Mucoactives in Acute Respiratory failure: Carbocisteine and Hypertonic saline

MARCH

Site Feasibility Questionnaire

- Please complete the questionnaire below if you would like to participate in the MARCH study and to help the study team assess the feasibility of conducting this study at your site.
- Consultation may be required with departments within your site to enable completion of the form e.g. pharmacy, laboratories, ICT
- If you do not fulfil all the criteria required for this study, this does not necessarily mean that the study cannot take place at your site (For example, we may be able to provide additional training).

HSC/NHS Trust Details	
Trust:	
Address: *(NB: Please insert the legally registered address of the Trust to be used on regulatory documentation)*	

PROPOSED CLINICAL SITE(S)	
Please complete ONE form for each participating Trust. If there is more than one site within the Trust, please provide site details below (add rows if necessary).	
Site name:	
Site name:	

PLEASE INDICATE THE STAFF AT YOUR SITE YOU ENVISAGE TAKING ON THE FOLLOWING ROLES:

PRINCIPAL INVESTIGATOR	
Name (including title):	**Postal Address:**
Post:	**Tel No:**
Qualifications:	**Email address:**
Please indicate if Good Clinical Practice training has been completed in the last 3 years and certification is available ☐	

PLEASE INDICATE THE STAFF AT YOUR SITE YOU ENVISAGE TAKING ON THE FOLLOWING ROLES:

CRITICAL CARE PHYSIOTHERAPY LINK	
Name (including title):	**Postal Address:**
Post:	**Tel No:**
Qualifications:	**Email address:**
Please indicate if Good Clinical Practice training has been completed in the last 3 years and certification is available ☐	

MAIN RESEARCH CONTACT *Please identify the main contact for recruitment, data collection and follow-up of MARCH participants e.g. research nurse or site co-ordinator*	
If there is not currently a member of staff available with capacity to support the trial, please indicate here ☐	
Name (including title):	**Postal Address:**
Post:	**Tel No:**
Email address:	
Please indicate if Good Clinical Practice training has been completed in the last 3 years and certification is available ☐	

PERSON RESPONSIBLE FOR R&D APPROVALS		
Name (including title):	**Postal Address:**	
	Tel No:	**Fax No:**
	Email address:	

PERSON RESPONSIBLE FOR CLINICAL TRIAL AGREEMENTS (if different from above)		
Name (including title):	**Postal Address:**	
	Tel No:	**Fax No:**
	Email address:	

RECRUITMENT TO MARCH	
The recruitment process began February 2022 and will end in October 2024 How many eligible participants do you estimate this site can recruit into the MARCH study (See Appendix 1) per month?	Please provide recruitment estimates for this site in the space provided: _____**per month**
Is your site experienced with clinical trials?	☐ Yes ☐ No If YES, which trials: ☐ UK-ROX ☐ A2B ☐ REST ☐ 65 ☐ ADAPT-Sepsis ☐ REMAP-CAP ☐ Other, please specify:

CLINICAL EQUIPOISE	
Are clinicians at your site willing to randomise participants to all four treatment groups within the study, including the comparator group (usual airway clearance management alone), and adhere to treatment allocation ? If no, please comment:	☐ Yes ☐ No

RECRUITING SITE FACILITIES	
Will your site be able to screen daily for patients?	☐ Yes ☐ No
Will your site be able to carry out the Schedule of Assessments as detailed in Appendix 1? If no, please specify which assessments you cannot provide:	☐ Yes ☐ No

SAMPLE STORAGE FACILITIES		
Please note, ability to collect, process, and store samples, **is not a prerequisite** for site eligibility to take part in the study.		
Ability to process and store research samples with access to secure freezer prior to batch transfer	☐ -80°C freezer ☐ Back up -80°C freezer	**Additional comments**

MAIN PHARMACY CONTACT	
If there is not currently a member of staff available with capacity to support the trial please indicate here ☐	
Name (including title):	**Postal Address:**
Post:	**Tel No:**
Email address:	
Please indicate if Good Clinical Practice training has been completed in the last 3 years and certification is available ☐	

ICT INFORMATION *The following information is required in order to demonstrate the minimum requirements for connection to the CTU Clinical Data Management System. The following specifically relates to the machine to be used for data entry*		
		Additional comments
Please identify the operating system you intend to use:	☐ Windows 7 SP1 (x86 or x64) ☐ Windows 10 (x64)	
Please identify the web browser you intend to use: (Please note MACRO 4 is only compatible with the Internet Explorer and Firefox versions listed)	☐ Microsoft Internet Explorer v11 ☐ Mozilla Firefox v52 ESR ☐ Google Chrome ** ☐ Microsoft Edge	
Do you have Adobe Reader 9? (required for printing)	☐ Yes ☐ No	

MISCELLANEOUS	
Any other site specific information or issues to raise:	

Signature ———————————————— **Date ____/____/_____**

(Principal Investigator)

Please email a signed completed form to: MARCH@nictu.hscni.net

APPENDIX 1

STUDY SUMMARY	
Protocol Title:	Mucoactives in Acute Respiratory failure: Carbocisteine and Hypertonic saline (MARCH)
Protocol Acronym:	MARCH
Chief Investigators:	Professor Danny McAuley Dr Bronwen Connolly
Proposed Start Date of Recruitment:	1st February 2022
Proposed Duration of Recruitment:	33 months
Sample Size:	1956 patients
Clinical Trials Unit:	Northern Ireland Clinical Trials Unit, 7 Lennoxvale, Belfast, Northern Ireland, BT9 5BY Tel: +44 (0)28 9615 1447 Email: MARCH@nictu.hscni.net
Funder:	The study is funded by the National Institute for Health Research Health Technology Assessment Programme; NIHR130454, www.fundingawards.nihr.ac.uk/award/NIHR130454

Study Details

Background

Acute respiratory failure (ARF) accounts for the majority of patient admissions to the intensive care unit (ICU). Invasive mechanical ventilation is the cornerstone of treatment but increases the risk of respiratory tract secretion retention due to altered secretion rheology and impaired mucociliary clearance. Usual airway clearance management includes suctioning, heated humidification, use of isotonic saline, and respiratory physiotherapy techniques, and may be supplemented with mucoactive drugs.

However, use of mucoactive drugs is empirical, common, and with wide variation in prescribing across ICUs and amongst clinicians, indicating considerable uncertainty. Typically, the major clinical feature prompting their use in patients with ARF is presence of thick secretions. Two of the most commonly used drugs are topical (nebulised/inhaled) hypertonic saline and systemic carbocisteine; drugs with distinct mechanisms of action which may confer differing benefits to secretion clearance. However, there is minimal evidence to support their effectiveness in UK practice. Establishing the clinical- and cost-effectiveness of mucoactive drugs will ensure that their delivery is to the most appropriate patients, where applicable, thus minimising the potential for harm and unnecessary expense.

Trial Objectives & Design

Primary objective
To determine the clinical effectiveness of two mucoactive drugs (carbocisteine or hypertonic saline), or a combination of both, on duration of mechanical ventilation.

Secondary objectives
1. To determine the clinical effectiveness of two mucoactive drugs (carbocisteine or hypertonic saline), or a combination of both, on a range of secondary clinical outcomes
2. To estimate, in an integrated economic evaluation, the cost-effectiveness of the mucoactive drugs

Eligibility

Inclusion criteria

1. Adult (≥16 years)
2. An acute and potentially reversible cause of acute respiratory failure as determined by the treating physician
3. Receiving invasive mechanical ventilation
4. Anticipated to remain on invasive mechanical ventilation for at least 48 hours
5. Secretions that are difficult to clear and usual airway clearance management is insufficient

Exclusion criteria

1. Pre-existing chronic respiratory condition requiring routine use of any mucoactive drug
2. Mucoactive drug treatment started more than 24 hours before trial enrolment
3. Known adverse reaction to either study mucoactive
4. Treatment withdrawal expected within 24 hours
5. Known pregnancy
6. Previous enrolment in the MARCH trial
7. Declined consent
8. The treating clinician believes that participation in the trial would not be in the best interests of the patient

Patient Screening

All mechanically ventilated patients in the ICU will be screened daily for eligibility. Patients clinically judged to have acute hypoxaemic respiratory failure will be screened against the inclusion and exclusion criteria. Eligible patients will then be discussed with their treating ICU physician to confirm their agreement with trial enrolment.

Study Interventions

Patients will be randomised to one of the following interventions:

Intervention 1: Carbocisteine: 750 mg three times daily, for up to 28 days, delivered systemically, plus usual airway clearance management. (Where extubation occurs on Day 27 or Day 28, carbocisteine will be administered up to Day 29 and Day 30 respectively).

Intervention 2: Hypertonic saline: 4 ml of 6 or 7% concentration, delivered via nebulisation, four times daily, for up to 28 days, plus usual airway clearance management. (Where extubation occurs on Day 27 or Day 28, hypertonic saline will be administered up to Day 29 and Day 30 respectively).

Intervention 3: Carbocisteine and hypertonic saline (as described in 1. and 2.), plus usual airway clearance management

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

Study Mucoactives

Study mucoactives will be supplied from locally available, commercial stock, at each site. Study mucoactives are as follows:

- Carbocisteine, 250 mg/5 ml syrup, Carbocisteine 750mg/10ml oral solution in sachets or
- 375 mg capsules
- Hypertonic saline, 4 ml ampoule, 6% or 7% concentration

Outcome Measures

Primary Outcome Measure

The primary outcome is duration of mechanical ventilation.

This outcome is defined (measured) as time from randomisation until first successful unassisted breathing (defined as maintaining unassisted breathing for 48 hours) or death.

Secondary Outcome Measures
The following secondary clinical outcomes will also be assessed:

In hospital
1. Extubation
2. Re-intubation
3. Duration of intensive care unit and hospital stay
4. Mortality
5. Respiratory physiotherapy input
6. Antibiotic usage
7. Adverse events

At 60 days
1. Health-related quality of life
2. All-cause mortality

At 6 months
1. Health-related quality of life
2. All-cause mortality
3. Health service use since hospital discharge

Clinical outcomes will be measured at baseline and daily up to Day 28 or until the patient is discharged from ICU or death occurs, whichever comes first. (Where extubation occurs on Day 27 or Day 28, clinical outcomes will be recorded up to Day 29 and Day 30 respectively).

Schedule of Assessments

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

Day 0 (Baseline)
Baseline data (Day 0) is the 24 hours preceding randomisation. 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 is not limited to, the following:

- Date of birth
- Sex
- Medical history including chronic comorbidities
- ICNARC Case Mix Programme (CMP) number or equivalent
- Date and time of ICU admission
- Date/time of onset of invasive mechanical ventilation
- Date/time of consent and randomisation
- Aetiology of acute respiratory failure
- Acute Physiology And Chronic Health Evaluation II score (APACHE II)
- 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: FiO2, PaO2, PaCO2, 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 1-28 (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 extubated 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)

<u>Day 60</u>
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

<u>6 months</u>
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

Exploratory Mechanistic Studies
In order to determine the potential mechanism of action of mucoactive drugs, baseline endotracheal aspirates and blood samples will be taken prior to study drug administration, and on Days 3 and 7 (if patient remains invasively mechanically ventilated). The study will investigate the following:
1. Dynamic rheology measurements including sputum elasticity and viscosity
2. Sputum inflammation
3. Sputum bacterial load/composition
4. Systemic inflammatory responses
5. Pulmonary and systemic epithelial and endothelial function and injury

However, ability to collect, process, and store samples, **is not a prerequisite** for site eligibility, and in sites where sample collection is in operation, if samples cannot be collected on any occasion this will not be recorded as a protocol deviation.