Mucoactives in Acute Respiratory failure: Carbocisteine and Hypertonic saline

The MARCH Trial

Site Feasibility Questionnaire

- Please complete the questionnaire below if you would like to participate in the MARCH study and to help the MARCH 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 will run from November 2021 until 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: ☐ HARP-2 ☐ REST ☐ PROMISE ☐ 65 ☐ BREATHE ☐ REMAP-CAP ☐ Other, if other please specify	

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
Research Title and Acronym	Mucoactives in Acute Respiratory failure: Carbocisteine and Hypertonic saline (MARCH)
Chief Investigator **Co-Chief Investigator**	Professor Danny McAuley Dr Bronwen Connolly
Proposed Start Date of Recruitment	01/11/2021
Proposed Duration of Recruitment	36 months
Sample Size	1956 patients
Clinical Trials Unit	Northern Ireland Clinical Trials Unit, 1st Floor Elliot Dynes Building, The Royal Hospitals, Grosvenor Road, Belfast, Northern Ireland, BT12 6BA 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 drug
4. Contraindication to enteral drug administration e.g. patients with mechanical bowel obstruction; patients with high gastric aspirates due to an ileus will not be excluded
5. Treatment withdrawal expected within 24 hours
6. Known pregnancy
7. Previous enrolment in the MARCH trial
8. Declined consent
9. Prisoners

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: 750mg three times daily, for up to 28 days, delivered systemically via the enteral feeding tube, or orally, plus usual care
Intervention 2:	Hypertonic saline: 6 or 7% concentration, for delivery via nebulisation, four times daily, for up to 28 days, plus usual care
Intervention 3:	Carbocisteine and hypertonic saline (as described in 1. and 2.), plus usual care
Intervention 4:	Usual care (usual airway clearance management including suctioning, heated humidification, and respiratory physiotherapy; use of isotonic saline allowed)

Study Drugs

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

- Carbocisteine, 750mg
- Hypertonic saline, 6 or 7% concentration (according to local site usage)

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

Outcomes will be measured at baseline and daily up to day 28 or until the patient is discharged from ICU or death occurs, and thereafter to 60 days and 6 months as required for secondary and cost effectiveness outcomes.

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: 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 1-28 (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 but after the time of randomisation will be recorded. All other daily measurements will be recorded between 6-10am or as close to this time as possible, unless otherwise stated in the CRF. Daily data will be collected up to Day 28 (or first unassisted breathing (defines primary outcome of duration of mechanical ventilation), ICU discharge, or death, whichever comes first; or in the event the study drug is terminated for any other reason), and will include, but is not limited to:

- Respiratory physiotherapy airway clearance management
- Administration of non-trial mucoactive drug
- Study drug administration
- Antibiotic usage
- Pulmonary complications
- Adverse events
- Assessment for extubation readiness

The following will also be recorded:

- Date/time of discontinuation of mechanical ventilation
- Date/time of extubation
- Date/time of re-intubation
- Date/time of ICU discharge
- Date/time of hospital discharge
- Date of death

Day 60

- Health-related quality of life
- All-cause mortality

6 months

- EQ-5D-5L (post or telephone)
- Patients use of health and social care resources collected by resource logs
- 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.