ISRCTN10086050 https://doi.org/10.1186/ISRCTN10086050

# 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**
01/07/2022

**Recruitment status**
No longer recruiting

**Registration date**
04/07/2022

**Overall study status**
Completed

**Last Edited**
09/04/2025

**Condition category**
Respiratory

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[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

# Contact information

### Type(s)
Principal investigator

### Contact name
Dr Cliff Taggart

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### Type(s)

Scientific

### Contact name
Dr Naomi Dickson

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## Additional identifiers

### Clinical Trials Information System (CTIS)
Nil known

### Integrated Research Application System (IRAS)
293630

### ClinicalTrials.gov (NCT)
Nil known

### Protocol serial number
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

### Study type(s)
Other

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

### Key secondary outcome(s))
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

### 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

### Healthy volunteers allowed
No

### Age group
Adult

### Lower age limit
16 years

### Sex
All

### 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
United Kingdom

England

Northern Ireland

Scotland

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

**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, Health Technology Assessment (HTA), 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, Efficacy and Mechanism Evaluation (EME), EME

**Funding Body Type**
Government organisation

**Funding Body Subtype**

National government

### Location
United Kingdom

# Results and Publications

### 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

### Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Participant information sheet | Participant information sheet | 11/11/2025 | 11/11/2025 | No | Yes |
| Study website | Study website | 11/11/2025 | 11/11/2025 | No | Yes |