# To determine if critically ill patients with acute respiratory failure treated with carbocisteine, hypertonic saline, or both, experience increased hydration of airway mucus.

Submission date	Recruitment status	[X] Prospectively registered
01/07/2022	No longer recruiting	Protocol
Registration date	Overall study status	Statistical analysis plan
04/07/2022	Ongoing	Results
Last Edited	Condition category	Individual participant data
09/04/2025	Respiratory	[X] Record updated in last year

#### Plain English summary of protocol

Background and study aims

When patients are critically ill, one of the main complications is called 'acute respiratory failure'. This is when a patient's illness causes their lungs to fail to work (lung failure). Patients need to be admitted to the Intensive Care Unit (ICU) and often need to have a breathing machine, or ventilator, to help them breathe and ensure that enough oxygen gets into their blood. However, one problem that can occur as a result of being on a ventilator, is difficulty clearing secretions (mucus, or sputum) from the lungs. Not being able to clear secretions from the lungs can make breathing harder, and this may result in developing a lung infection.

In some cases, medications called 'mucoactives' may be prescribed for patients to reduce the problem of thick secretions. Mucoactives are medications that work to help clear secretions from the airways. Two examples of mucoactives are 'Carbocisteine' and 'Hypertonic saline'. Carbocisteine can help by changing the thickness and stickiness of secretions, which may help clear mucus from the lungs. It is given to patients in the ICU whilst they are on a breathing machine, in either liquid form or as powder dissolved in water, via the patient's feeding tube. Hypertonic saline is salty water that is delivered into the airways via a device called a nebuliser, which turns the salty water into a mist. The mist may stimulate coughing to help clear thick secretions from the lungs.

A study called MARCH is already investigating whether using one, or both, of these mucoactives (carbocisteine and hypertonic saline), really helps patients when they have difficulty clearing secretions, and if as a result, this means patients spend less time on the breathing machine (ventilator).

This study is named EME and is a part of the MARCH study. The EME Study hopes to find out biologically the ways these mucoactives might work to help clear secretions from the airways and so shorten the time patients need a ventilator to breathe. This information will allow doctors to prescribe the correct amount of medication to help critically ill patients, and improve lung failure treatments for patients in the future.

#### Who can participate?

Patients who have provided their consent to be enrolled in the main MARCH trial and to have biological samples (airway secretions) collected and analysed.

#### What does the study involve?

Samples of airway secretions will be taken from patients in the MARCH study who are being treated by one of these mucoactives, both of them, or neither of them. The EME study will test the samples to measure their thickness, stickiness, and the level of inflammation present.

#### What are the possible benefits and risks of participating?

The information gained from the tests on the biological samples will benefit doctors and patients as it will improve treatments for patients with lung failure in the future. We do not anticipate any risks associated with being the EME part of this study. All patients enrolled in the MARCH study will be carefully monitored.

# Where is the study run from?

The Trial Coordinating Centre is the Northern Ireland Clinical Trials Unit (NICTU) (UK). The Sponsor is the Belfast Health and Social Care Trust (BHSCT) (UK).

When is the study starting and how long is it expected to run for? From May 2022 to November 2025

## Who is funding the study?

National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation Programme (UK)

Who is the main contact? Dr Naomi Dickson MARCH@nictu.hscni.net

#### Study website

https://nictu.hscni.net/march-trial/

# Contact information

## Type(s)

Principal Investigator

#### Contact name

Dr Cliff Taggart

#### **ORCID ID**

http://orcid.org/0000-0002-9930-2978

#### Contact details

Wellcome Wolfson Institute of Experimental Medicine Queens University Belfast Belfast United Kingdom BT9 7BL +44(0)2890976383 c.taggart@qub.ac.uk

# Type(s)

Scientific

#### Contact name

Dr Naomi Dickson

#### Contact details

Northern Ireland Clinical Trials Unit (NICTU)
7 Lennoxvale
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United Kingdom
BT9 5BY
+44 (0)28961 51447
MARCH@nictu.hscni.net

# Additional identifiers

# **EudraCT/CTIS** number

Nil known

#### IRAS number

293630

# ClinicalTrials.gov number

Nil known

# Secondary identifying numbers

IRAS 293630, NIHR130454, CPMS 51165

# Study information

#### Scientific Title

Is the mechanism of action of hypertonic saline and/or carbocisteine in the treatment of patients with acute respiratory failure due to an increase in mucus hydration?

# Acronym

MARCH EME

# **Study objectives**

Treatment of critically ill patients with ARF with carbocisteine, hypertonic saline, or both, will lead to increased mucus hydration and changes in sputum viscosity and elasticity.

# Ethics approval required

Old ethics approval format

# Ethics approval(s)

Approved 29/06/2022, Faculty of Medicine, Health & Life Sciences (MHLS) Research Ethics Committee (REC) (Research & Enterprise Directorate, Queen's University Belfast, 63 University Road, Belfast, BT7 1NN, United Kingdom; +44 (0)28 9097 2529; facultyrecmhls@qub.ac.uk), ref: MHLS 22 79

# Study design

Multi-centre, exploratory mechanistic, observational cohort study embedded within the MARCH trial

#### Primary study design

Observational

# Secondary study design

Cohort study

#### Study setting(s)

Hospital

## Study type(s)

Other

#### Participant information sheet

Not available in web format, please use contact details to request a MARCH trial participant information sheet as the samples are collected via this study.

# Health condition(s) or problem(s) studied

Critically ill patients with acute respiratory failure (ARF)

#### **Interventions**

Sputum samples will be collected from patients recruited to the MARCH clinical trial (https://www.fundingawards.nihr.ac.uk/award/NIHR130454).

The proposed study will involve collection of sputum samples from patients randomised to each of the four trial groups:

- 1. Carbocisteine plus usual airway clearance management
- 2. Hypertonic saline plus usual airway clearance management
- 3. Carbocisteine and hypertonic saline plus usual airway clearance management
- 4. Usual airway clearance management alone

Sputum samples will be collected at 3 time-points during the study; baseline (Day 0) (at randomisation), Day 3, and Day 7. The solids concentration of mucus will be measured and dynamic rheology measurements will be recorded including G' and G" of samples from which the Tc value will be obtained. Inflammatory mediators will be measured by ELISA.

# Intervention Type

Other

#### Primary outcome measure

Percentage mucus solid content (dry-to-wet weight ratio) of sputum measured from sputum samples collected at baseline and 3 days

# Secondary outcome measures

- 1. Percentage mucus solid content (dry-to-wet weight ratio) of sputum measured from sputum samples collected at baseline and 7 days
- 2. Sputum elasticity (G') and viscosity (G'') (and yield stress, Tc) measured using dynamic rheology of sputum samples collected at baseline and 3 days
- 3. Sputum IL-6, IL-8, and 8-isoprostane levels measured by ELISA of sputum samples collected at baseline and 3 days
- 4. Sputum elasticity (G') and viscosity (G'') (and yield stress, Tc) measured using dynamic rheology of sputum samples collected at baseline and 7 days
- 5. Sputum IL-6, IL-8, and 8-isoprostane levels measured by ELISA of sputum samples collected at baseline and 7 days

## Overall study start date

01/05/2022

#### Completion date

30/11/2025

# Eligibility

#### Key inclusion criteria

- 1. Participating in the MARCH trial
- 2. Provide consent to have biological samples (airway secretions) collected and analysed and the data generated from these analyses to be used

# Participant type(s)

**Patient** 

# Age group

Adult

#### Lower age limit

16 Years

#### Sex

Both

# Target number of participants

360 patients

#### Key exclusion criteria

- 1. Suspected/confirmed COVID disease
- 2. Do not meet the MARCH trial inclusion criteria

#### Date of first enrolment

01/08/2022

#### Date of final enrolment

30/04/2025

# **Locations**

# Countries of recruitment

England

Northern Ireland

Scotland

United Kingdom

Wales

# Study participating centre Royal Victoria Hospital

274 Grosvenor Road Belfast United Kingdom BT12 6BA

# Study participating centre Bristol Royal Infirmary

Marlborough Street Bristol United Kingdom BS2 8HW

# Study participating centre Sunderland Royal Hospital

Kayll Road Sunderland United Kingdom SR4 7TP

# Study participating centre Belfast City Hospital

51 Lisburn Rd Belfast United Kingdom BT9 7AB

# Study participating centre Royal Infirmary of Edinburgh at Little France

51 Little France Crescent Old Dalkeith Road Edinburgh Lothian United Kingdom EH16 4SA

# Study participating centre Royal Liverpool University Hospital NHS Trust, Royal Liverpool University Hospital, Prescot Street, Liverpool, L7 8XP

Prescot Street Liverpool United Kingdom L7 8XP

# Study participating centre Royal Cornwall Hospitals NHS Trust

Royal Cornwall Hospital Treliske Truro United Kingdom TR1 3LJ

# Study participating centre Mersey Care NHS Trust at Aintree Hospital

C/o University Hospital Aintree Fazakerley Hospital Lower Lane Liverpool United Kingdom L9 7AL

# Study participating centre Manchester Royal Royal Infirmary

Cobbett House Oxford Road Manchester United Kingdom M13 9WL

# Study participating centre Wythenshawe Hospital

Southmoor Road Wythenshawe Manchester United Kingdom M23 9LT

# Study participating centre Western General Hospital

Crewe Road South Edinburgh Lothian United Kingdom EH4 2XU

# Study participating centre Royal Stoke University Hospital

Newcastle Road Stoke-on-trent United Kingdom ST4 6QG

# Study participating centre Watford General Hospital

60 Vicarage Road Watford United Kingdom WD18 0HB

# Study participating centre The Royal Oldham Hospital

Rochdale Road Oldham United Kingdom OL1 2JH

# Study participating centre University Hospital (coventry) Clifford Bridge Road

Coventry United Kingdom CV2 2DX

# Study participating centre Southmead Hospital

Southmead Road Westbury-on-trym Bristol United Kingdom BS10 5NB

# Study participating centre John Radcliffe Hospital

Headley Way Headington Oxford United Kingdom OX3 9DU

# Study participating centre Glasgow Royal Infirmary

84 Castle Street Glasgow United Kingdom G4 0SF

# Study participating centre Preston Acute Hospitals NHS Trust

Royal Preston Hospital Sharoe Green Lane North Fulwood Preston United Kingdom PR2 9HT

# Study participating centre Royal Devon & Exeter Foundation Hospital

Barrack Road

Exeter United Kingdom EX2 5DW

# Study participating centre Morriston Hospital

Heol Maes Eglwys Cwmrhydyceirw Swansea United Kingdom SA6 6NL

# Study participating centre Queen Elizabeth University Hospital

1345 Govan Road Glasgow United Kingdom G51 4TF

# Study participating centre Derriford Hospital

Derriford Road Crownhill Plymouth United Kingdom PL6 8DH

# Study participating centre William Harvey Hospital

Kennington Road Willesborough Ashford United Kingdom TN24 0LZ

# Study participating centre Northern General Hospital

Northern General Hospital NHS Trust C Floor, Huntsmnan Building Herries Road Sheffield United Kingdom S5 7AU

# Study participating centre Aberdeen Royal Infirmary

Foresterhill Road Aberdeen United Kingdom AB25 2ZN

# Study participating centre University College London Hospitals NHS Foundation Trust

250 Euston Road London United Kingdom NW1 2PG

# Study participating centre Pinderfields General Hospital

Aberford Road Wakefield United Kingdom WF1 4DG

# Study participating centre Sandwell District General Hospital

Lyndon West Bromwich United Kingdom B71 4HJ

# Study participating centre Northern Devon Healthcare NHS Trust

North Devon District Hospital Raleigh Park Barnstaple United Kingdom EX31 4JB

# Study participating centre University Hospital Monklands

Monkscourt Avenue Airdrie United Kingdom ML6 0JS

# Sponsor information

#### Organisation

Queen's University Belfast

#### Sponsor details

Research, Governance, Ethics and Integrity Queen's University Belfast 63 University Road Belfast Northern Ireland United Kingdom BT7 1NN +44 (0)28 90245133 researchgovernance@qub.ac.uk

# Sponsor type

University/education

#### Website

http://www.qub.ac.uk/

#### ROR

https://ror.org/00hswnk62

# Funder(s)

#### Funder type

Government

#### **Funder Name**

National Institute for Health Research

#### Alternative Name(s)

National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

#### **Funding Body Type**

Government organisation

## **Funding Body Subtype**

National government

#### Location

**United Kingdom** 

#### **Funder Name**

Health Technology Assessment Programme

#### Alternative Name(s)

NIHR Health Technology Assessment Programme, HTA

#### Funding Body Type

Government organisation

### **Funding Body Subtype**

National government

#### Location

United Kingdom

#### **Funder Name**

Efficacy and Mechanism Evaluation Programme

#### Alternative Name(s)

NIHR Efficacy and Mechanism Evaluation Programme, EME

#### **Funding Body Type**

Government organisation

#### Funding Body Subtype

National government

#### Location

United Kingdom

# **Results and Publications**

# Publication and dissemination plan

Planned publication of results in a high-impact peer-reviewed journal. Planned publication of protocol in a leading peer-reviewed respiratory journal.

# Intention to publish date

30/11/2026

# Individual participant data (IPD) sharing plan

The datasets generated and/or analysed during the current study will be available upon request following publication of the primary and secondary outcomes. Formal requests for data should be made in writing to Prof Cliff Taggart (Chief Investigator) via the Trial Manager (Naomi Dickson; MARCH@nictu.hscni.net) at the Northern Ireland Clinical Trials Unit (NICTU) and will be reviewed on a case by case basis in collaboration with the Sponsor.

## IPD sharing plan summary

Available on request