of invasive mechanical ventilation
- Date, time, and type of consent
- Date and time of randomisation
- Aetiology of acute respiratory failure
- Receipt of antibiotics for pulmonary infection
- Acute Physiology and Chronic Health Evaluation II score (APACHE II) (provided either by local participating site or national registry)
- Determinants of the SOFA score
- Temperature
- Ventilation parameters including but not limited to: minute volume, respiratory rate, plateau pressure, positive end expiratory pressure (PEEP)
- Arterial blood gas including, but not limited, to: FiO_2, PaO_2, $PaCO_2$, pH, lactate, bicarbonate
- Clinical laboratory assessments: renal function, liver function, haematological, and coagulation parameters where possible
- Other clinical parameters required for classifying inflammatory phenotype

Day 1 to 28 (Daily data)

Day 1 is from the time of randomisation to the end of that calendar day (i.e. Day 1 will be less than 24 hours' duration). If more than one value is available for this period, the value closest to but after the time of randomisation will be recorded. All other daily measurements will be recorded between 6am and 10am (or as close to this time as possible) on subsequent days, unless otherwise stated in the CRF. Daily data will be collected up to and including Day 28 (or up to 29 or 30 days for patients who commence unassisted breathing on Day 27 or Day 28 respectively), or until the primary outcome is reached, or ICU discharge, or death, whichever comes first, and will include, but not be limited to:

- Respiratory physiotherapy airway clearance management
- Administration of any non-trial mucoactive
- Study mucoactive administration
- Antibiotic usage
- Study mucoactive-related serious adverse event
- Safety outcomes

The following data will also be recorded as/when occurring throughout the ICU and hospital stay:

- Date and time of discontinuation of mechanical ventilation (to determine duration of mechanical ventilation)
- Date and time of extubation
- Date and time of re-intubation
- Date and time of ICU discharge
- Date and time of hospital discharge
- Date and time of death
- Level of care days (at Levels 0, 1, 2, 3)

Discharge from ICU (critical care) is defined as first discharge to a medical ward in the hospital or another hospital. A transfer between ICUs is not considered to be a discharge from ICU. Hospital discharge is the first date that the patient is discharged to home or the community. A transfer between hospitals is not considered as a hospital discharge.

Time of consent to continue

The following will be recorded at the time of consent to continue (+/- 1 working day):

- Health related quality of life (using the EQ-5D-5L completed at site or by telephone)

Participant Follow Up

Patient survival after discharge from hospital will be determined either from hospital/regional information systems (e.g. electronic care record) or by using NHS Digital if available in that region or by contacting the GP (which will be undertaken centrally by Northern Ireland Clinical Trials Unit (NICTU) staff).

Study participants will be asked to let the CTU know if they move house at any time after hospital discharge.

Day 60

The following will be recorded at Day 60 (± 14 days) after randomisation:

- Health-related quality of life (using the EQ-5D-5L by post/telephone/email)
- All-cause mortality

6 months

The following will be recorded 6 months (± 14 days) after randomisation:

- Health-related quality of life (using the EQ-5D-5L by post/telephone/email)
- Patient's use of health and social care resources (using a study specific questionnaire by post/telephone/email)
- All-cause mortality

3.4 Data verification

The CTU will provide training to site staff on trial processes and procedures including CRF completion and data collection. Source data verification (SDV) will be completed by the CTU and will check the accuracy of entries on the electronic CRF against the source documents and adherence to the protocol. The extent of SDV to be completed is detailed in the Monitoring Plan.

Quality control is implemented by the CTU in the form of SOPs which encompass aspects of the clinical data management process, and ensure standardisation and adherence to International Conference of Harmonisation Good Clinical Practice (ICH GCP) guidelines and regulatory requirements.

Data validation will be implemented and discrepancy reports will be generated following data entry to identify discrepancies such as out of range, inconsistencies or protocol deviations based on data validation checks programmed in the clinical trial database. The process of data validation ensuring the accuracy and quality of the data will be carried out according to SOP DM04 Data Validation and Discrepancy Management

A DMEC (Data Monitoring and Ethics Committee) will be convened to carry out reviews of the study data at staged intervals during the study.

3.5 Data coding

The variable codings will be as specified on the CRF.

4. DEFINITION OF TERMS

Term	Definition
Duration of mechanical ventilation	This is defined (measured) as time from randomisation until first successful unassisted breathing (defined as maintaining unassisted breathing at 48 hours) or death. This outcome is one of the 'COVenT' core outcomes for trials of interventions intended to modify the duration of mechanical ventilation.[1] To clarify: i) Unassisted breathing is defined as no inspiratory support or extracorporeal lung support. ii) Success is defined as maintaining unassisted breathing at 48 hours. iii) Duration includes time receiving extracorporeal lung support, invasive mechanical ventilation and non-invasive ventilation delivering volume or pressure support ventilation. iv) Duration excludes time receiving high-flow oxygen therapy and continuous positive airway pressure. v) Patients with a tracheostomy in situ may still achieve successful unassisted breathing. vi) Follow-up to 60 days from randomisation.

Extubation	Time from randomisation to first successful extubation (success defined as remaining free from endotracheal or tracheostomy tubes at 48 hours). Censored at 60 days.
Re-intubation	Event of reintubation of endotracheal tube after a planned extubation (censored at hospital discharge); excludes temporary reinsertion of endotracheal.
Duration of ICU and hospital stay	Time from randomisation until patient first leaves the relevant facility or dies. Censored at 6 months.
Per protocol population	Per protocol analysis will be undertaken on the population who receive the complete treatment dose. Patients randomised to receive usual airway clearance management will be excluded from the per protocol analysis if they commence a non-trial mucoactive.
Overall Compliance	Patients who receive ≥90% available doses will be considered as compliant.
Carbocisteine Administration Compliance	*Carbocisteine Administration Compliance =* *((Total doses- excluded doses)/(expected doses – 6))*100* Where Total doses (TotNumDoseCarbo) = Sum of all doses Excluded doses = sum of doses on day 1 and last day Expected doses = (total. no days*3) Expected doses excluding day 1 and last day = 2* 3 = 6
Hypertonic Saline Administration Compliance	*Hypertonic Saline Administration Compliance =* *((Total doses- excluded doses)/(expected doses – 8))*100* Total doses (TotHSdoses) = Sum of all doses Excluded doses = sum of doses on day 1 and last day Expected doses = (total. no days*4) Expected doses excluding day 1 and last day = 2* 4 = 8
Contamination	Any episode of non-trial mucoactive (NTM) administration that has ≥24 hour duration (regardless of when the NTM commenced) should be counted as contamination i.e. this means the patient receives >4 individual doses of HTS and/or >3 individual doses carbocisteine (assuming that beyond Day 0, a 24 hour dose = 4 HTS, 3 carbocisteine) NB: Any episode that stops on day of randomisation do not count as contamination (i.e. NTM that are within a 24 hour period around the timepoint of randomisation)
Handling Ineligible Patients (not on IMV at randomisation **only**)	Group 1. Patients not on MV at randomisation but who go back on it sometime within 48 hours and then have to resume another period of unassisted breathing in due course

	Group 2. Patients not on MV at randomisation and who complete a 48 hour period of unassisted breathing, therefore achieving the PO, and for whom 0 is a true value Rules: Group 1. Continue to define the PO as normal These patients will have a portion of their overall MV duration that wasn't 'true' i.e. the initial period immediately after randomisation until they resumed MV This approach maintains the accurate definition of the PO starting from time of randomisation (rather than asking sites to recalculate based on time the MV was resumed and which would also deviate from the protocol) Group 2. Continue to define the PO as normal These patients will have a '0' value Sites to be instructed on entering data onto MACRO that reflect this i.e. where the date and time of first successful unassisted breathing is currently blank, they will be advised to enter a date and time 48 hours after randomisation (screenshot below) This will allow a MACRO calculation of '0' If this is not possible in the MACRO database, the data for these patients will be held outside the database on a partner Excel spreadsheet and will be combined with the MACRO data for analysis We will not undertake a database change to accommodate the reporting of these '0' values on MACRO This process can be noted internally in the CTU as necessary for CTU records
Conversion of H+ to pH	Where patients have both H+ and pH values recorded, pH values only will be reported. Where patients only have H+ available, this will be log converted to pH and added to pH values for other patients

5. SAMPLE SIZE CALCULATIONS

The total sample size is **1956** (489 in each of the four randomised groups).

The sample size has been calculated using a median duration of mechanical ventilation of 7 days[6, 7] with a minimal clinically important difference of 1 day[8] resulting in a median duration of 6 days in the three intervention groups. This minimum clinically important value is also based on discussion with our PPIE advisors, who emphasised the importance of reducing time spent on the ventilator as a priority outcome[9] This median duration of mechanical ventilation and 1 day reduction treatment effect result in a hazard ratio of 0.86. Based on a log-rank test and at 90% power and a significance level of 0.05, this requires a sample size of 1856. Previous critical care trials have demonstrated low levels of loss to follow-up, at less than 5%[10-14], and the nature of the proposed trial where all primary outcome data will be acquired whilst patients are in the ICU and identifiable to the research team, should minimise loss to

follow up. Allowing loss to follow at the 5% level, this then requires a sample size of 1956 (489 in each of the four randomised groups).

As there is no clinical or biological rationale for, or expectation of, any interaction between the two mucoactives the sample size has not been inflated for this purpose. This is in keeping with systematic review findings highlighting appropriate restriction of the factorial design to scenarios where treatments do not have the potential for substantive interaction[15]

6. RANDOMISATION AND BLINDING

6.1 Randomisation

Participants will be randomised using an automated web-based or telephone system via randomly permuted blocks in a 1:1:1:1 ratio. There will be stratification by recruitment centre.

6.2 Blinding and Allocation Concealment

The randomisation sequence will be saved in a restricted section of the TMF, which can only be accessed by the trial statistician and not those who enrol or assign interventions.

After informed consent, patients will be randomised via an automated web-based or telephone system. Sites will be provided with trial specific randomisation guidelines. Randomisation will be completed by an appropriately trained and delegated member of the research team. Each patient will be allocated their own unique Participant Study Number during the randomisation process, which will be used throughout the study for participant identification on all data collection forms and questionnaires. An entry will be recorded in the patients' medical notes noting enrolment into the study.

This study will be a prospective, randomised, open label, unblinded trial. The patients, those who provide health care to them, and outcome assessors, will not be blinded to the allocated intervention in this trial in order to reflect routine practice when mucoactives are (or are not) used in critical care[16] This is unlikely to introduce bias to the estimate of the true treatment effect, and a recent meta-epidemiological study found no evidence for an average difference in treatment effects between trials with and without blinded patients, healthcare providers, or outcome assessors[17]. Furthermore, we will mitigate against potential bias in the absence of blinding by using an objective outcome measure (duration of mechanical ventilation), and collecting data on readiness to wean, and readiness to extubate, and reasons why this might not occur as planned, to confirm consistency across randomised groups and assess performance bias on the part of treating clinicians.

The trial statistician, who has no role in decision-making with regards the conduct of the trial, will be unblinded and this will also facilitate linkage with the DMEC. The remainder of the trial team will also be unblinded for the purposes of managing data collection, reviewing cases to assess protocol deviations, and to undertake pharmacovigilance duties.

7. ANALYSIS PRINCIPLES

7.1 Analysis Population

The primary analysis will be conducted on outcome data from all randomised patients according to the group to which they were allocated, regardless of the subsequent treatment they received (i.e. intention to treat). Trial results will be reported in accordance with Consolidated Standards of Reporting Trials guidance (CONSORT)[18].

It is possible that some participants may not receive the full treatment dose, therefore a secondary per protocol analysis will be undertaken on the population who receive the complete treatment dose.

7.2 Statistical Methods

We will describe baseline characteristics, follow-up measurements and safety data, using suitable measures of central tendencies; means and medians with the associated standard deviations/95% confidence intervals (CI) and interquartile ranges for continuous data; and frequencies and proportions for categorical data (including binary data).

In keeping with the 2x2 factorial design, the main comparisons will be the use versus non-use of carbocisteine, and the use versus non-use of hypertonic saline

Primary outcome for the comparison groups will be compared using a Cox proportional hazards (Cox-PH) model including site and adjusting for age and illness severity (APACHE II) with hazard ratio and 95% CI will be presented. For this analysis, no interaction between interventions will be assumed. In addition to the adjusted analysis, an unadjusted analysis will also be conducted.

The primary outcome will be reported for survivors and non-survivors.
If the primary analysis of main effects using the Cox-PH model indicates statistically significant differences in the duration of mechanical ventilation, post hoc pairwise comparisons will be conducted to explore differences between individual treatment arms.

Pairwise comparisons will be performed using Cox-PH models for each relevant treatment pair. Adjustments for multiple comparisons will be made using the Bonferroni correction or an alternative method appropriate for controlling the family-wise error rate.

The following comparisons will be evaluated:

- Carbocisteine + usual airway clearance management (UACM) vs UACM alone
- Hypertonic saline + UACM vs UACM alone
- Both mucoactives + UACM vs UACM alone
- Both mucoactives + UACM vs carbocisteine + UACM
- Both mucoactives + UACM e vs hypertonic saline + UACM
- Carbocisteine + UACM vs hypertonic saline + UACM

Hazard ratios and 95% confidence intervals will be reported for each comparison. These analyses are exploratory and will be interpreted with caution.

Comparison for other continuous outcomes will use analysis of covariance to adjust for baseline characteristics and covariates such as age, severity of hypoxemia (based on PaO_2/FiO_2 ratio) and APACHE II). In addition to the adjusted analyses, unadjusted analyses will also be conducted.

Comparison for binary outcomes will use generalised linear models (GLM) as appropriate to estimate Risk Ratio and Risk Differences. 95% CI and p-value will be presented alongside the estimates.

Analyses will be two-sided and tested at an *a priori* significance level of p=0.05.

The factorial design permits separate testing of the effects of carbocisteine and hypertonic saline on outcomes.

Although there is no biologic rationale for, or expectation that, either mucoactive will have an effect on death, we will include a sensitivity analysis for competing risk of death.

We will also conduct a sensitivity analysis to investigate the impact of any potential interaction between the interventions on the primary analysis and also to investigate the impact of contamination between the interventions. A further sensitivity analysis to investigate the impact of compliance on the primary analysis will be conducted and also excluding those patients not on IMV at randomisation.

An independent CTU statistician will conduct an interim analysis for the primary outcome (duration of mechanical ventilation) when follow-up is available for 978 patients (half the estimated sample size), to ascertain whether assumptions made in the sample size calculations are correct. In accordance with the Haybittle-Peto stopping rule, the DMEC will be asked to make a recommendation about the future of the trial, considering a p-value of less than 0.001 as "significant" and the likely impact of the interim result on future practice.

7.3 Additional Analysis

The following pre-specified exploratory sub-group analyses for the primary outcome will be conducted in the observed dataset on the basis of the ITT principle using interaction tests (treatment group by subgroup) and reported using 99% CI for the following subgroups:

i) Baseline APACHE II (quintiles)
ii) Baseline PF ratio (201-300mmHg or 26.7-39.9kPa (Mild); 101-200mmHg or 13.3-26.6kPa (Moderate); <100mmHg or <13.3kPa (Severe))
iii) Pre-existing chronic respiratory condition prior to randomisation (Yes/No)
iv) Neurological diagnosis prior to randomisation (Yes/No)
v) Admission diagnostic categories (pulmonary vs. non-pulmonary)
vi) Receiving antibiotics for pulmonary infection at randomisation (Yes/No)

The following Intercurrent Events have been identified which would prevent measurement of the primary outcome or change the interpretation of the measured primary outcome:

1. Death prior to the timepoint at which randomised treatment is due to start
2. (a) Hypertonic Saline allocated in randomisation but not started
   (b) Carbocisteine allocated in randomisation but not started
3. Death before successful unassisted breathing.
4. Transfer to another ICU before successful unassisted breathing.
5. Use of non-trial mucoactives
6. Patient withdrawal from intervention

Events 1, 2(a) and 2(b) are expected to be rare and no specific actions will be taken: analysis of these events will be by intention to treat, except for event 1 which will be handled in the same way as event 3.

Event 3 will be treated as a competing risk for the primary outcome, and will therefore be analysed using a hypothetical strategy.

Event 5 will be dealt with using an intention to treat approach.

Event 6 will also be handled using a hypothetical strategy, in which the time to unassisted breathing will be censored at the point of withdrawal and the withdrawals will be assumed to lead to missing at random (MAR) data on the primary outcome. Complete follow up should still be possible for most participants in whom event 4 occurs; if not, the hypothetical strategy used for event 6 will also be implemented.

7.4 **Missing Data**

Every effort will be made to minimise missing baseline and outcome data. Standard approaches will be used to detect patterns in missing data. The level and pattern of the missing data in the baseline variables and outcomes will be established by forming appropriate tables and the likely causes of any missing data will be investigated. This information will be used to determine whether the level and type of missing data has the potential to introduce bias into the analysis results for the proposed statistical methods, or substantially reduce the precision of estimates related to treatment effects. If necessary, these issues will be dealt with using multiple imputation or Bayesian methods for missing data as appropriate.

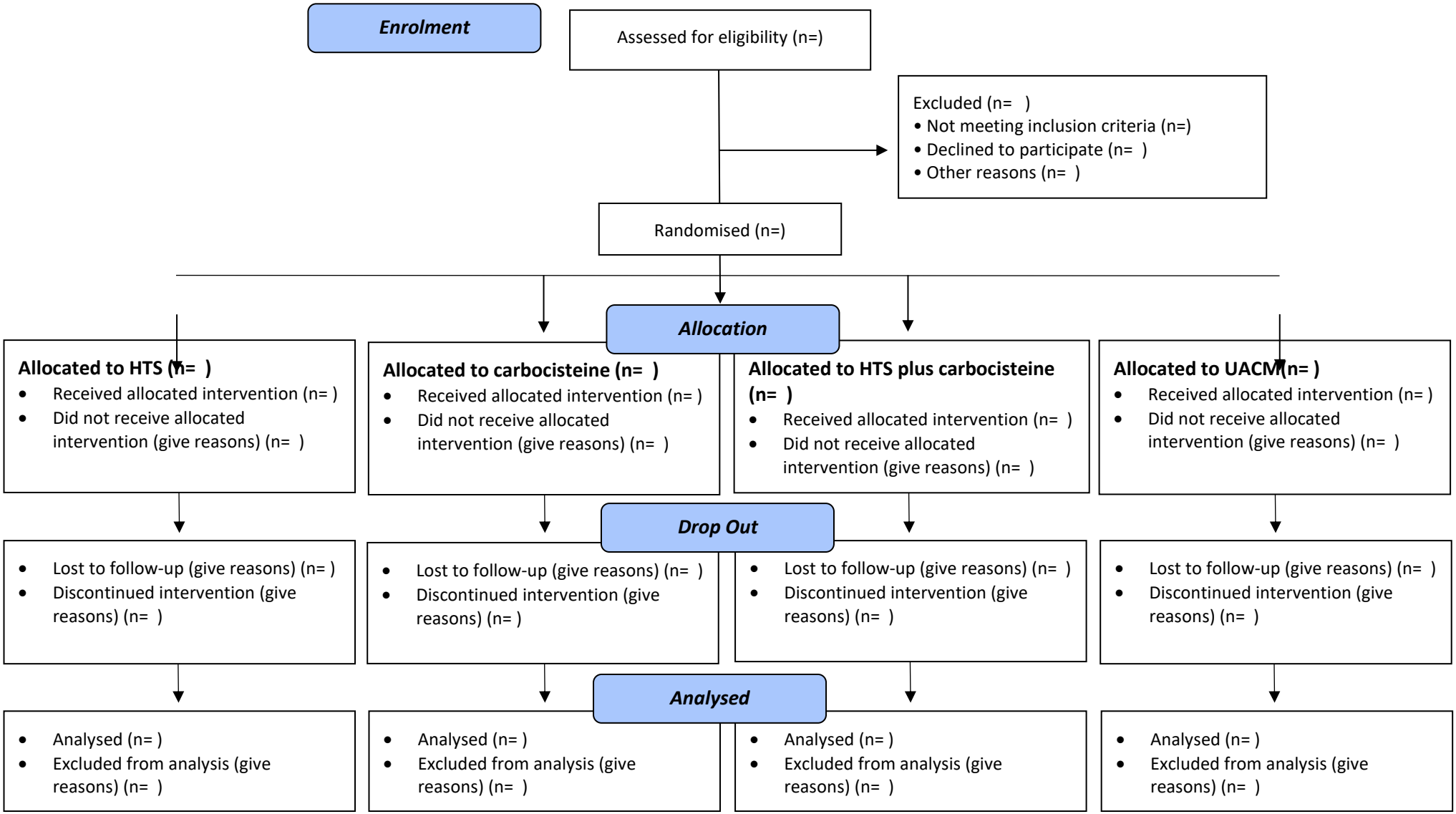
8. ANALYSIS DETAILS

The results of the analyses will be reported following the principles of the ICH E3 guidelines on the Structure and Content of Clinical Study Reports. Refer to the CONSORT[18] Extensions for various trial designs.

8.1 Recruitment and follow-up patterns

- Recruitment by year, centre.
- Withdrawals by site - this should include the timing of withdrawals.

8.2 CONSORT Flow Diagram



Consort will also be presented by comparison

8.3 Baseline Characteristics

- Age (years), mean(sd) by treatment arm
- Sex, n(%) by treatment arm
- Ethnicity, n(%) by treatment arm
- Temperature (°C), mean(sd) by treatment arm
- APACHE II Score, mean(sd) by treatment arm
- ABG (Worst)
    - PaO_2 (kPa), mean(sd) by treatment arm
    - FiO_2 %, mean(sd) by treatment arm
    - P/F Ratio (PaO_2/FiO_2), mean(sd) by treatment arm
- ABG (Closest to but prior to randomisation)
    - PaO_2 (kPa), mean(sd) by treatment arm
    - FiO_2 %, mean(sd) by treatment arm
    - P/F Ratio (PaO_2/FiO_2), mean(sd) by treatment arm
    - $PaCO_2$ (kPa), mean(sd) by treatment arm
    - Lactate (mmol/L), mean(sd) by treatment arm
    - pH, mean(sd) by treatment arm (refer to section 4 definition of terms)
    - Bicarbonate (mmol/L), mean(sd) by treatment arm
- ARF Aetiology
    - Main admission diagnosis, n(%) by treatment arm
    - Pulmonary/Non Pulmonary Categorisation, n(%) by treatment arm
    - Presence of ARDS, n(%) by treatment arm
- Medical History
    - Is the patient currently receiving antibiotics to treat a pulmonary infection?, n(%) by treatment arm
    - Does the patient have a pre-existing chronic respiratory condition?, n(%) by treatment arm
    - Does the patient have a neurological diagnosis?, n(%) by treatment arm
    - Functional Co-morbidity Score, mean(SD) by treatment arm
    - Angina, n(%) by treatment arm
    - Anxiety or panic disorders, n(%) by treatment arm
    - Arthritis, n(%) by treatment arm
    - Asthma, n(%) by treatment arm
    - Chronic Obstructive Pulmonary Disease (COPD); Acquired Respiratory Distress Syndrome (ARDS); or Emphysema, n(%) by treatment arm
    - Congestive Heart Failure (or heart disease), n(%) by treatment arm
    - Degenerative Disc Disease (Back Disease, Spinal Stenosis or Severe Chronic Back Pain) , n(%) by treatment arm
    - Depression, n(%) by treatment arm
    - Diabetes Types I and II, n(%) by treatment arm
    - Hearing Impairments (very hard of hearing, even with hearing aids), n(%) by treatment arm

  - Heart Attack (Myocardial Infarction), n(%) by treatment arm
  - Neurological disease (such as Multiple Sclerosis or Parkinson's Disease), n(%) by treatment arm
  - Obesity and/or Body Mass Index > 30 (weight in kg/height in m^2), n(%) by treatment arm
  - Osteoporosis, n(%) by treatment arm
  - Peripheral Vascular Disease, n(%) by treatment arm
  - Stroke or Transient Ischaemic Attack, n(%) by treatment arm
  - Upper Gastrointestinal Disease (e.g. Ulcer, Hernia, Reflux), n(%) by treatment arm
  - Visual Impairment (e.g. Cataracts, Glaucoma, Macular Degeneration), n(%) by treatment arm
- Ventilation Parameters
  - Mode of ventilation, n(%) by treatment arm
  - Minute Volume (ml), mean(sd) by treatment arm
  - Total Respiratory Rate, mean(sd) by treatment arm
  - Plateau Pressure (cmH2O), mean(sd) by treatment arm
  - PEEP (cmH_2O), mean(sd) by treatment arm
  - Tidal Volume (Minute Volume/Total Respiratory Rate), mean(sd) by treatment arm
  - Respiratory Compliance (ml/cmH2O), mean(sd) by treatment arm
  - Driving Pressure (cmH_2O), mean(sd) by treatment arm
  - Was humidification used?, n(%) by treatment arm
  - Type of humidification, n(%) by treatment arm
- SOFA Score, mean(sd) by treatment arm

Data will also be presented by comparison

8.4 Trial treatment

- Number of days on treatment, mean(sd) by treatment arm
- Number of doses, mean(sd) by treatment arm
- Treatment compliance, n(%) by treatment arm
- Reasons for termination of study drug, n(%) by treatment arm
- Did not receive allocated treatment, n(%) by treatment arm
- Reasons for omission of doses, n(%) by treatment arm
- Received treatment of other group, n(%) by treatment arm
- Antibiotic Usage
  - Number of patients prescribed antibiotics at least once, n(%) by treatment arm
  - Number of days on antibiotics, mean(sd) by treatment arm
  - Overall dose (antibiotics), mean (sd) by treatment arm
- Usual Airway Clearance Management
  - Number of sessions, mean(sd) by treatment arm
- Non-trial mucoactive administration
  - No. patients with non-trial mucoactive administered, n(%) by treatment arm
  - Name of mucoactive, n(%) by treatment arm
  - Total number of days on non-trial mucoactive, mean(sd) by treatment arm
- Consent to Continue/Withdrawal of Consent, n(%) by treatment arm

- Protocol Deviations, no. events (%) by treatment arm, no. patients (%) by treatment arm

Data will also be presented by comparison

8.5 Trial Outcomes

- **Primary Outcome (ITT and Per Protocol)**
    - Duration of mechanical ventilation (hours), median(IQR) by comparison (i.e. Carbocisteine vs No Carbocisteine and Hyptertonic Saline vs No Hypertonic Saline), hazard ratio and 95% CI, p-value from Cox-PH adjusted for age and APACHE II and also unadjusted
    - Subgroup analyses
        - Baseline APACHE II (quintiles)
        - Baseline PaO_2/FiO_2 (PF) ratio (201-300mmHg or 26.7-39.9kPa (Mild); 101-200mmHg or 13.3-26.6kPa (Moderate); <100mmHg or <13.3kPa (Severe))
        - Pre-existing chronic respiratory condition prior to randomisation (Yes/No)
        - Neurological diagnosis prior to randomisation (Yes/No)
        - Admission diagnostic categories (pulmonary/non-pulmonary)
        - Receiving antibiotics for pulmonary infection at randomisation (Yes/No)
        - Compliant (Yes/No)
        - Contaminated (Yes/No)
    - Sensitivity Analyses
        - Competing risk of death, sub hazard ratio (SHR) and 95% CI, p-value
        - Impact of potential interaction
        - Impact of contamination
        - Excluding patients not on IMV at the point of randomisation
    - Secondary analyses
        - Survivors only
        - Non survivors only
    - Secondary Analyses (only if the main effects primary analyses are statistically significant and with adjustments for multiple comparisons (using the Bonferroni correction or an alternative method appropriate for controlling the family-wise error rate.))
        - Carbocisteine + usual airway clearance management (UACM) vs UACM alone, median(IQR), HR and 95%CI will be presented
        - Hypertonic saline + UACM vs UACM alone, median(IQR), HR and 95%CI will be presented
        - Both mucoactives + UACM vs UACM alone, median(IQR), HR and 95%CI will be presented
        - Both mucoactives + UACM vs carbocisteine + UACM, median(IQR), HR and 95%CI will be presented
        - Both mucoactives + UACM e vs hypertonic saline + UACM, median(IQR), HR and 95%CI will be presented
        - Carbocisteine + UACM vs hypertonic saline + UACM, median(IQR), HR and 95%CI will be presented

- **Secondary Outcomes**
    - Extubation
        - Time to 1st successful extubation, mean(sd) by comparison and median(IQR) by treatment arm, hazard ratio 95% CI
        - Incidence of extubation, n(%) by comparison , RR, RD, 95% CI and p-value from GLM
    - Re-intubation
        - Incidence of reintubation, n(%) by comparison , RR, RD, 95% CI and p-value from GLM
    - Respiratory physiotherapy input
        - Incidence of respiratory physiotherapy input, n(%) by comparison , RR, RD, 95% CI and p-value from GLM
        - Total number of sessions, mean(SD) by comparison , difference in means and 95% CI presented and p-value from ANCOVA and also unadjusted
    - Antibiotic Usage (To treat a respiratory tract infection)
        - Number of patients prescribed antibiotics at least once, n(%) by comparison , RR, RD, 95% CI and p-value from GLM
        - Number of days on antibiotics, mean(sd) by comparison , difference in means and 95% CI presented and p-value from ANCOVA and also unadjusted
    - Duration of ICU stay, median(IQR) by comparison , p-value from Wilcoxon rank sum
    - Duration of hospital stay, median(IQR) by comparison, p-value from Wilcoxon rank sum
    - All-cause mortality, n(%) by comparison , RR, RD, 95% CI and p-value from GLM
    - Health Related Quality of Life[a]

[a]Outcomes will be analysed as per the Health Economics Analysis Plan (HEAP)

- **Safety Outcomes**
    - Clinically important upper gastrointestinal (GI) bleeding due to peptic ulceration confirmed on upper GI endoscopy, no. events (%) by comparison , no. patients (%) by comparison and system organ class. RR, RD, 95% CI and p-value from GLM
    - Bronchoconstriction requiring nebulised bronchodilators, no. events (%) by comparison and system organ class, no. patients (%) by comparison . RR, RD, 95% CI and p-value from GLM
    - Ventilator or circuit dysfunction with respiratory deterioration, no. events (%) by comparison and system organ class, no. patients (%) by comparison . RR, RD, 95% CI and p-value from GLM
    - Hypoxaemia during nebulisation, no. events (%) by comparison and system organ class, no. patients (%) by comparison. RR, RD, 95% CI and p-value from GLM

8.6 Toxicity/Symptoms

- Serious Adverse Reactions (SARs), no. events (%) by comparison , no. patients (%) by comparison . RR, RD, 95% CI and p-value from GLM
- Suspected Unexpected Serious Adverse Reactions (SUSARs), no. events (%) by comparison and, no. patients (%) by comparison . RR, RD, 95% CI and p-value from GLM

- Serious Adverse Reactions (SARs), no. events (%) by comparison and system organ class, no. patients (%) comparison
- Suspected Unexpected Serious Adverse Reactions (SUSARs), no. events (%) by comparison and system organ class, no. patients (%) by comparison

8.7 Interim analysis

An independent CTU statistician will conduct an interim analysis for the primary outcome (duration of mechanical ventilation) when follow-up is available for 978 patients (half the estimated sample size), to ascertain whether assumptions made in the sample size calculations are correct. In accordance with the Haybittle-Peto stopping rule, the DMEC will be asked to make a recommendation about the future of the trial, considering a p-value of less than 0.001 as "significant" and the likely impact of the interim result on future practice.

9. TRIAL OVERSIGHT

9.1 Trial Steering Committee (TSC)

The conduct of the trial will be overseen by a TSC, which includes members of the trial management group Frequency of TSC meetings will be listed in the TSC charter and all meetings will be formally minuted. The TSC oversees the progress of the trial and is advisory to the Sponsor. The Study Statistician is responsible for the committee reports regarding the recruitment, adverse events and treatment withdrawal.

9.2 Data Monitoring and Ethics Committee (DMEC)

A DMEC has been appointed comprising clinicians with experience in undertaking clinical trials and a statistician who are independent of the trial. Meetings will be held approximately biannually and formally minuted. The DMEC's responsibility is to safeguard the interests of the trial participants, in particular with regard to safety and assist and advise the TSC so as to protect the validity and credibility of the trial. The DMEC monitors recruitment, adverse events and outcome data. The Study Statistician is responsible for the unblinded (if applicable) committee reports regarding the trial progress, safety of the participants, treatment withdrawal. An independent statistician will be responsible for the interim analysis.

The DMEC will advise the TSC if, in their view, the randomised comparisons have provided both (i) 'proof beyond reasonable doubt' that for all, or some, the treatment is clearly indicated or clearly contra-indicated and (ii) evidence that might reasonably be expected to materially influence future patient management. Following a report from the DMEC, the TSC will decide what actions, if any, are required. Unless the DMEC request cessation of the trial the TSC and the collaborators will not be informed of the interim results.

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11. SIGNATURES OF APPROVAL

CC 26/11/2025

Date: ~~03/11/2025~~ 13/11/2025

Version: Final 3.0

This document has completed a final review and is understood and approved by the following:

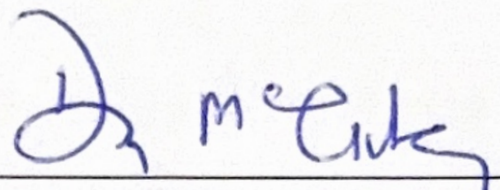
Professor Danny McAuley Chief Investigator Name	*Chief Investigator Signature*	CC. 26/11/25 ~~14.12.2025~~ Date dd/mm/yyyy
Cliona McDowell Senior Statistician or designee Name	*Senior Statistician or designee Signature*	26/11/2025 Date dd/mm/yyyy
Christina Campbell Study Statistician Name	*Study Statistician Signature*	26/11/2025 Date dd/mm/yyyy
Dr Bronwen Connolly Co-Chief Investigator Name	*Co-Chief Investigator Signature*	19/11/2025 Date dd/mm/yyyy

11. SIGNATURES OF APPROVAL

Date: 03/11/2025

Version: Final 3.0

This document has completed a final review and is understood and approved by the following:

Professor Danny McAuley		26.11.2025
Chief Investigator Name	*Chief Investigator Signature*	Date dd/mm/yyyy
Cliona McDowell		
Senior Statistician or designee Name	*Senior Statistician or designee Signature*	Date dd/mm/yyyy
Christina Campbell		
Study Statistician Name	*Study Statistician Signature*	Date dd/mm/yyyy
Dr Bronwen Connolly		
Co-Chief Investigator Name	*Co-Chief Investigator Signature*	Date dd/mm/yyyy

APPENDIX 1: EXAMPLE SUMMARY TABLES

- Put Intervention on left and Control on right.
- No hard spaces or hard returns (create new rows in tables)
- Use superscript letters for footnotes and list in order in footers as they appear in the table
- When reporting n(%) for a variable – list in descending order from largest to smallest as per intervention
- Include the primary /secondary outcomes in one table making clear what is primary and what is secondary

Table x.x.x. Baseline Characteristics at trial entry by treatment arm

		Group 1 = CS+UACM	Group 2 = HTS +UACM	Group 3 = CS+HTS+UACM	Group 4 = UACM alone
		n=	n=	n=	n=
Age (years)		xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
Sex	**Male**	n(%)	n(%)	n(%)	n(%)
	Female	n(%)	n(%)	n(%)	n(%)
Ethnicity	**White**	n(%)	n(%)	n(%)	n(%)
	Black	n(%)	n(%)	n(%)	n(%)
	Asian	n(%)	n(%)	n(%)	n(%)
	Unknown	n(%)	n(%)	n(%)	n(%)
	Other*	n(%)	n(%)	n(%)	n(%)
Temperature(°C)		xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
APACHE II Score		xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
ABG (Worst)	**PaO_2 (kPa)**	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	FiO_2 %	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	P/F Ratio (PaO_2/FiO_2)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	PaO_2 (kPa)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)

		Group 1 = CS+UACM	Group 2 = HTS +UACM	Group 3 = CS+HTS+UACM	Group 4 = UACM alone
		n=	n=	n=	n=
ABG (Closest but prior to randomisation)		(xx.x-xx.x)	(xx.x-xx.x)	(xx.x-xx.x)	(xx.x-xx.x)
	FiO_2 %	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	P/F Ratio (PaO_2/FiO_2)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	$PaCO_2$ (kPa)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	Lactate (mmol/L)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	pH	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	Bicarbonate (mmol/L)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
Admission Diagnostic Category	Central nervous system	n(%)	n(%)	n(%)	n(%)
	Cardiovascular system	n(%)	n(%)	n(%)	n(%)
	Respiratory system	n(%)	n(%)	n(%)	n(%)
	Gastrointestinal	n(%)	n(%)	n(%)	n(%)
	Hepatobiliary	n(%)	n(%)	n(%)	n(%)
	Renal and urinary	n(%)	n(%)	n(%)	n(%)
	Toxicology/poisoning	n(%)	n(%)	n(%)	n(%)
	Haematology	n(%)	n(%)	n(%)	n(%)
	Orthopaedics/Trauma	n(%)	n(%)	n(%)	n(%)
	Infection	n(%)	n(%)	n(%)	n(%)
	Surgical and medical procedures	n(%)	n(%)	n(%)	n(%)
	Other*	n(%)	n(%)	n(%)	n(%)
ARDS Aetiology	Smoke/toxin inhalation	n(%)	n(%)	n(%)	n(%)
	Gastric content aspiration	n(%)	n(%)	n(%)	n(%)
	Near - drowning	n(%)	n(%)	n(%)	n(%)
	Thoracic trauma	n(%)	n(%)	n(%)	n(%)

		Group 1 = CS+UACM	Group 2 = HTS +UACM	Group 3 = CS+HTS+UACM	Group 4 = UACM alone
		n=	n=	n=	n=
	Pneumonia	n(%)	n(%)	n(%)	n(%)
	Sepsis	n(%)	n(%)	n(%)	n(%)
	Cardiopulmonary bypass	n(%)	n(%)	n(%)	n(%)
	Pancreatitis	n(%)	n(%)	n(%)	n(%)
	Non-thoracic trauma	n(%)	n(%)	n(%)	n(%)
	COVID-19	n(%)	n(%)	n(%)	n(%)
	Other*	n(%)	n(%)	n(%)	n(%)
Currently receiving antibiotics to treat a pulmonary infection?		n(%)	n(%)	n(%)	n(%)
Pre-existing chronic respiratory condition?	**COPD**	n(%)	n(%)	n(%)	n(%)
	Asthma	n(%)	n(%)	n(%)	n(%)
	Lung Cancer	n(%)	n(%)	n(%)	n(%)
	Bronchiectasis	n(%)	n(%)	n(%)	n(%)
	Cystic Fibrosis	n(%)	n(%)	n(%)	n(%)
	Interstitial Lung Disease	n(%)	n(%)	n(%)	n(%)
	Sarcoidosis	n(%)	n(%)	n(%)	n(%)
	Other*	n(%)	n(%)	n(%)	n(%)
Neurological diagnosis?	**Head Injury**	n(%)	n(%)	n(%)	n(%)
	Brain Tumor	n(%)	n(%)	n(%)	n(%)
	Epilepsy	n(%)	n(%)	n(%)	n(%)
	Stroke	n(%)	n(%)	n(%)	n(%)
	Guillain-Barre Syndrome	n(%)	n(%)	n(%)	n(%)
	Other*	n(%)	n(%)	n(%)	n(%)
Functional Co-morbidity Score (Components)	**Angina**	n(%)	n(%)	n(%)	n(%)
	Anxiety or Panic Disorders	n(%)	n(%)	n(%)	n(%)
	Arthritis *(Rheumatoid or Osteoarthritis)*	n(%)	n(%)	n(%)	n(%)
	Asthma	n(%)	n(%)	n(%)	n(%)
	Chronic Obstructive Pulmonary Disease (COPD); Acquired Respiratory Distress Syndrome (ARDS); or Emphysema	n(%)	n(%)	n(%)	n(%)

			Group 1 = CS+UACM	Group 2 = HTS +UACM	Group 3 = CS+HTS+UACM	Group 4 = UACM alone
			n=	n=	n=	n=
	Congestive Heart Failure *(or heart disease)*		n(%)	n(%)	n(%)	n(%)
	Degenerative Disc Disease *(Back Disease, Spinal Stenosis or Severe Chronic Back Pain)*		n(%)	n(%)	n(%)	n(%)
	Depression		n(%)	n(%)	n(%)	n(%)
	Diabetes Types I and II		n(%)	n(%)	n(%)	n(%)
	Hearing Impairments *(very hard of hearing, even with hearing aids)*		n(%)	n(%)	n(%)	n(%)
	Heart Attack *(Myocardial Infarction)*		n(%)	n(%)	n(%)	n(%)
	Neurological disease *(such as Multiple Sclerosis or Parkinson's Disease)*		n(%)	n(%)	n(%)	n(%)
	Obesity and/or Body Mass Index > 30 (weight in kg/height in m^2)		n(%)	n(%)	n(%)	n(%)
	Osteoporosis		n(%)	n(%)	n(%)	n(%)
	Peripheral Vascular Disease		n(%)	n(%)	n(%)	n(%)
	Stroke or Transient Ischaemic Attack		n(%)	n(%)	n(%)	n(%)
	Upper Gastrointestinal Disease *(e.g. Ulcer, Hernia, Reflux)*		n(%)	n(%)	n(%)	n(%)
	Visual Impairment *(e.g. Cataracts, Glaucoma, Macular Degeneration)*		n(%)	n(%)	n(%)	n(%)
Functional Co-morbidity Score (Total)			xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
Ventilation Parameters	Mode of Ventilation	SIMV	n(%)	n(%)	n(%)	n(%)
		APRV	n(%)	n(%)	n(%)	n(%)
		HFOV	n(%)	n(%)	n(%)	n(%)
		BIPAP	n(%)	n(%)	n(%)	n(%)
		PC	n(%)	n(%)	n(%)	n(%)
		PRVC	n(%)	n(%)	n(%)	n(%)
		PS	n(%)	n(%)	n(%)	n(%)

			Group 1 = CS+UACM	Group 2 = HTS +UACM	Group 3 = CS+HTS+UACM	Group 4 = UACM alone
			n=	n=	n=	n=
		CPAP/ASB	n(%)	n(%)	n(%)	n(%)
		Other*	n(%)	n(%)	n(%)	n(%)
		None	n(%)	n(%)	n(%)	n(%)
	Minute Volume (ml)		xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	Total Respiratory Rate		xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	Plateau Pressure (cmH_2O)		xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	PEEP (cmH_2O)		xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	Tidal Volume (Minute Volume/Total Respiratory Rate)		xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	Respiratory Compliance (ml/cmH_2O)		xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	Driving Pressure (cmH_2O)		xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	Type of Humidification	None	n(%)	n(%)	n(%)	n(%)
		Heated Humidification	n(%)	n(%)	n(%)	n(%)
		Heat Moisture Exchange	n(%)	n(%)	n(%)	n(%)
		Other*	n(%)	n(%)	n(%)	n(%)
SOFA Score			xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)

Mean (SD) & 95% CI or median(IQR) presented for continuous variables and no. (%) for all categorical variables.

*Other reasons may be summarised

Table x.x.x. Baseline Characteristics at trial entry by comparison

		Carbocisteine	No Carbocisteine	Hypertonic Saline	No Hypertonic Saline
		n=	n=	n=	n=
Age (years)		xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
Sex	**Male**	n(%)	n(%)	n(%)	n(%)
	Female	n(%)	n(%)	n(%)	n(%)
Ethnicity	**White**	n(%)	n(%)	n(%)	n(%)
	Black	n(%)	n(%)	n(%)	n(%)
	Asian	n(%)	n(%)	n(%)	n(%)
	Unknown	n(%)	n(%)	n(%)	n(%)
	Other*	n(%)	n(%)	n(%)	n(%)
Temperature(°C)		xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
APACHE II Score		xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
ABG (Worst)	**PaO_2 (kPa)**	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	FiO_2 %	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	P/F Ratio (PaO_2/FiO_2)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
ABG (Closest but prior to randomisation)	**PaO_2 (kPa)**	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	FiO_2 %	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	P/F Ratio (PaO_2/FiO_2)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	$PaCO_2$ (kPa)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	Lactate (mmol/L)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)

		Carbocisteine	No Carbocisteine	Hypertonic Saline	No Hypertonic Saline
		n=	n=	n=	n=
	pH	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	Bicarbonate (mmol/L)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
Admission Diagnostic Category	Central nervous system	n(%)	n(%)	n(%)	n(%)
	Cardiovascular system	n(%)	n(%)	n(%)	n(%)
	Respiratory system	n(%)	n(%)	n(%)	n(%)
	Gastrointestinal	n(%)	n(%)	n(%)	n(%)
	Hepatobiliary	n(%)	n(%)	n(%)	n(%)
	Renal and urinary	n(%)	n(%)	n(%)	n(%)
	Toxicology/poisoning	n(%)	n(%)	n(%)	n(%)
	Haematology	n(%)	n(%)	n(%)	n(%)
	Orthopaedics/Trauma	n(%)	n(%)	n(%)	n(%)
	Infection	n(%)	n(%)	n(%)	n(%)
	Surgical and medical procedures	n(%)	n(%)	n(%)	n(%)
	Other*	n(%)	n(%)	n(%)	n(%)
ARDS Aetiology	Smoke/toxin inhalation	n(%)	n(%)	n(%)	n(%)
	Gastric content aspiration	n(%)	n(%)	n(%)	n(%)
	Near - drowning	n(%)	n(%)	n(%)	n(%)
	Thoracic trauma	n(%)	n(%)	n(%)	n(%)
	Pneumonia	n(%)	n(%)	n(%)	n(%)
	Sepsis	n(%)	n(%)	n(%)	n(%)
	Cardiopulmonary bypass	n(%)	n(%)	n(%)	n(%)
	Pancreatitis	n(%)	n(%)	n(%)	n(%)
	Non-thoracic trauma	n(%)	n(%)	n(%)	n(%)
	COVID-19	n(%)	n(%)	n(%)	n(%)
	Other*	n(%)	n(%)	n(%)	n(%)
Currently receiving antibiotics to treat a pulmonary infection?		n(%)	n(%)	n(%)	n(%)
	COPD	n(%)	n(%)	n(%)	n(%)

		Carbocisteine	No Carbocisteine	Hypertonic Saline	No Hypertonic Saline
		n=	n=	n=	n=
Pre-existing chronic respiratory condition?	**Asthma**	n(%)	n(%)	n(%)	n(%)
	Lung Cancer	n(%)	n(%)	n(%)	n(%)
	Bronchiectasis	n(%)	n(%)	n(%)	n(%)
	Cystic Fibrosis	n(%)	n(%)	n(%)	n(%)
	Interstitial Lung Disease	n(%)	n(%)	n(%)	n(%)
	Sarcoidosis	n(%)	n(%)	n(%)	n(%)
	Other*	n(%)	n(%)	n(%)	n(%)
Neurological diagnosis?	**Head Injury**	n(%)	n(%)	n(%)	n(%)
	Brain Tumor	n(%)	n(%)	n(%)	n(%)
	Epilepsy	n(%)	n(%)	n(%)	n(%)
	Stroke	n(%)	n(%)	n(%)	n(%)
	Guillain-Barre Syndrome	n(%)	n(%)	n(%)	n(%)
	Other*	n(%)	n(%)	n(%)	n(%)
Functional Co-morbidity Score (Components)	**Angina**	n(%)	n(%)	n(%)	n(%)
	Anxiety or Panic Disorders	n(%)	n(%)	n(%)	n(%)
	Arthritis *(Rheumatoid or Osteoarthritis)*	n(%)	n(%)	n(%)	n(%)
	Asthma	n(%)	n(%)	n(%)	n(%)
	Chronic Obstructive Pulmonary Disease (COPD); Acquired Respiratory Distress Syndrome (ARDS); or Emphysema	n(%)	n(%)	n(%)	n(%)
	Congestive Heart Failure *(or heart disease)*	n(%)	n(%)	n(%)	n(%)
	Degenerative Disc Disease *(Back Disease, Spinal Stenosis or Severe Chronic Back Pain)*	n(%)	n(%)	n(%)	n(%)
	Depression	n(%)	n(%)	n(%)	n(%)
	Diabetes Types I and II	n(%)	n(%)	n(%)	n(%)

			Carbocisteine	No Carbocisteine	Hypertonic Saline	No Hypertonic Saline
			n=	n=	n=	n=
	Hearing Impairments *(very hard of hearing, even with hearing aids)*		n(%)	n(%)	n(%)	n(%)
	Heart Attack *(Myocardial Infarction)*		n(%)	n(%)	n(%)	n(%)
	Neurological disease *(such as Multiple Sclerosis or Parkinson's Disease)*		n(%)	n(%)	n(%)	n(%)
	Obesity and/or Body Mass Index > 30 (weight in kg/height in m^2)		n(%)	n(%)	n(%)	n(%)
	Osteoporosis		n(%)	n(%)	n(%)	n(%)
	Peripheral Vascular Disease		n(%)	n(%)	n(%)	n(%)
	Stroke or Transient Ischaemic Attack		n(%)	n(%)	n(%)	n(%)
	Upper Gastrointestinal Disease *(e.g. Ulcer, Hernia, Reflux)*		n(%)	n(%)	n(%)	n(%)
	Visual Impairment *(e.g. Cataracts, Glaucoma, Macular Degeneration)*		n(%)	n(%)	n(%)	n(%)
Functional Co-morbidity Score (Total)			xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
Ventilation Parameters	**Mode of Ventilation**	**SIMV**	n(%)	n(%)	n(%)	n(%)
		APRV	n(%)	n(%)	n(%)	n(%)
		HFOV	n(%)	n(%)	n(%)	n(%)
		BIPAP	n(%)	n(%)	n(%)	n(%)
		PC	n(%)	n(%)	n(%)	n(%)
		PRVC	n(%)	n(%)	n(%)	n(%)
		PS	n(%)	n(%)	n(%)	n(%)
		CPAP/ASB	n(%)	n(%)	n(%)	n(%)
		Other*	n(%)	n(%)	n(%)	n(%)
		None	n(%)	n(%)	n(%)	n(%)
	Minute Volume (ml)		xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	Total Respiratory Rate		xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)

			Carbocisteine	No Carbocisteine	Hypertonic Saline	No Hypertonic Saline
			n=	n=	n=	n=
			(xx.x-xx.x)	(xx.x-xx.x)	(xx.x-xx.x)	(xx.x-xx.x)
	Plateau Pressure (cmH_2O)		xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	PEEP (cmH_2O)		xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	Tidal Volume (Minute Volume/Total Respiratory Rate)		xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	Respiratory Compliance (ml/cmH_2O)		xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	Driving Pressure (cmH_2O)		xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	Type of Humidification	**None**	n(%)	n(%)	n(%)	n(%)
		Heated Humidification	n(%)	n(%)	n(%)	n(%)
		Heat Moisture Exchange	n(%)	n(%)	n(%)	n(%)
		Other*	n(%)	n(%)	n(%)	n(%)
SOFA Score			xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)

Mean (SD) & 95% CI or median(IQR) presented for continuous variables and no. (%) for all categorical variables.

*Other reasons may be summarised

Table x.x.x. Treatment after Trial Entry by treatment arm

		Group 1 = CS+UACM	Group 2 = HTS +UACM	Group 3 = CS+HTS+UACM	Group 4 = UACM alone
		n=	n=	n=	n=
No. of days on treatment*		xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
No. of doses		xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	n/a
Treatment Compliance	**Compliant**	n(%)	n(%)	n(%)	n/a
	Not Compliant	n(%)	n(%)	n(%)	n/a
	Compliance Rate (%)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	n/a
Did not receive allocated treatment		n(%)	n(%)	n(%)	n/a
Received treatment of other group		n(%)	n(%)	n(%)	n(%)
Reasons for termination of study drug	**28 days elapsed since randomisation**	n(%)	n(%)	n(%)	n/a
	First successful unassisted breathing (maintained for 48 hours)	n(%)	n(%)	n(%)	n/a
	Study mucoactive related serious adverse event	n(%)	n(%)	n(%)	n/a
	Discharge from ICU	n(%)	n(%)	n(%)	n/a
	Death	n(%)	n(%)	n(%)	n/a
	Discontinuation of active medical treatment	n(%)	n(%)	n(%)	n/a
	Request from Legal Representative or Patient to withdraw from the trial	n(%)	n(%)	n(%)	n/a
	Decision from the attending ICU physician that the study drug should be discontinued on safety grounds	n(%)	n(%)	n(%)	n/a
	Other Reason**	n(%)	n(%)	n(%)	n/a
Reasons for omission of doses	**Patient not present in unit/receiving procedure**	n(%)	n(%)	n(%)	n/a
	Mucoactive not available	n(%)	n(%)	n(%)	n/a
	Study mucoactive terminated	n(%)	n(%)	n(%)	n/a
	Clinician decision	n(%)	n(%)	n(%)	n/a
	Omitted in error	n(%)	n(%)	n(%)	n/a
	Insufficient time that day after randomisation	n(%)	n(%)	n(%)	n/a

		Group 1 = CS+UACM	Group 2 = HTS +UACM	Group 3 = CS+HTS+UACM	Group 4 = UACM alone
		n=	n=	n=	n=
	Intervention delivery issue - technical	n(%)	n(%)	n(%)	n/a
	Discharged/transferred from ICU	n(%)	n(%)	n(%)	n/a
	Death/deterioration requiring end of life care	n(%)	n(%)	n(%)	n/a
	Patient decline/refusal	n(%)	n(%)	n(%)	n/a
	Primary outcome achieved	n(%)	n(%)	n(%)	n/a
	Other	n(%)	n(%)	n(%)	n/a
Non-trial Mucoactive Administration	**Number of patients with non-trial mucoactives administered at least once**	n(%)	n(%)	n(%)	n(%)
	Carbocisteine	*n(%)*	*n(%)*	*n(%)*	*n(%)*
	Hypertonic Saline	*n(%)*	*n(%)*	*n(%)*	*n(%)*
	Heparin (non-anticoagulation purposes)	*n(%)*	*n(%)*	*n(%)*	*n(%)*
	N-acetylcysteine	*n(%)*	*n(%)*	*n(%)*	*n(%)*
	Dornase Alfa	*n(%)*	*n(%)*	*n(%)*	*n(%)*
	Other**	*n(%)*	*n(%)*	*n(%)*	*n(%)*
	Number of days on non-trial mucoactive	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
Antibiotic Usage	**Number of patients prescribed antibiotics at least once**	n(%)	n(%)	n(%)	n(%)
	Number of days on antibiotic	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
	Overall dose	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
Usual Airway Clearance Management	**Number of sessions**	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x)
Post-randomisation withdrawal	**Mucoactive administration if ongoing**	n(%)	n(%)	n(%)	n(%)
	Ongoing data collection during hospital admission	n(%)	n(%)	n(%)	n(%)
	On-going data collection following hospital discharge	n(%)	n(%)	n(%)	n(%)
	Confirmation of vital status	n(%)	n(%)	n(%)	n(%)
	Use of samples collected to date	n(%)	n(%)	n(%)	n(%)
	Use of data collected to date	n(%)	n(%)	n(%)	n(%)

		Group 1 = CS+UACM	Group 2 = HTS +UACM	Group 3 = CS+HTS+UACM	Group 4 = UACM alone
		n=	n=	n=	n=
	Other**	n(%)	n(%)	n(%)	n(%)

Mean (SD) & 95% CI or median(IQR) presented for continuous variables and no. (%) for all categorical variables.

*Mean (SD) no. of days on treatment

**Other reasons include <specify>

Table x.x.x. Treatment after Trial Entry by comparison

		Carbocisteine	No Carbocisteine	Hypertonic Saline	No Hypertonic Saline
		n=	n=	n=	n=
No. of days on treatment*		xx.x(xx.x) (xx.x-xx.x)	xx.x(xx.x) (xx.x-xx.x	xx.x(xx.x) (xx.x-xx.x	xx.x(xx.x) (xx.x-xx.x
No. of doses		xx.x(xx.x) (xx.x-xx.x	xx.x(xx.x) (xx.x-xx.x	xx.x(xx.x) (xx.x-xx.x	n/a
Treatment Compliance	**Compliant**	n(%)	n(%)	n(%)	n/a
	Not Compliant	n(%)	n(%)	n(%)	n/a
	Compliance Rate (%)	xx.x(xx.x) (xx.x-xx.x	xx.x(xx.x) (xx.x-xx.x	xx.x(xx.x) (xx.x-xx.x	n/a
Did not receive allocated treatment		n(%)	n(%)	n(%)	n/a
Received treatment of other group		n(%)	n(%)	n(%)	n(%)
Reasons for termination of study drug	**28 days elapsed since randomisation**	n(%)	n(%)	n(%)	n/a
	First successful unassisted breathing (maintained for 48 hours)	n(%)	n(%)	n(%)	n/a
	Study mucoactive related serious adverse event	n(%)	n(%)	n(%)	n/a
	Discharge from ICU	n(%)	n(%)	n(%)	n/a
	Death	n(%)	n(%)	n(%)	n/a
	Discontinuation of active medical treatment	n(%)	n(%)	n(%)	n/a
	Request from Legal Representative or Patient to withdraw from the trial	n(%)	n(%)	n(%)	n/a
	Decision from the attending ICU physician that the study drug should be discontinued on safety grounds	n(%)	n(%)	n(%)	n/a
	Other Reason**	n(%)	n(%)	n(%)	n/a
Reasons for omission of doses	**Patient not present in unit/receiving procedure**	n(%)	n(%)	n(%)	n/a
	Mucoactive not available	n(%)	n(%)	n(%)	n/a
	Study mucoactive terminated	n(%)	n(%)	n(%)	n/a
	Clinician decision	n(%)	n(%)	n(%)	n/a
	Omitted in error	n(%)	n(%)	n(%)	n/a
	Insufficient time that day after randomisation	n(%)	n(%)	n(%)	n/a
	Intervention delivery issue - technical	n(%)	n(%)	n(%)	n/a

		Carbocisteine	No Carbocisteine	Hypertonic Saline	No Hypertonic Saline
		n=	n=	n=	n=
	Discharged/transferred from ICU	n(%)	n(%)	n(%)	n/a
	Death/deterioration requiring end of life care	n(%)	n(%)	n(%)	n/a
	Patient decline/refusal	n(%)	n(%)	n(%)	n/a
	Primary outcome achieved	n(%)	n(%)	n(%)	n/a
	Other	n(%)	n(%)	n(%)	n/a
Non-trial Mucoactive Administration	**Number of patients with non-trial mucoactives administered at least once**	n(%)	n(%)	n(%)	n(%)
	Carbocisteine	*n(%)*	*n(%)*	*n(%)*	*n(%)*
	Hypertonic Saline	*n(%)*	*n(%)*	*n(%)*	*n(%)*
	Heparin (non-anticoagulation purposes)	*n(%)*	*n(%)*	*n(%)*	*n(%)*
	N-acetylcysteine	*n(%)*	*n(%)*	*n(%)*	*n(%)*
	Dornase Alfa	*n(%)*	*n(%)*	*n(%)*	*n(%)*
	Other**	*n(%)*	*n(%)*	*n(%)*	*n(%)*
	Number of days on non-trial mucoactive	xx.x(xx.x) (xx.x-xx.x	xx.x(xx.x) (xx.x-xx.x	xx.x(xx.x) (xx.x-xx.x	xx.x(xx.x) (xx.x-xx.x
Antibiotic Usage	**Number of patients prescribed antibiotics at least once**	n(%)	n(%)	n(%)	n(%)
	Number of days on antibiotic	xx.x(xx.x) (xx.x-xx.x	xx.x(xx.x) (xx.x-xx.x	xx.x(xx.x) (xx.x-xx.x	xx.x(xx.x) (xx.x-xx.x
	Overall dose	xx.x(xx.x) (xx.x-xx.x	xx.x(xx.x) (xx.x-xx.x	xx.x(xx.x) (xx.x-xx.x	xx.x(xx.x) (xx.x-xx.x
Usual Airway Clearance Management	**Number of sessions**	xx.x(xx.x) (xx.x-xx.x	xx.x(xx.x) (xx.x-xx.x	xx.x(xx.x) (xx.x-xx.x	xx.x(xx.x) (xx.x-xx.x
Post-randomisation withdrawal	**Mucoactive administration if ongoing**	n(%)	n(%)	n(%)	n(%)
	Ongoing data collection during hospital admission	n(%)	n(%)	n(%)	n(%)
	On-going data collection following hospital discharge	n(%)	n(%)	n(%)	n(%)
	Confirmation of vital status	n(%)	n(%)	n(%)	n(%)
	Use of samples collected to date	n(%)	n(%)	n(%)	n(%)
	Use of data collected to date	n(%)	n(%)	n(%)	n(%)
	Other**	n(%)	n(%)	n(%)	n(%)

Mean (SD) & 95% CI or median(IQR) presented for continuous variables and no. (%) for all categorical variables.

*Mean (SD) no. of days on treatment

**Other reasons include <specify>

Table x.x.x. Treatment after Trial Entry – Protocol Deviations by treatment arm

	Number of Events					Number of Patients				
	Total	Group 1 = CS+UACM	Group 2 = HTS +UACM	Group 3 = CS+HTS+UACM	Group 4 = UACM alone	Total	Group 1 = CS+UACM	Group 2 = HTS +UACM	Group 3 = CS+HTS+UACM	Group 4 = UACM alone
	n=	n=	n=	n=	n=	n=	n=	n=	n=	n=
Eligibility	n	n(%)	n(%)	n(%)	n(%)	n	n(%)	n(%)	n(%)	n(%)
Consent	n	n(%)	n(%)	n(%)	n(%)	n	n(%)	n(%)	n(%)	n(%)
Randomisation/ Treatment Allocation	n	n(%)	n(%)	n(%)	n(%)	n	n(%)	n(%)	n(%)	n(%)
SAE Reporting	n	n(%)	n(%)	n(%)	n(%)	n	n(%)	n(%)	n(%)	n(%)
Other	n	n(%)	n(%)	n(%)	n(%)	n	n(%)	n(%)	n(%)	n(%)
Total	n	n	n	n	n	n	n	n	n	n

Table x.x.x. Treatment after Trial Entry – Protocol Deviations by comparison

	Number of Events				Number of Patients			
	Carbocisteine	No Carbocisteine	Hypertonic Saline	No Hypertonic Saline	Carbocisteine	No Carbocisteine	Hypertonic Saline	No Hypertonic Saline
	n=	n=	n=	n=	n=	n=	n=	n=
Eligibility	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Consent	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Randomisation/ Treatment Allocation	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
SAE Reporting	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Other	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Total	n	n	n	n	n	n	n	n

Table x.x.x Main Primary Outcome (ITT)

Primary Outcome[a] - duration of mechanical ventilation		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (UACM)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (Carbocisteine)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (Carbocisteine)
Total		xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (no HTS)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS)	

	Carbocisteine	**No Carbocisteine**	**Hypertonic Saline**	**No Hypertonic Saline**
Duration of mechanical ventilation	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)
Hazard Ratio (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value[b]	0.xxx		0.xxx	

Mean (SD) and 95% CI (or median[IQR] if appropriate) presented <*Add comment re interaction*>

[a]adjusted for age and illness severity (APACHE II)

[b]from Cox-PH

Table x.x.x Main Primary Outcome (PP)

Primary Outcome[a] - duration of mechanical ventilation		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (UACM)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (Carbocisteine)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (Carbocisteine)
Total		xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (no HTS)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS)	

	Carbocisteine	**No Carbocisteine**	**Hypertonic Saline**	**No Hypertonic Saline**
Duration of mechanical ventilation	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)
Hazard Ratio (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value[b]	0.xxx		0.xxx	

Mean (SD) and 95% CI(or median[IQR] if appropriate) presented

[a]adjusted for age and illness severity (APACHE II)

[b]from Cox-PH

Table x.x.x Main Primary Outcome Subgroup Analyses

Primary Outcome[a] - duration of mechanical ventilation		Carbocisteine vs No Carbocisteine				Hypertonic Salinevs No Hypertonic Saline			
		Carbocisteine	No Carbocisteine	HR(99%CI)	p-value	Hypertonic Saline	No Hypertonic Saline	HR(99%CI)	p-value
APACHE II(Quintiles)	Q1	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx
	Q2	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx
	Q3	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx
	Q4	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx
	Q5	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx
PF Ratio	201-300mmHg or 26.7-39.9kPa (Mild);	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx
	101-200mmHg or 13.3-26.6kPa (Moderate)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx
	<100mmHg or <13.3kPa (Severe))	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx
Pre-existing chronic respiratory condition prior to randomisation (Yes/No)	Yes	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx
	No	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx
Neurological diagnosis prior to randomisation(Yes/No)	Yes	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx
	No	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx

Primary Outcome[a] - duration of mechanical ventilation		Carbocisteine vs No Carbocisteine				Hypertonic Salinevs No Hypertonic Saline			
		Carbocisteine	No Carbocisteine	HR(99%CI)	p-value	Hypertonic Saline	No Hypertonic Saline	HR(99%CI)	p-value
Receiving antibiotics for pulmonary infection at randomisation (Yes/No)	Yes	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx
	No	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx
Admission diagnostic categories (pulmonary/non-pulmonary)	Pulmonary	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx
	Non-Pulmonary	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x – xx.x)	0.xx

[a]p-value from COX-PH model including interaction term

Table x.x.x Main Primary Outcome Sensitivity Analyses

Primary Outcome[a] - duration of mechanical ventilation	Carbocisteine	No Carbocisteine	Hypertonic Saline	No Hypertonic Saline
Competing risk of death				
Mean (SD) and 95%CI	xx.x(xx.x) (xx.x – xx.x)	xx.x(xx.x) (xx.x – xx.x)	xx.x(xx.x) (xx.x – xx.x)	xx.x(xx.x) (xx.x – xx.x)
Median (IQR)	xx.x(xx.x – xx.x)	xx.x(xx.x – xx.x)	xx.x(xx.x – xx.x)	xx.x(xx.x – xx.x)
Sub Hazard Ratio (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value[b]	0.xxx		0.xxx	
Impact of interaction between interventions				
Mean (SD)	xx.x(xx.x) (xx.x – xx.x)	xx.x(xx.x) (xx.x – xx.x)	xx.x(xx.x) (xx.x – xx.x)	xx.x(xx.x) (xx.x – xx.x)
Median (IQR)	xx.x(xx.x – xx.x)	xx.x(xx.x – xx.x)	xx.x(xx.x – xx.x)	xx.x(xx.x – xx.x)
Hazard Ratio (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from Cox-PH	0.xxx		0.xxx	
Impact of contamination between interventions				
Mean (SD)	xx.x(xx.x) (xx.x – xx.x)	xx.x(xx.x) (xx.x – xx.x)	xx.x(xx.x) (xx.x – xx.x)	xx.x(xx.x) (xx.x – xx.x)
Median (IQR)	xx.x(xx.x – xx.x)	xx.x(xx.x – xx.x)	xx.x(xx.x – xx.x)	xx.x(xx.x – xx.x)
Hazard Ratio (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from Cox-PH	0.xxx		0.xxx	
Excluding patients not on IMV at the point of randomisation				
Mean (SD)	xx.x(xx.x) (xx.x – xx.x)	xx.x(xx.x) (xx.x – xx.x)	xx.x(xx.x) (xx.x – xx.x)	xx.x(xx.x) (xx.x – xx.x)
Median (IQR)	xx.x(xx.x – xx.x)	xx.x(xx.x – xx.x)	xx.x(xx.x – xx.x)	xx.x(xx.x – xx.x)
Hazard Ratio (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from Cox-PH	0.xxx		0.xxx	

[a]ITT population

[b]p-value from competing risks regression model

Table x.x.x Main Primary Outcome Secondary Analyses (Survivors/Non Survivors)

Primary Outcome[a] - duration of mechanical ventilation - Survivors		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (UACM)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (Carbocisteine)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (Carbocisteine)
Total		xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (no HTS)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS)	

	Carbocisteine	**No Carbocisteine**	**Hypertonic Saline**	**No Hypertonic Saline**
Duration of mechanical ventilation	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)
Hazard Ratio (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value[b]	0.xxx		0.xxx	

Primary Outcome[a] - duration of mechanical ventilation – Non survivors		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (UACM)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (Carbocisteine)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (Carbocisteine)
Total		xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (no HTS)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS)	

	Carbocisteine	**No Carbocisteine**	**Hypertonic Saline**	**No Hypertonic Saline**
Duration of mechanical ventilation	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)

Hazard Ratio (95% CI)	xx.x(xx.x – xx.x)	xx.x(xx.x – xx.x)
p-value[b]	0.xxx	0.xxx

Table x.x.x Main Primary Outcome Secondary Analyses

Primary Outcome[a] - duration of mechanical ventilation		
	Group 1 = CS + UACM	**Group 4 = UACM alone**
Mean (SD) and 95% CI	xx.x(xx.x) (xx.x – xx.x)	xx.x(xx.x) (xx.x – xx.x)
Median (IQR)	xx.x(xx.x – xx.x)	xx.x(xx.x – xx.x)
Mean Difference (95% CI)	xx.x(xx.x – xx.x)	
p-value[b]	0.xxx	
	Group 2 = HTS + UACM	**Group 4 = UACM alone**
Mean (SD)	xx.x(xx.x) (xx.x – xx.x)	xx.x(xx.x) (xx.x – xx.x)
Median (IQR)	xx.x(xx.x – xx.x)	xx.x(xx.x – xx.x)
Mean Difference (95% CI)	xx.x(xx.x – xx.x)	
p-value[b]	0.xxx	
	Group 3 = CS+HTS+UACM	**Group 4 = UACM alone**
Mean (SD)	xx.x(xx.x) (xx.x – xx.x)	xx.x(xx.x) (xx.x – xx.x)
Median (IQR)	xx.x(xx.x – xx.x)	xx.x(xx.x – xx.x)
Mean Difference (95% CI)	xx.x(xx.x – xx.x)	
p-value[b]	0.xxx	
	Group 3 = CS+HTS+UACM	**Group 1 = CS + UACM & Group 4 =UACM Alone**
Mean (SD)	xx.x(xx.x) (xx.x – xx.x)	xx.x(xx.x) (xx.x – xx.x)
Median (IQR)	xx.x(xx.x – xx.x)	xx.x(xx.x – xx.x)
Mean Difference (95% CI)	xx.x(xx.x – xx.x)	
p-value[b]	0.xxx	
	Group 3 = CS+HTS+UACM	**Group 2 = HTS + UACM & Group 4 =UACM Alone**
Mean (SD)	xx.x(xx.x) (xx.x – xx.x)	xx.x(xx.x) (xx.x – xx.x)
Median (IQR)	xx.x(xx.x – xx.x)	xx.x(xx.x – xx.x)
Mean Difference (95% CI)	xx.x(xx.x – xx.x)	
p-value[b]	0.xxx	

[a] Only if the main effects primary analyses are statistically significant

[b]p-value from Cox-PH with Bonferroni correction

Table x.x.x Secondary outcome (Time to 1st successful extubation)

Time to 1st successful extubation		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	xx.x(xx.x) xx.x(xx.x – xx.x) (UACM)	xx.x(xx.x) xx.x(xx.x – xx.x) (HTS)	xx.x(xx.x) xx.x(xx.x – xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) xx.x(xx.x – xx.x) (Carbocisteine)	xx.x(xx.x) xx.x(xx.x – xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) xx.x(xx.x – xx.x) (Carbocisteine)
Total		xx.x(xx.x) xx.x(xx.x – xx.x) (no HTS)	xx.x(xx.x) xx.x(xx.x – xx.x) (HTS)	

	Carbocisteine	**No Carbocisteine**	**Hypertonic Saline**	**No Hypertonic Saline**
Time to 1st successful extubation	xx.x(xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) xx.x(xx.x – xx.x)
Hazard Ratio (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from Cox-PH	0.xxx		0.xxx	

Table x.x.x Secondary outcome (Incidence of extubation)

Incidence of extubation		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	n(%) (UACM)	n(%) (HTS)	n(%) (No Carbocisteine)
	Yes	n(%) (Carbocisteine)	n(%) (HTS plus Carbocisteine)	n(%) (Carbocisteine)
Total		n(%) (no HTS)	n(%) (HTS)	

	Carbocisteine	**No Carbocisteine**	**Hypertonic Saline**	**No Hypertonic Saline**
Incidence of extubation	n(%)	n(%)	n(%)	n(%)
Risk Ratio (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from GLM	0.xxx		0.xxx	
Risk Difference (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from GLM	0.xxx		0.xxx	

Table x.x.x Secondary outcome (Incidence of reintubation)

Incidence of reintubation		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	n(%) (UACM)	n(%) (HTS)	n(%) (No Carbocisteine)
	Yes	n(%) (Carbocisteine)	n(%) (HTS plus Carbocisteine)	n(%) (Carbocisteine)
Total		n(%) (no HTS)	n(%) (HTS)	

	Carbocisteine	**No Carbocisteine**	**Hypertonic Saline**	**No Hypertonic Saline**
Incidence of reintubation	n(%)	n(%)	n(%)	n(%)
Risk Ratio (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from GLM	0.xxx		0.xxx	
Risk Difference (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from GLM	0.xxx		0.xxx	

Table x.x.x Secondary outcome (Respiratory physiotherapy input)

Incidence of respiratory physiotherapy input		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	n(%) (UACM)	n(%) (HTS)	n(%) (No Carbocisteine)
	Yes	n(%) (Carbocisteine)	n(%) (HTS plus Carbocisteine)	n(%) (Carbocisteine)
Total		n(%) (no HTS)	n(%) (HTS)	

	Carbocisteine	**No Carbocisteine**	**Hypertonic Saline**	**No Hypertonic Saline**
Incidence of respiratory physiotherapy input	n(%)	n(%)	n(%)	n(%)
Risk Ratio (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from GLM	0.xxx		0.xxx	
Risk Difference (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from GLM	0.xxx		0.xxx	

Number of sessions		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (UACM)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (Carbocisteine)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (Carbocisteine)
Total		xx.x(xx.x) xx.x(xx.x – xx.x) (no HTS)	xx.x(xx.x) xx.x(xx.x – xx.x) (HTS)	

	Carbocisteine	**No Carbocisteine**	**Hypertonic Saline**	**No Hypertonic Saline**
Number of sessions	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)
Mean Diff (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from ANCOVA[a]	0.xxx		0.xxx	

[a]adjusted for age and apache II

Table x.x.x Secondary outcome (Antibiotic Usage – Number of days on antibiotics)

Number of days on antibiotics		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (UACM)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (Carbocisteine)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (Carbocisteine)
Total		xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (no HTS)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS)	

	Carbocisteine	**No Carbocisteine**	**Hypertonic Saline**	**No Hypertonic Saline**
Number of days on antibiotics	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)
Mean Diff (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from ANCOVA[a]	0.xxx		0.xxx	

[a]adjusted for age and apache II

Table x.x.x Secondary outcome (Antibiotic Usage – number of patients prescribed antibiotics at least once)

number of patients prescribed antibiotics at least once		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	n(%) (UACM)	n(%) (HTS)	n(%) (No Carbocisteine)
	Yes	n(%) (Carbocisteine)	n(%) (HTS plus Carbocisteine)	n(%) (Carbocisteine)
Total		n(%) (no HTS)	n(%) (HTS)	

	Carbocisteine	**No Carbocisteine**	**Hypertonic Saline**	**No Hypertonic Saline**
number of patients prescribed antibiotics at least once	n(%)	n(%)	n(%)	n(%)
Risk Ratio (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from GLM	0.xxx		0.xxx	
Risk Difference (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from GLM	0.xxx		0.xxx	

Table x.x.x Secondary outcome (Duration of ICU stay)

Duration of ICU stay		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (UACM)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (Carbocisteine)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (Carbocisteine)
Total		xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (no HTS)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS)	

	Carbocisteine	**No Carbocisteine**	**Hypertonic Saline**	**No Hypertonic Saline**
Duration of ICU stay	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)
p-value from Wilcoxon rank sum	0.xxx		0.xxx	

Mean(SD) and 95% CI alongside Median(IQR) presented

Table x.x.x Secondary outcome (Duration of hospital stay)

Duration of hospital stay		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (UACM)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (No Carbocisteine)
	Yes	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (Carbocisteine)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS plus Carbocisteine)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (Carbocisteine)
Total		xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (no HTS)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x) (HTS)	

	Carbocisteine	**No Carbocisteine**	**Hypertonic Saline**	**No Hypertonic Saline**
Duration of hospital stay	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)	xx.x(xx.x) (xx.x-xx.x) xx.x(xx.x – xx.x)
Mean Diff (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from Wilcoxon Rank Sum	0.xxx		0.xxx	

Mean(SD) and 95% CI alongside Median(IQR) presented

Table x.x.x Secondary outcome (All-cause mortality)

All-cause mortality		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	n(%) (UACM)	n(%) (HTS)	n(%) (No Carbocisteine)
	Yes	n(%) (Carbocisteine)	n(%) (HTS plus Carbocisteine)	n(%) (Carbocisteine)
Total		n(%) (no HTS)	n(%) (HTS)	

	Carbocisteine	**No Carbocisteine**	**Hypertonic Saline**	**No Hypertonic Saline**
All-cause mortality	n(%)	n(%)	n(%)	n(%)
Risk Ratio (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from GLM	0.xxx		0.xxx	
Risk Difference (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from GLM	0.xxx		0.xxx	

Table x.x.x. Safety by Treatment Group by treatment group

		No Events				No. Patients			
		Group 1 = CS+UACM	Group 2 = HTS +UACM	Group 3 = CS+HTS+ UACM	Group 4 = UACM alone	Group 1 = CS+UACM	Group 2 = HTS +UACM	Group 3 = CS+HTS+ UACM	Group 4 = UACM alone
		n=	n=	n=	n=	n=	n=	n=	n=
SAEs and SUSAR	**Total SAES**	n	n	n	n	n(%)	n(%)	n(%)	n(%)
	Related to study drug	n	n	n	n	n(%)	n(%)	n(%)	n(%)
	Related to study drug and unexpected	n	n	n	n	n(%)	n(%)	n(%)	n(%)
	Total Deaths	n	n	n	n	n(%)	n(%)	n(%)	n(%)
SARs	**Cardiac Arrhythmia**	n	n	n	n	n(%)	n(%)	n(%)	n(%)
	Cardiac General	n	n	n	n	n(%)	n(%)	n(%)	n(%)
	Gastrointestinal	n	n	n	n	n(%)	n(%)	n(%)	n(%)
	Etc…..	n	n	n	n	n(%)	n(%)	n(%)	n(%)
SUSARs	**Cardiac Arrhythmia**	n	n	n	n	n(%)	n(%)	n(%)	n(%)
	Cardiac General	n	n	n	n	n(%)	n(%)	n(%)	n(%)
	Gastrointestinal	n	n	n	n	n(%)	n(%)	n(%)	n(%)
	Etc…..	n	n	n	n	n(%)	n(%)	n(%)	n(%)

Will also be presented by comparison

Table x.x.x. Safety Outcomes by Treatment Group

		No. Events				No. Patients			
		Group 1 = CS+UACM	**Group 2 = HTS +UACM**	**Group 3 = CS+HTS+ UACM**	**Group 4 = UACM alone**	**Group 1 = CS+UACM**	**Group 2 = HTS +UACM**	**Group 3 = CS+HTS+ UACM**	**Group 4 = UACM alone**
		n=	**n=**	**n=**	**n=**	**n=**	**n=**	**n=**	**n=**
Safety outcome	Clinically important upper gastrointestinal (GI) bleeding due to peptic ulceration confirmed on upper GI endoscopy	n	n	n	n	n(%)	n(%)	n(%)	n(%)
	Bronchoconstriction requiring nebulised bronchodilators	n	n	n	n	n(%)	n(%)	n(%)	n(%)
	Ventilator or circuit dysfunction with respiratory deterioration	n	n	n	n	n(%)	n(%)	n(%)	n(%)
	Hypoxaemia during nebulisation	n	n	n	n	n(%)	n(%)	n(%)	n(%)

Table x.x.x Safety outcome (Clinically important upper gastrointestinal (GI) bleeding due to peptic ulceration confirmed on upper GI endoscopy)

Clinically important upper gastrointestinal (GI) bleeding due to peptic ulceration confirmed on upper GI endoscopy		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	n(%) (UACM)	n(%) (HTS)	n(%) (No Carbocisteine)
	Yes	n(%) (Carbocisteine)	n(%) (HTS plus Carbocisteine)	n(%) (Carbocisteine)
Total		n(%) (no HTS)	n(%) (HTS)	

	Carbocisteine	**No Carbocisteine**	**Hypertonic Saline**	**No Hypertonic Saline**
Clinically important upper gastrointestinal (GI) bleeding due to peptic ulceration confirmed on upper GI endoscopy	n(%)	n(%)	n(%)	n(%)
Risk Ratio (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from GLM	0.xxx		0.xxx	
Risk Difference (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from GLM	0.xxx		0.xxx	

Table x.x.x Safety outcome (Bronchoconstriction requiring nebulised bronchodilators)

Bronchoconstriction requiring nebulised bronchodilators		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	n(%) (UACM)	n(%) (HTS)	n(%) (No Carbocisteine)
	Yes	n(%) (Carbocisteine)	n(%) (HTS plus Carbocisteine)	n(%) (Carbocisteine)
Total		n(%) (no HTS)	n(%) (HTS)	

	Carbocisteine	**No Carbocisteine**	**Hypertonic Saline**	**No Hypertonic Saline**
Bronchoconstriction requiring nebulised bronchodilators	n(%)	n(%)	n(%)	n(%)
Risk Ratio (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from GLM	0.xxx		0.xxx	
Risk Difference (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from GLM	0.xxx		0.xxx	

Table x.x.x Safety outcome (Ventilator or circuit dysfunction with respiratory deterioration)

Ventilator or circuit dysfunction with respiratory deterioration		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	n(%) (UACM)	n(%) (HTS)	n(%) (No Carbocisteine)
	Yes	n(%) (Carbocisteine)	n(%) (HTS plus Carbocisteine)	n(%) (Carbocisteine)
Total		n(%) (no HTS)	n(%) (HTS)	

	Carbocisteine	**No Carbocisteine**	**Hypertonic Saline**	**No Hypertonic Saline**
Ventilator or circuit dysfunction with respiratory deterioration	n(%)	n(%)	n(%)	n(%)
Risk Ratio (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from GLM	0.xxx		0.xxx	
Risk Difference (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from GLM	0.xxx		0.xxx	

Table x.x.x Safety outcome (Hypoxaemia during nebulisation)

Hypoxaemia during nebulisation		**HTS**		**Total**
		No	**Yes**	
Carbocisteine	**No**	n(%) (UACM)	n(%) (HTS)	n(%) (No Carbocisteine)
	Yes	n(%) (Carbocisteine)	n(%) (HTS plus Carbocisteine)	n(%) (Carbocisteine)
Total		n(%) (no HTS)	n(%) (HTS)	

	Carbocisteine	**No Carbocisteine**	**Hypertonic Saline**	**No Hypertonic Saline**
Hypoxaemia during nebulisation	n(%)	n(%)	n(%)	n(%)
Risk Ratio (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from GLM	0.xxx		0.xxx	
Risk Difference (95% CI)	xx.x(xx.x – xx.x)		xx.x(xx.x – xx.x)	
p-value from GLM	0.xxx		0.xxx	