The MARCH Trial

Mucoactives in Acute Respiratory failure: Carbocisteine and Hypertonic saline

Mucoactive drugs for acute respiratory failure: A 2x2 factorial, randomised, controlled, open-label, Phase 3, pragmatic, clinical and cost effectiveness trial with internal pilot

Protocol Number	20131DMcA-AS
Protocol Version *(See Summary of Key Changes Form for Differences From Last Version)*	V3.0 Final
Protocol Date	06/10/2023
Protocol Amendment Number	2
EudraCT Number	2021-003763-94
ISRCTN	ISRCTN17683568
SWAT ISRCTN	ISRCTN16675252
Ethics Reference Number	21/YH/0234
Sources of Monetary or Material Support	
Funder	National Institute for Health and Care Research Health Technology Assessment Programme; NIHR130454 www.fundingawards.nihr.ac.uk/award/NIHR130454
Sponsor Details	
Sponsor	Belfast Health and Social Care Trust The Royal Hospitals Grosvenor Road Belfast, BT12 6BA Northern Ireland
Chief Investigator	Professor Danny McAuley Wellcome-Wolfson Institute for Experimental Medicine Queen's University Belfast 97 Lisburn Road Belfast, BT9 7BL Northern Ireland
Co-Chief Investigator	Dr Bronwen Connolly Wellcome-Wolfson Institute for Experimental Medicine Queen's University Belfast 97 Lisburn Road Belfast, BT9 7BL Northern Ireland

PROTOCOL AUTHORISATION

Protocol Title	Mucoactives in Acute Respiratory failure: Carbocisteine and Hypertonic saline
Protocol Acronym (if applicable)	MARCH
Protocol Number	20131DMcA-AS
Protocol Version Number/Date	V3.0 Final, 06/10/2023
Protocol Amendments	V1.0-V2.0 • Addition of Carbocisteine 750 mg/10 ml oral solution in sachets as a Study Investigational Medicinal Product (Section 9, page 28). • Removal of Prisoners from the trial's exclusion criteria and update to bullet numbering on pages 10, 24 and 34. • Removal of 'allocation concealed' on pages 9 and 19. • Addition of Trial Identifiers on page 1 – ISRCTN; SWAT ISRCTN; and Ethics Reference Number. V2.0-V3.0 (the following points are not strictly changes, but have been included with the intention of ensuring precision of existing phrasing) • Removal of reference to INVOLVE open access database as no longer in existence (Section 3.3.4) • Confirmation that a blood pregnancy test (in addition to urine) is also acceptable to exclude pregnant patients from participation (Section 7.3.2) • Minor clarifications to timing of outcome measurements (Section 10.3) • Removal of wording that suggests only doctors and nurses may obtain informed consent (Section 11.2) • Confirmation that a Professional Legal Representative must be a doctor of consultant level (Section 11.2.2) • Clarification that the safety reporting period for the study ends upon termination of the mucoactive (Section 16.1) • Update to Professor Danny McAuley's role at the National Institute for Health and Care Research (NIHR) (Section 18.9) • Clarification of wording throughout related to start of unassisted breathing on Day 27 or 28

A review of the protocol has been completed and is understood and approved by the following:

Danny McAuley	See attached email	_____ / _____ / _____
Chief Investigator	Signature	Date
Bronwen Connolly	See attached email	_____ / _____ / _____
Co-Chief Investigator	Signature	Date
Christina Campbell	See attached email	_____ / _____ / _____
Statistician	Signature	Date

TABLE OF CONTENTS

LIST OF ABBREVIATIONS **8**

1 STUDY SUMMARY **10**

2 STUDY TEAM **12**

3 ROLES AND RESPONSIBILITIES **14**

3.1 Funder *14*

3.2 Sponsor *14*

3.3 Trial Oversight Committees *14*

3.3.1 Trial Management Group (TMG) 14

3.3.2 Trial Steering Committee (TSC) 14

3.3.3 Data Monitoring and Ethics Committee 15

3.3.4 User Involvement or Any Other Relevant Committees 15

4 BACKGROUND AND RATIONALE **16**

4.1 Mucoactives for Acute Respiratory Failure *16*

4.2 Rationale for the Study *16*

4.3 Rationale for the Intervention *17*

4.3.1 Safety Considerations of the Intervention 17

4.4 Rationale for the Comparator *18*

5 STUDY AIM AND OBJECTIVES **19**

5.1 Research Hypothesis *19*

5.2 Study Aim *19*

5.3 Study Objectives *19*

5.3.1 Primary Objective 19

5.3.2 Secondary Objectives 19

6 STUDY DESIGN **20**

6.1 Study Design *20*

6.2 Internal Pilot *20*

6.3 Study Schematic Diagram *22*

6.4 Study Timelines *23*

6.5 End of Study *23*

7 PARTICIPANTS **24**

7.1 Study Setting *24*

7.2 Study Population *24*

7.3 Eligibility Criteria 24
7.3.1 Inclusion Criteria 24
7.3.2 Exclusion Criteria 25
7.3.3 Co-enrolment Guidelines 25

8 INTERVENTIONS 26

8.1 Study Interventions and Comparator 26

8.2 Assignment of Intervention 28
8.2.1 Sequence Generation 28
8.2.2 Allocation Concealment Mechanism 28
8.2.3 Allocation Implementation 28
8.2.4 Blinding 28

9 STUDY INVESTIGATIONAL MEDICINAL PRODUCTS 29

9.1 Study Mucoactive Supply 29

9.2 Study Mucoactive Storage 29

9.3 Study Mucoactive Prescribing, Labelling and Dispensing 29

9.4 Study Mucoactive Accountability 29

9.5 Study Mucoactive Administration 29

9.6 Study Mucoactive Termination Criteria 30

9.7 Study Mucoactive Compliance 30

9.8 Concomitant Care 30
9.8.1 Respiratory Physiotherapy Airway Clearance Management 30

10 OUTCOMES and OUTCOME MEASURES 31

10.1 Primary Outcome 31

10.2 Secondary Outcomes 31

10.3 Outcome Measurement 31

11 SCREENING, CONSENT and RECRUITMENT 34

11.1 Screening Procedure and Screening Logs 34

11.2 Informed Consent Procedure 35
11.2.1 Personal Legal Representative 35
11.2.2 Professional Legal Representative 35
11.2.3 Retrospective Patient Consent 36

11.3 Withdrawal of Consent 36

11.4 GP Contact 36

12 SCHEDULE of ASSESSMENTS 37

12.1 Participant Assessments 37

12.2 Participant Follow-Up 38

12.2.1 Study Instruments for Participant Follow-Up 39
12.3 Process Evaluation 39
12.4 Mechanistic Studies 39
12.4.1 Sputum Samples 40
12.4.2 Blood Sampling 40
12.5 Long-Term Follow-Up 40
13 DATA COLLECTION and MANAGEMENT 41
13.1 Data Collection 41
13.2 Data Quality 41
13.3 Data Management 41
14 STATISTICAL CONSIDERATIONS 42
14.1 Sample Size 42
14.2 Data Analysis 42
14.2.1 Analysis Population 42
14.2.2 Statistical Methods 42
14.3 Health Economics Evaluation 43
14.4 Additional Analysis 44
14.5 Missing Data 44
15 STUDY WITHIN A TRIAL 45
16 PHARMACOVIGILANCE 47
16.1 Adverse Event (AE) / Serious Adverse Event (SAE) Reporting 47
16.2 Suspected Unexpected Serious Adverse Reaction (SUSAR) 47
16.3 Definition of Adverse Events 47
16.4 Assessment of Causality 49
16.5 Assessment of Severity 49
16.6 Assessment of Seriousness 50
16.7 Assessment of Expectedness 50
16.8 Recording and Reporting Urgent Safety Measures 50
17 DATA MONITORING 51
17.1 Data Access 51
17.2 Monitoring Arrangements 51
18 REGULATIONS, ETHICS AND GOVERNANCE 52
18.1 Regulatory and Ethical Approvals 52
18.2 Ethical Considerations 52

18.3 Protocol Compliance 52
18.4 Protocol Amendments 53
18.5 Good Clinical Practice 53
18.6 Indemnity 53
18.7 Patient Confidentiality 53
18.8 Record Retention 53
18.9 Competing Interests 53
19 DISSEMINATION/PUBLICATIONS 54
19.1 Publication Policy 54
19.2 Authorship Policy 54
19.3 Data Access/Sharing 54
20 REFERENCES 55

LIST OF ABBREVIATIONS

Abbreviation/ Acronym	Full Wording
AE	Adverse Event
APACHE II	Acute Physiology and Chronic Health Evaluation II
AR	Adverse Reaction
ARF	Acute Respiratory Failure
BHSCT	Belfast Health and Social Care Trust
CHI	Community Health Index
CI	Chief Investigator
CMP	Case Mix Programme
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
EQ-5D-5L	EuroQol-5 Dimension-5 Level
GCP	Good Clinical Practice
HTA	Health Technology Assessment
HRA	Health Research Authority
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
ICH	International Conference of Harmonisation
ICNARC	Intensive Care National Audit & Research Centre
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
MHRA	Medicine and Healthcare Products Regulatory Agency
NICTU	Northern Ireland Clinical Trials Unit
NIHR	National Institute for Health and Care Research
PerLR	Personal Legal Representative
PI	Principal Investigator
PIL	Product Instructions for Use Leaflet
PPIE	Patient and Public Involvement and Engagement
ProfLR	Professional Legal Representative
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
R&D	Research & Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Procedure

SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWAT	Study Within a Trial
TMG	Trial Management Group
TSC	Trial Steering Committee

1 STUDY SUMMARY

Scientific title	Mucoactives in Acute Respiratory failure: Carbocisteine and Hypertonic saline: MARCH
Public title	A trial of common mucoactives used to help airway clearance in patients with respiratory failure requiring mechanical ventilation
Health condition(s) or problem(s) studied	Acute respiratory failure
Study Design	A 2x2 factorial, randomised, controlled, open-label, Phase 3, pragmatic, clinical and cost effectiveness trial with internal pilot, to determine whether mucoactives (carbocisteine and hypertonic saline) in critically ill patients with acute respiratory failure (ARF) reduce duration of mechanical ventilation
Study Aim and Objectives	**Aim** To determine whether use of mucoactives in critically ill patients with acute respiratory failure improves outcomes and is cost effective, compared to usual airway clearance management **Objectives** To conduct a large, UK, multi-centre, pragmatic, randomised controlled trial to: 1. Determine the clinical effectiveness of two mucoactives (carbocisteine or hypertonic saline), or a combination of both, on duration of mechanical ventilation (primary outcome), and a range of secondary clinical and safety outcomes 2. Estimate, in an integrated economic evaluation, the cost-effectiveness of the mucoactives
Study Interventions and Comparator	1. Carbocisteine: delivered enterally plus usual airway clearance management 2. Hypertonic saline: delivered via airway nebulisation, plus usual airway clearance management 3. Combination of carbocisteine and hypertonic saline plus usual airway clearance management 4. Usual airway clearance management alone (including suctioning, heated humidification, respiratory physiotherapy; isotonic saline may also be used depending on clinician preference)
Primary Outcome	**Duration of mechanical ventilation** Time from randomisation until first successful unassisted breathing (defined as maintaining unassisted breathing at 48 hours) or death
Secondary Outcomes	In hospital Extubation; Re-intubation; Duration of stay in intensive care unit and in hospital from randomisation; All-cause mortality; Respiratory physiotherapy input; Antibiotic usage; Safety At 60 days Health-related quality of life; All-cause mortality

	At 6 months Health-related quality of life; All-cause mortality; Health service use since hospital discharge
Key Inclusion and Exclusion Criteria	**Inclusion criteria** 1. Aged ≥16 years 2. An acute and potentially reversible cause of ARF as determined by the treating physician 3. Receiving invasive mechanical ventilation via endotracheal tube or tracheostomy 4. Anticipated to remain on invasive mechanical ventilation for at least 48 hours 5. Presence of secretions that are difficult to clear with usual airway clearance management (as assessed by the treating clinical team) **Exclusion criteria** 1. Pre-existing chronic respiratory condition requiring routine use of any mucoactive 2. Mucoactive 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
Countries of Recruitment	England, Northern Ireland, Wales, Scotland
Study Setting	Intensive care units
Target Sample Size	1956
Study Duration	51 months

Funder Statement

This study/project is funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme (Project Reference NIHR 130454). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

2 STUDY TEAM

Chief Investigator	**Professor Danny McAuley** Wellcome-Wolfson Institute for Experimental Medicine Queen's University Belfast 97 Lisburn Road Belfast, BT9 7BL Northern Ireland Email: d.f.mcauley@qub.ac.uk
Co-Chief Investigator	**Dr Bronwen Connolly** Wellcome-Wolfson Institute for Experimental Medicine Queen's University Belfast 97 Lisburn Road Belfast, BT9 7BL Northern Ireland Email: b.connolly@qub.ac.uk
Co-Investigators	**Professor Bronagh Blackwood** Queen's University Belfast
	Mr Mark Borthwick Oxford University Hospitals NHS Foundation Trust
	Professor Judy Bradley Queen's University Belfast
	Dr Marc Chikhani University of Nottingham
	Professor Mike Clarke Queen's University Belfast
	Professor Paul Dark University of Manchester
	Professor Ranjit Lall University of Warwick
	Mrs Cliona McDowell Northern Ireland Clinical Trials Unit
	Professor Cecilia O'Kane Queen's University Belfast
	Dr Brenda O'Neill University of Ulster
	Professor Gavin Perkins University of Warwick
	Dr Murali Shyamsundar Queen's University Belfast
	Mr Gordon Sturmey Patient Representative
	Professor Cliff Taggart Queen's University Belfast
	Mr John Warburton University Hospitals Bristol NHS Foundation Trust
	Mr Barry Williams Patient Representative

Statistician	**Ms Christina Campbell** Northern Ireland Clinical Trials Unit
Health Economist	**Dr Ashley Agus** Northern Ireland Clinical Trials Unit
Clinical Trials Unit	**Northern Ireland Clinical Trials Unit (NICTU)** 7 Lennoxvale Belfast, BT9 5BY Northern Ireland
Sponsor	**Belfast Health and Social Care Trust (BHSCT)** **Alison Murphy** Research Manager Research Office 2nd Floor King Edward Building The Royal Hospitals Grosvenor Road Belfast, BT12 6BA Northern Ireland Email: alison.murphy@belfasttrust.hscni.net
Sponsor Pharmacist	**Margaret McFarland** Lead Clinical Trials Pharmacist The Royal Hospitals Grosvenor Road Belfast, BT12 6BA Northern Ireland Email: margaret.mcfarland@belfasttrust.hscni.net
Sponsor's Reference	20131DMcA-AS
Contact for public queries	**Clinical Trial Manager** Northern Ireland Clinical Trials Unit (NICTU) 7 Lennoxvale Belfast, BT9 5BY Northern Ireland Email: MARCH@nictu.hscni.net
Contact for scientific queries	**Dr Bronwen Connolly** Wellcome-Wolfson Institute for Experimental Medicine Queen's University Belfast 97 Lisburn Road Belfast, BT9 7BL Northern Ireland Email: b.connolly@qub.ac.uk

3 ROLES AND RESPONSIBILITIES

3.1 Funder

The National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme is providing the research costs to the MARCH trial (Reference NIHR130454), as the result of a commissioned call (HTA 19/73). Further details can be found at www.fundingawards.nihr.ac.uk/award/NIHR130454, and the formal Funder Statement can be found in Section 1, Study Summary.

The funder has no role in the study design, data acquisition, analysis and interpretation, or manuscript preparation.

3.2 Sponsor

The Belfast Health and Social Care Trust (BHSCT) will act as Sponsor for the study and the Chief Investigator (CI) will take overall responsibility for the conduct of the trial. Separate agreements will be put in place between the Sponsor and each organisation undertaking Sponsor-delegated duties in relation to the management of the study. The Sponsor will have no role in the collection, analysis, and interpretation of data, writing of the report, and the decision to submit the report for publication.

3.3 Trial Oversight Committees

3.3.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be established and Chaired by the CI or Co-CI. It will comprise the CI and the Co-CI, representatives from the Clinical Trials Unit (CTU), and any other co-investigators who provide trial specific expertise as required at the time. The TMG will meet face to face or by teleconference on a monthly basis, and will communicate between times via telephone and email as needed. The roles and responsibilities of the TMG will be detailed in the TMG Charter. Meetings will be formally minuted and a list of actions recorded and stored in the Trial Master File (TMF). All day-to-day activity will be managed by the Trial Manager/Co-ordinators, in consultation with the CI and Co-CI as needed, providing a streamlined approach for handling enquiries regarding the trial and disseminating communications.

3.3.2 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be convened to provide oversight with respect to the conduct of the study on behalf of the Funder and Sponsor. An independent chair will lead the TSC, with at least 75% independent membership. The TSC will include the CI and Co-CI, two Patient and Public Involvement and Engagement (PPIE) representatives, and a group of experienced critical care clinicians and trialists. The TSC will meet at least annually, however as the Data Monitoring and Ethics Committee (DMEC) will meet to assess the accumulating data, the TSC may be convened to discuss issues and recommendations raised by the DMEC. Membership and roles of the TSC will be listed in the TSC Charter. The TSC, in the development of this protocol and throughout the trial, will take responsibility for monitoring and guiding overall progress, scientific standards, operational delivery and protecting the rights and safety of trial participants. Meetings will be formally minuted and stored in the TMF. On occasion, observers may be invited and in attendance at TSC meetings, such as the Sponsor or Funder representatives or the Trial Manager/Co-ordinator to provide input on behalf of the CTU.

3.3.3 Data Monitoring and Ethics Committee

An independent Data Monitoring and Ethics Committee (DMEC) will be convened, comprising at least two independent clinicians with experience in undertaking clinical trials, caring for critically ill patients, and an independent statistician. The DMEC's overarching responsibility is to safeguard the interests of 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 will meet to agree conduct and remit, and the roles and responsibilities of the DMEC will be detailed in the DMEC Charter to include: monitoring the data and making recommendations to the TSC on whether there are any ethical, safety, or other reasons why the trial should not continue; considering the need for any interim analysis; advising the TSC regarding the release of data and/or information; considering data emerging from other related studies; and making recommendations to stop the trial for benefit on the basis of an effect estimate that is likely to influence decisions about the use of the relevant therapy by clinicians outside of the trial.

The independent DMEC will meet approximately every 6 months and additional meetings can be convened in the event of any safety concerns. Separate records will be required for open and closed sessions with minutes made by the appropriate attending member of the trial team, which will be the NICTU Facilitator for the open session, and the Chair, another DMEC member, or the Trial Statistician, for the closed session. The DMEC Chair should approve any minutes or notes prior to circulation to the rest of the members. Meetings will be formally minuted and stored in the TMF.

Following recommendations from the DMEC, the TSC will decide what actions, if any, are required. It will be the responsibility of the TSC to inform the Sponsor if concerns exist about patient safety, following which the Sponsor will take appropriate action.

If a trial extension and/or funding is required above the level originally requested, the independent DMEC may be asked by the CI, TSC, Sponsor or Funder to provide advice and, where appropriate, information on the data gathered to date in a way that will not compromise the trial.

3.3.4 User Involvement or Any Other Relevant Committees

Patient and relative experience of critical illness will be taken into consideration when preparing patient information leaflets and consent forms. There will be two independent PPIE members on the TSC to ensure appropriate representation of, and sensitivity to, the views of patients and their families. In addition, the two PPIE co-applicants will be supported to convene a Patient & Family Advisory Group that will actively contribute to the design and content of all patient-facing materials throughout the course of the study. PPIE members' involvement will be supported, and related activities conducted in line with, NIHR guidance (https://www.nihr.ac.uk/documents/ppi-patient-and-public-involvement-resources-for-applicants-to-nihr-research-programmes/23437).

4 BACKGROUND AND RATIONALE

4.1 Mucoactives for Acute Respiratory Failure

Acute respiratory failure (ARF) accounts for the majority of patient admissions to the intensive care unit (ICU)[1-3] in the UK healthcare system[4]. Invasive mechanical ventilation is the cornerstone of treatment[2] but increases the risk of respiratory tract secretion retention due to altered secretion rheology and impaired mucociliary clearance[5]. Usual airway clearance management includes suctioning, humidification, use of isotonic saline, and respiratory physiotherapy techniques, and may be supplemented with use of mucoactives[6]. However, current use of mucoactives is empirical, common, and with wide variation in prescribing practice across ICUs and amongst clinicians, indicating considerable uncertainty about their effectiveness[7]. Typically, the major clinical feature prompting their use in patients with ARF is presence of thick, difficult to clear, secretions. Two of the most common agents are topical (nebulised/inhaled) hypertonic saline and systemic carbocisteine[7]. These mucoactives have distinct mechanisms of action, which may confer differing benefits to secretion clearance[8]. However, there is minimal evidence to support their effectiveness in UK practice[9]. Establishing evidence for the clinical- and cost-effectiveness of mucoactives in critical care will ensure that they are delivered to the most appropriate patients, where applicable, thus minimising the potential for harm and unnecessary expense.

In a recent systematic review investigating the clinical effectiveness of mucoactives in patients with ARF, the evidence base overall was found to be minimal, heterogenous and with a high-risk of bias[9]. However, it did show that N-acetylcysteine was ineffective, that there was inconsistent and low-quality evidence for the use of hypertonic saline, and that there was no evidence to support or refute the use of carbocisteine[9]. Previous systematic reviews have shown N-acetylcysteine to be widely investigated, but also with no evidence of effectiveness[10,11].

National UK surveys at both ICU- and clinician-level investigating the rationale for, and use of, mucoactives in ICUs[7], have reported that mucoactives are actively prescribed in 83% of ICUs, and at any given time, approximately 30% of patients receiving mechanical ventilation are prescribed at least one mucoactive agent. The most highly ranked indication for the use of mucoactives is 'thick secretions' based on clinical assessment, and the most commonly used (outwith topical isotonic saline considered to be part of usual airway clearance management should clinicians wish to use it[6]) are systemic carbocisteine and nebulised hypertonic saline (6-7% concentration)[7]. However, based on current evidence, this practice is empirical. One observational study has shown use of mucoactives (most commonly carbocisteine and hypertonic saline) to be unexpectedly associated with increased duration of mechanical ventilation and antibiotic use, although this is likely confounded by severity of illness[12]. Qualitative work, in the form of focus groups with senior critical care physiotherapists, has helped delineate the key features of usual practice with regards respiratory physiotherapy techniques for facilitating secretion clearance[6], which includes escalation to use of mucoactives in patients with thick, difficult to clear, secretions where usual airway clearance management is insufficient.

4.2 Rationale for the Study

Currently, critically ill patients with ARF who require mechanical ventilation may receive a mucoactive if they present with thick, difficult to clear, secretions. The decision on prescription (individual agent and dose) is empirical and at the discretion of the treating physician. It is usually based on local availability, personal preference, and prior experience. There are no national guidelines for direction and practice is widely variable and not evidence-based. This clinical trial will deliver definitive evidence on the clinical and cost effectiveness of two of the most common mucoactives in UK ICUs: carbocisteine and hypertonic saline[7,12]. The lack of existing large-scale randomised control trials (RCTs) comparing mucoactives to usual airway clearance management in ARF patients in the ICU, coupled

with their extensive empirical use, highlights the importance of this trial to provide the evidence base needed to inform patient care. This is an area of clinical practice where the UK critical care community has also highlighted their concerns regarding the absence of evidence to guide decision making[13,14], with 79% of surveyed respondents reporting the need for further research in this area and 87% of respondents being supportive of participating in a clinical trial[7].

Reducing uncertainty around the use of mucoactives will result in improved outcomes at patient and service level. If effective, they can be used more appropriately and efficiently. If ineffective, unnecessary, or potentially harmful, delivery can be prevented with associated cost savings. Escalating pressures on ICU bed occupancy (monthly average >80%[15]) makes it a priority to determine effective treatments to reduce the morbidity associated with mechanical ventilation and consequent burden on ICU resources. A 1-day reduction in duration of mechanical ventilation (time to first successful unassisted breathing or death[16]), as could be shown by this trial, across the approximately 50,000 patients admitted to ICU for ARF and receiving ventilation each year would result in significant patient, service, and economic benefits.

This trial is unique. As of July 2021, there are no other ongoing large trials listed in any clinical trial registry which are concurrently evaluating carbocisteine and hypertonic saline in the critically ill population with ARF.

4.3 Rationale for the Intervention

The interventions being assessed are mucoactives, specifically carbocisteine and hypertonic saline. Both mucoactives are available commercially in the UK, and widely used in UK ICUs[7], thus enhancing their adoption into routine clinical practice should the trial demonstrate effectiveness. The two mucoactives have distinct mechanisms of action, and selected doses for each are those indicated in the British National Formulary[17]. Both mucoactives are also currently under investigation in a separate HTA-funded trial (15/100/01) in non-cystic fibrosis bronchiectasis involving some of the co-investigators on the MARCH trial[18]. They are relatively easy to administer, have reliable supplies and long shelf lives, and are relatively inexpensive. The chosen study design will allow for comparison of each mucoactive individually, and in combination.

1. *Carbocisteine*
   Carbocisteine, an antioxidant, is a muco-regulatory agent that regulates mucus secretion through restoring the viscoelastic properties of mucus and an anti-inflammatory effect[8,19].

2. *Hypertonic saline*
   Hypertonic saline is an expectorant mucoactive, defined as one which elicits expulsion of mucus from the respiratory tract, typically via a cough mechanism[8], either orally, or via the endotracheal tube in mechanically ventilated patients.

4.3.1 Safety Considerations of the Intervention

The MARCH trial has been categorised as a Type A CTIMP meaning that the risk associated with the use of both carbocisteine and hypertonic saline in this study is considered to be no higher than the risk of standard medical care, and a risk-adapted approach to their management as investigational medicinal products has been adopted[20]. Both agents are being used within their licensed range of indications, dosage, and form (according to the Summary of Product Characteristics (SPC) for carbocisteine, and the Product Instructions for Use Leaflet (PIL) for hypertonic saline), and represent usual clinical practice within UK ICUs[6,7].

Summary of Product Characteristics for carbocisteine contraindicate its use in patients with active peptic ulceration. Current data from the MHRA Interactive Drug Analysis Profile for carbocisteine for the period spanning 1973 to 31st March 2021 indicate a total of 904 reactions from 485 suspected Adverse Drug Reaction (ADR) reports via the 'Yellow Card' scheme (available at https://info.mhra.gov.uk/drug-analysis-profiles/dap.html?drug=./UK_EXTERNAL/NONCOMBINED/UK_NON_000937251968.zip&agency=MHRA) . Of these 904 reactions, 10 (1.1%) were categorised as gastrointestinal ulceration and perforation (n=3 duodenal ulcer, n=2 duodenal ulcer haemorrhage, n=2 gastrointestinal ulcer haemorrhage, n=2 peptic ulcer, and n=1 duodenal ulcer perforation). However, adverse reactions are reported across all populations and are not specific to critically ill patients in the ICU. More importantly, there is no established causal relationship with carbocisteine (reported adverse reactions are not proven to be related to the drug in use).

For these reasons, whilst critically ill patients with active peptic ulceration will be excluded by the clinician from the MARCH trial where they believe that participation would not be in the best interests of the patient, all other patients remain potentially eligible. Although critically ill patients in the ICU are *at risk of* peptic ulceration, they will not be routinely excluded from the MARCH trial as gastric protection with proton pump inhibition or H2-receptor antagonists is well established and widespread in ICUs[21]. All trial patients will be closely monitored for development of symptoms of upper gastrointestinal bleeding, and occurrence of upper gastrointestinal bleeding will be captured as a safety outcome in the trial.

Furthermore, Summary of Product Characteristics for carbocisteine state that patients with rare hereditary problems of fructose or galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency should not take carbocisteine. In these instances, patients would be excluded from the trial where participation would not be in their best interests.

This risk-adapted approach reflects current clinical practice, ensures generalisability of trial findings, and maintains appropriate safety monitoring.

Product Instructions for Use Leaflets for hypertonic saline contraindicate its use in patients with a hypersensitive bronchial system, such as asthma. Where treating clinicians know this to be the case and therefore believe that participation would not be in the best interests of the patient, they will exclude these patients. However, all trial patients will be closely monitored for signs of bronchoconstriction, episodes of which requiring nebulised bronchodilators will be captured as a safety outcome.

4.4 Rationale for the Comparator

Carbocisteine and hypertonic saline will be delivered individually, and also in combination, in this trial. In each of these three randomised groups, mucoactive delivery will be in addition to usual airway clearance management. The fourth randomised group will receive usual airway clearance management alone, without mucoactives.

Usual airway clearance management includes airway suctioning, heated humidification, and respiratory physiotherapy. Humidification may be via active heated humidification devices, or passive heat and moisture exchangers[22]. Isotonic saline may also be used depending on clinician preference. Specifically, focus group work with senior critical care physiotherapists from across the UK has defined the key features of respiratory physiotherapy airway clearance practice, including in relation to use of mucoactives[6]. These key features include: a patient-centred approach; individualised assessment to determine clinical need; tailored treatment to specific patient presentation; use of both subjective and objective outcome measures to indicate effectiveness; and mucoactives used to treat thick, difficult to clear, secretions.

5 STUDY AIM AND OBJECTIVES

5.1 Research Hypothesis

Patients with ARF who are treated with mucoactives will have shorter duration of mechanical ventilation compared to patients receiving usual airway clearance management alone.

5.2 Study Aim

We aim to determine whether the use of mucoactives in critically ill patients with ARF improves clinical outcomes and is cost effective, compared to usual airway clearance management alone.

5.3 Study Objectives

5.3.1 Primary Objective

We will conduct a large, UK, multi-centre, pragmatic, randomised controlled trial to determine the clinical effectiveness (for duration of mechanical ventilation) of two mucoactives (carbocisteine or hypertonic saline), or a combination of both, when compared with usual airway clearance management.

5.3.2 Secondary Objectives

When compared with usual airway clearance management, to:

1. Determine the clinical effectiveness of carbocisteine or hypertonic saline, or a combination of both, on a range of secondary clinical and safety outcomes.

2. Estimate, in an integrated economic evaluation, the cost-effectiveness of these mucoactives.

6 STUDY DESIGN

6.1 Study Design

This is a 2x2 factorial, randomised, controlled, 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

6.2 Internal Pilot

An internal pilot study will run for the first 6 months of the trial to confirm recruitment and adherence assumptions that have contributed to study design and will inform the decision to progress to the main trial. This pilot will run from months 7-12 and will follow the processes described in the main study section below. Formal commencement of the pilot study will be defined as the date of the first site opening to recruitment. Pilot data will come from approximately 30 sites set up during this period (out of the minimum of 40 in total for the full trial) that will enrol approximately 200 patients; this figure is in keeping with recommendations for the sample size required for a pilot trial[23]. The pilot will be used to confirm screening, consent procedures, recruitment rates, and randomisation processes. Full details of the criteria for progression from the pilot to the full trial are given below.

If recruitment of 200 patients occurs more quickly than anticipated, progression to the full trial may occur earlier than 6 months at the discretion of the Funder. The main parameters of interest to guide the progress of the trial and inform the procedures to be used in its delivery, are recruitment rates. Participants enrolled in the pilot will be included in the analysis of the main study.

The recommended traffic light system will guide progression[24], with appropriate actions according to observed performance:

Recruitment rate:

1. Green: Progression without major modification if at least 75% of the recruitment target is reached, with analysis and resolution of any identified barriers to successful recruitment.
2. Amber: Progression with addition of further trial sites if between 40-74% of the target is reached, with detailed analysis of the screening log and protocol review.

3. Red: Progression unlikely if less than 40% of the recruitment target is reached. A rescue plan will be proposed and a decision on implementing this and progression will be made by the TSC in association with the NIHR HTA Secretariat.

Table 1 presents a detailed breakdown of the internal pilot recruitment outcomes. Total number of participants recruited is based on recruitment rate and number of sites open during the pilot period[24], with the intention of having 15 sites open in the first 3 months, and a further 15 sites open in the second 3 months.

Table 1. Detail of internal pilot phase during the first 6 months of recruitment

	Red	**Amber**	**Green**
% Threshold	<40	40-74	75-100
Recruitment rate/site/month	<0.6	0.6-<1.1	1.1-1.5
Number of sites opened	<12	12-22	23-30
Total number of participants recruited	<81	81-151	152-203

6.3 Study Schematic Diagram

The flow diagram depicting an overview of the trial is presented in Figure 1.

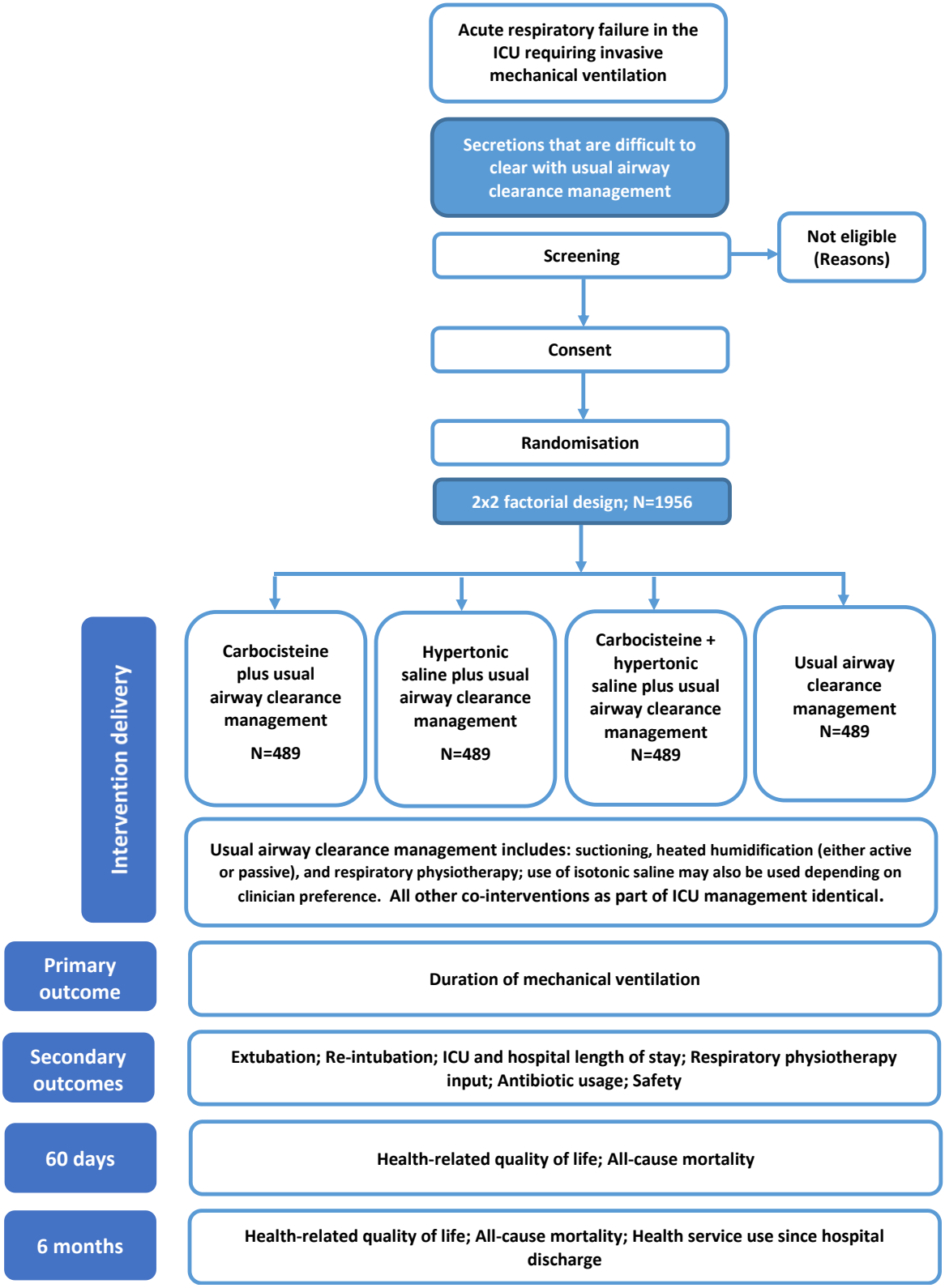

Figure 1. Flow diagram for MARCH trial

6.4 Study Timelines

The overall duration of the study is 51 months, including patient follow-up to 6 months after randomisation. Details of specific trial tasks and timelines are presented in Table 2.

Table 2. Study timeline and key tasks

Milestones	Pre Grant	Set Up		Internal Pilot		Main Trial										Follow Up		Analysis & Reporting
Year		Year 1				Year 2				Year 3				Year 4				Year 5
Quarter		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1
Trial Set Up	x	x	x															
Trial Staff Recruitment	x	x	x															
Protocol Development	x	x	x															
Site Identification	x	x	x															
REC Approval	x	x	x															
MHRA Approval	x	x	x															
HRA Approval	x	x	x															
R&D Approval			x															
Site Set Up and Training			x															
Internal Pilot Study				x	x													
Main Study						x	x	x	x	x	x	x	x	x	x			
Sites Initiated/Open to Recruitment				15	30	40	40	40	40	40	40	40	40	40	40			
Patient Recruitment/Month				22.5	45	60	60	60	60	60	60	60	60	60	60			
Patient Recruitment Cumulative				68	203	383	563	743	923	1103	1283	1463	1643	1823	1956			
Follow Up					x	x	x	x	x	x	x	x	x	x	x	x	x	
Data Collection/Cleaning				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Internal Pilot Review						x												
TMG Meetings	x	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
TSC Meetings		x				x		x				x		x				x
DMEC Meetings		x				x		x		x		x		x				x
PPIE Advisory Group		x				x		x				x						x
Site Closure																	x	x
Statistical Analysis																	x	x
Health Economics Analysis																	x	x
Reporting and Dissemination																		x
Collaborator Meeting																		x

Abbreviations: REC = Research Ethics Committee; MHRA = Medicines and Healthcare products Regulatory Agency; HRA = Health Research Authority; R&D = Research and Development; TMG = Trial Management Group; TSC = Trial Steering Committee; DMEC = Data Monitoring and Ethics Committee; PPIE = Patient and Public Involvement and Engagement

6.5 End of Study

The trial will end when all patients have completed their 6-month follow-up and database lock occurs. The trial will be stopped early if:

- Mandated by the Research Ethics Committee
- Mandated by the Medicines and Healthcare products Regulatory Agency
- Mandated by the Sponsor e.g. following recommendations from the DMEC
- Funding ceases

The REC that originally gave a favourable opinion of the trial and the MHRA who issued the clinical trial authorisation will be notified in writing if the trial has been concluded or stopped early.

7 PARTICIPANTS

7.1 Study Setting

Recruitment for the trial will take place in at least 40 adult, general ICUs, across all four UK nations, that are able to care for Level 3 critical care patients[25]. The ICUs must provide evidence that they have:

- A proven track record of participating in ICU research
- Access to the target population
- Local PI willing to lead the trial at that site, with local trial team including medical, physiotherapy, and pharmacy representatives
- Clinicians in the ICU who have clinical equipoise for use of mucoactives in this patient population and agree to maintain trial allocation in patients randomised by their colleagues

Staff must also comply with the protocol, standard operating procedures (SOPs), the principles of GCP (Good Clinical Practice), regulatory requirements, and be prepared to participate in appropriate trial training. A training package will be provided to sites who participate in the study. A list of study sites will be maintained in the TMF.

7.2 Study Population

Patients will be prospectively screened daily. All patients with ARF who meet the study inclusion criteria will be entered into a screening log. If the patient is not recruited the reason will be recorded. This information is required to ensure the study can be reported in keeping with CONSORT guidelines (www.consort-statement.org).

7.3 Eligibility Criteria

Patients will be assessed using the inclusion and exclusion criteria set out below. Eligibility to participate in the trial will be confirmed by a physician who is named on the Delegation Log. The medical care given to, and medical decisions made on behalf of, trial participants will be the responsibility of an appropriately qualified treating physician.

Patients will be eligible to participate in the study in accordance with the following criteria:

7.3.1 Inclusion Criteria

1. Aged ≥16 years
2. An acute and potentially reversible cause of ARF as determined by the treating physician
3. Receiving invasive mechanical ventilation via endotracheal tube or tracheostomy
4. Anticipated to remain on invasive mechanical ventilation for at least 48 hours
5. Presence of secretions that are difficult to clear with usual airway clearance management (as assessed by the treating clinical team)

7.3.2 Exclusion Criteria

1. Pre-existing chronic respiratory condition receiving routine use of any mucoactive
2. Mucoactive treatment started more than 24 hours prior to 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 physician believes that participation in the trial would not be in the best interests of the patient

Our eligibility criteria will allow enrolment of a broad and generalisable population of critically ill patients who may benefit from the therapeutic intervention, while excluding patients who may be more likely to experience an adverse reaction. Specifically, we will exclude patients with chronic respiratory disease who are already receiving mucoactive therapy because this may modify their response to the trial mucoactives. Furthermore, withholding existing treatment (including mucoactives) that had been deemed clinically beneficial by a previous clinician, would be unethical (Criterion 1). Likewise, patients who commenced mucoactive therapy more than 1 day earlier may demonstrate a modified response to receiving either of the trial mucoactives (Criterion 2). Patients with known adverse reactions to the trial mucoactives, or where the treating clinician has concern around appropriateness to enrol, are excluded on the grounds of safety (Criterion 3 and 9). Criterion 4 will exclude patients known to be unlikely to survive.

Criterion 5 is consistent with recommendations to avoid carbocisteine in the first trimester of pregnancy[17]. A pregnancy test, either blood or urine, will be performed prior to enrolment in females with child-bearing potential (aged 15-55 years) and patients who are pregnant will be excluded. Given that the population being recruited is critically ill the need for contraception advice is not required, and the study mucoactives will cease on discharge from the ICU thereby limiting any potential exposure to the mucoactives thereafter.

Criterion 6 will exclude patients where previous exposure to critical illness and invasive mechanical ventilation, as well as potential exposure to receiving one of the interventional mucoactives, may modify response to either of the mucoactives under investigation. Patients will not be enrolled without consent in place (Criterion 7).

7.3.3 Co-enrolment Guidelines

Patients in the MARCH trial may be eligible for co-enrolment in other studies, and this will be decided on a case-by-case basis by the Trial Management Group, in keeping with standard UK national approaches to co-enrolment in critical care research[26].

The CTU should be informed if co-enrolment is being considered, co-enrolment agreements (where applicable) should be stored in the TMF, and details of co-enrolment with studies should be documented in the Case Report Form (CRF).

8 INTERVENTIONS

8.1 Study Interventions and Comparator

This study has been categorised as a Type A CTIMP, which means that the risk associated with the interventions is no higher than the risk of standard medical care, and has been submitted to the MHRA for approval under their notification scheme.

Intervention 1:	Carbocisteine: 750 mg three times daily, for up to 28 days, delivered systemically, plus usual airway clearance management. (Where unassisted breathing begins 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 unassisted breathing begins 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

Table 3 presents the detailed study intervention according to the TIDieR framework[27].

Table 3. 'TIDieR' summary of study intervention

TIDieR item number*	Item descriptor	Detail
1	Brief name	Mucoactives for Acute Respiratory failure: Carbocisteine and Hypertonic saline (MARCH)
2	Why	Mucoactives such as carbocisteine and hypertonic saline may improve management of secretions that are difficult to clear with usual airway clearance management, which is a common complication of mechanical ventilation in critically ill patients with ARF
3	What materials	Mucoactives investigated will be carbocisteine and hypertonic saline, delivered individually and in combination
4	What procedures	1. Carbocisteine: 750 mg three times daily, for up to 28 days (or up to 29 or 30 days for patients who commence unassisted breathing on Day 27 or Day 28 respectively), delivered systemically via the enteral feeding tube, or orally, plus usual airway clearance management 2. Hypertonic saline: 4 ml, 6 or 7% concentration, delivered via nebulisation, four times daily, for up to 28 days (or up to 29 or 30 days for patients who commence unassisted breathing on Day 27 or Day 28 respectively), plus usual airway clearance management 3. Carbocisteine and hypertonic saline (as described in 1. and 2.), plus usual airway clearance management 4. Usual airway clearance management 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
5	Who provides	Mucoactives prescribed by attending ICU physician and delivered by ICU nurses
6	How delivered	1. Carbocisteine: delivered systemically 2. Hypertonic saline: delivered via nebulisation
7	Where delivered	Participating general adult ICUs
8	When and how much	Commenced when patients have secretions that are difficult to clear with usual airway clearance management (as assessed by the treating clinical team). Continued for up to 28 days after randomisation (or up to 29 or 30 days for patients who commence unassisted breathing on Day 27 or Day 28 respectively), or until any other reason for discontinuation occurs as defined in the protocol
9	Tailoring	No individual tailoring planned
11	How well	Protocol fidelity will be assessed through data collection on mucoactive delivery, and reasons for non-delivery

*TIDieR items 10 and 12 are not applicable *a priori*

8.2 Assignment of Intervention

8.2.1 Sequence Generation

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.

8.2.2 Allocation Concealment Mechanism

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.

8.2.3 Allocation Implementation

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.

8.2.4 Blinding

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[28]. 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[29]. 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.

Any possible impact of loss of blinding may be explored in a process evaluation.

9 STUDY INVESTIGATIONAL MEDICINAL PRODUCTS

9.1 Study Mucoactive Supply

The following are regarded as investigational medicinal products (IMP) for the purposes of this study:

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

Both carbocisteine and hypertonic saline are commercially available, will be sourced by local site pharmacies, and formulation (for carbocisteine) or concentration (for hypertonic saline) will be as per normal local practices.

9.2 Study Mucoactive Storage

Study mucoactives will be stored in accordance with manufacturer recommendations and local site practice.

9.3 Study Mucoactive Prescribing, Labelling and Dispensing

When a patient is recruited an authorised member of the research team will contact the randomisation service to obtain the unique Participant Study Number and the treatment allocation assigned to the participant. Study mucoactives will be prescribed and dispensed in accordance with usual local site prescription practice. There will be no additional labelling outside the usual practice at local sites. Communication will be given between the research and clinical teams as to which arm of the trial a patient has been randomised to, and patient enrolment into the trial and treatment allocation will be recorded in the clinical notes.

9.4 Study Mucoactive Accountability

There will be no additional records of accountability for supply, administration or destruction of study mucoactives outside the standard clinical practice for these products at the local hospital site.

9.5 Study Mucoactive Administration

The first dose of study mucoactive will be administered as soon as possible, ideally within 4 hours of randomisation, albeit if this does not occur it will not be a protocol deviation. Subsequent doses will be given as per locally determined scheduled prescription. If for any reason a dose is not administered at the intended time, it may be administered subsequently but not within 1 hour of the next intended dose. Section 8.1 outlines the details of the doses of study mucoactives for each study group. The intended duration of treatment with study mucoactives will be up to and including Day 28 (or the primary outcome is reached), or ICU discharge, or death, whichever comes first. Patients should receive study mucoactives for 48 hours post commencement of unassisted breathing until the primary outcome of duration of mechanical ventilation (first successful unassisted breathing) is reached. NB Where unassisted breathing begins on Day 27 or Day 28, mucoactives should continue to be administered until Day 29 or Day 30 respectively. Additional termination criteria for the study mucoactives are listed below in Section 9.6. A patient achieving their first successful unassisted breathing (which marks the primary outcome of duration of mechanical ventilation) will have completed their intervention period in the trial. Continuation of any study mucoactive after this point will be at the discretion of the treating clinical team and should be clearly documented.

9.6 Study Mucoactive Termination Criteria

Study mucoactives (whether carbocisteine, or hypertonic saline, or both) will be continued until the first of the following:

1. 28 days elapse since randomisation
2. First successful unassisted breathing
3. Study mucoactive-related serious adverse event
4. Discharge from ICU
5. Death or discontinuation of active medical treatment
6. Request from Legal Representative or patient to withdraw from the trial
7. Decision from the attending ICU physician that the study mucoactive should be discontinued on safety grounds

The reason for discontinuation of treatment should be recorded on the CRF.

9.7 Study Mucoactive Compliance

Nursing staff at the site will administer the study mucoactives. The administration, including any omission of study mucoactives will be recorded in the case report form (CRF) to monitor treatment compliance. Any omission of study mucoactives will not be recorded separately as a protocol deviation.

Adherence to usual airway clearance management will be monitored throughout the study and as a preventative measure the trial management group will highlight and review any site that begins prescribing carbocisteine or hypertonic saline to participants who have been randomised to the usual airway clearance management group. Any administration of non-trial mucoactives will be recorded on the CRF. Any administration of non-trial mucoactives will not be recorded separately as a protocol deviation.

9.8 Concomitant Care

All aspects of intensive care management will be according to standard critical care guidelines. No part of routine ICU management is contraindicated for patients who are prescribed the study mucoactives.

9.8.1 Respiratory Physiotherapy Airway Clearance Management

Patients across all four randomised groups will receive respiratory physiotherapy as part of usual airway clearance management; the other components of usual airway clearance management include airway suctioning and heated humidification (either active heated humidification devices, or passive heat and moisture exchangers). Isotonic saline may also be used depending on individual clinician preference. Respiratory physiotherapy airway clearance management will not be protocolised but will be delivered at the discretion of treating physiotherapists based on assessment of the individual clinical need of patients[6]. The frequency, duration, and content of treatment sessions will therefore vary among patients. However, typical airway clearance management is characterised by tailored treatment according to the specific patient presentation using a range of available techniques (such as active cycle of breathing technique, positioning, manual or ventilator hyperinflation, chest wall percussion of vibration, assisted cough) and evaluated using both subjective (e.g. more effective cough, increased ease of secretion clearance) and objective (e.g. improved oxygen saturation levels, reduced oxygen requirements) outcome measures[6]. As is the case in usual clinical practice, individual treating physiotherapists will be able to schedule their treatment sessions in combination with the delivery of the prescribed study mucoactives to optimise patient management.

10 OUTCOMES and OUTCOME MEASURES

10.1 Primary Outcome

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[16].

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

10.2 Secondary Outcomes

Secondary clinical and safety outcomes, timing of their assessment, and measurement tools, are summarised in Table 4. 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[16]. Data contributing to the economic evaluations also represent those items recently recommended as a priority for this purpose[30].

10.3 Outcome Measurement

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. Where unassisted breathing begins on Day 27 or Day 28, clinical and safety outcomes will be recorded up to Day 29 or Day 30 respectively.

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 4. 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

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[21]

ii) Bronchoconstriction requiring nebulised bronchodilators

- During or up to 30 minutes following nebulisation[31]

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[32]

iv) Hypoxaemia during nebulisation

- A drop in SpO_2 to below 90% during or up to 30 minutes following nebulisation[31] requiring an increase in FiO_2

11 SCREENING, CONSENT and RECRUITMENT

11.1 Screening Procedure and Screening Logs

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

All screening data must be recorded by the Principal Investigator (PI) or designee onto the MARCH trial screening log. The PI or designee will be required to submit screening data to the CTU each month. Monthly screening log data will be used to monitor trial recruitment and provide feedback to sites. The collection of accurate screening data is also required to meet CONSORT 2010 trial reporting guidelines[33].

The outcome of the screening process and reasons for the non-enrolment of potentially eligible patients will be recorded on the MARCH study screening log using the Screened, Eligible, Approached, Randomised (SEAR) framework[34].

Screening: Enter ALL potentially eligible MARCH patients with ARF who meet the MARCH study inclusion criteria onto the screening log:

1. Aged ≥16 years
2. An acute and potentially reversible cause of ARF as determined by the treating physician
3. Receiving invasive mechanical ventilation via endotracheal tube or tracheostomy
4. Anticipated to remain on invasive mechanical ventilation for at least 48 hours
5. Presence of secretions that are difficult to clear with usual airway clearance management (as assessed by the treating clinical team)

Eligibility Assessment: an ICU physician will confirm the patient's eligibility or reason for exclusion. A patient may be eligible for enrolment at any stage during their ICU admission, assuming the eligibility criteria are met. If the patient is ineligible, the reason will be recorded on the screening log using the following codes:

1. Pre-existing chronic respiratory condition receiving routine use of any mucoactive
2. Mucoactive treatment started more than 24 hours prior to 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. The treating clinician believes that participation in the trial would not be in the best interests of the patient

Approach: the patient's Personal Legal Representative (PerLR) or Professional Legal Representative (ProfLR) (*if no PerLR available*) will be provided with information about the study and asked for their consent. If not approached, enter the reason for non-approach onto the screening log.

If **Randomised**: the patient's Participant Study Number will be recorded on the screening log. If the PerLR or ProfLR declined, enter the reason to decline consent onto the screening log.

11.2 Informed Consent Procedure

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The Principal Investigator (PI) (or designee) is responsible for ensuring that informed consent for trial participation is given by each patient or a legal representative. The person taking informed consent must be GCP trained, suitably qualified and experienced, and have been delegated this duty on the delegation log. Appropriate signatures and dates must be obtained on the informed consent documentation prior to collection of trial data and administration of the IMP. If no consent is given the patient cannot be enrolled into the trial.

The incapacitating nature of the condition precludes obtaining prospective informed consent from participants. In this situation informed consent will be sought from a Personal Legal Representative (PerLR) or Professional Legal Representative (ProfLR).

11.2.1 Personal Legal Representative

Informed consent will be sought from the patient's Personal Legal Representative (PerLR). For a CTIMP, the PerLR is defined as a person who is not connected with the conduct of the trial who is suitable to act as the legal representative by virtue of their relationship with the patient, and is available and willing to do so[35]. The PerLR will be informed about the trial by the responsible clinician or a member of the research team and provided with a copy of the covering statement for the PerLR with an attached participant information sheet (PIS). The PerLR will be asked to give an opinion as to whether the patient would be willing to participate in such medical research. If the PerLR decides that they are willing to provide consent for their relative/friend/partner to take part, they will be asked to sign the PerLR consent form. This form will then be countersigned by the person taking consent. The original will be retained in the investigator site file (ISF) and a copy given to the PerLR and another copy placed in the patients' medical records.

During the COVID-19 pandemic, there are likely to be visiting restrictions in place due to infection control measures and therefore it may not always be possible to obtain consent from the PerLR at the clinical site. If the PerLR is not available at site, the researcher may contact the PerLR by telephone and seek verbal agreement. This verbal agreement will be recorded in the PerLR Telephone Agreement Form. The PerLR Telephone Agreement Form will be signed by a second member of staff who has witnessed the telephone advice. This witness may be a member of the site study team or site medical staff. A copy of the PerLR Telephone Agreement Form should be placed in the patient's medical notes and a copy filed in the ISF. Written consent will then be obtained if possible and an information sheet sent to the PerLR for their records.

11.2.2 Professional Legal Representative

As the patient is unable to give informed consent and if no PerLR is available in person or by telephone, a Professional Legal Representative (ProfLR) may be approached to give consent. A ProfLR is defined as a doctor responsible for the medical treatment of the patient if they are independent of the study, or a person nominated by the healthcare provider[35]. A doctor acting as a ProfLR must be of consultant level. The doctor will be informed about the trial by the responsible clinician or a member of the research team and given a copy of the PIS. If the doctor decides that the patient is suitable for entry into the trial they will be asked to sign the ProfLR consent form. The original will be retained in the ISF and a copy given to the ProfLR and another copy placed in the patients' medical records.

11.2.3 Retrospective Patient Consent

Patients will be informed of their participation in the trial by the responsible clinician or a member of the research team, either within the ICU or acute hospitalisation period, once they regain capacity to understand the details of the trial. The responsible clinician or a member of the research team will discuss the study with the patient and the patient will be given a copy of the PIS to keep. The study team member will talk them through the PIS, stressing that joining the study is voluntary and that the standard of care the patient will receive will not differ, regardless of whether or not they choose to join the study. They will also be told that they are free to withdraw from the study at any time without giving a reason and without affecting their standard of care. The patient will be given adequate time to read through the PIS before making their decision. The patient will be asked for consent to continue to participate in the trial and to sign the consent to continue form which will then be countersigned by the person taking consent. The original will be retained in the ISF and a copy given to the patient and another copy placed in the patient's medical records. Where consent to continue is not obtained, consent from the legal representative will remain valid. If the patient does not consent to continue, permission to use data collected to that point and to access medical records for trial data will be requested from the patient.

11.3 Withdrawal of Consent

The ProfLR or the PerLR or the participant may withdraw consent from the study at any time without prejudice.

If consent is withdrawn this will be documented in the patient's notes and in the CRF. The researcher will determine which elements of the trial are to be withdrawn (from the following possibilities) and this will be documented:

- Mucoactive administration if ongoing
- On-going data collection during hospital admission
- On-going data collection following hospital discharge
- Confirmation of vital status

If the patient or patient representative declines on-going participation, anonymised data recorded, and samples taken up to the point of withdrawal, will be included in the study analysis unless the patient or patient representative requests otherwise. Similar consent mechanisms have been used successfully in other critical care trials[36-40].

11.4 GP Contact

To inform and enable the collection of follow up data, sites will be advised to send a letter to the participants GP to advise them of their participation in the MARCH study.

12 SCHEDULE of ASSESSMENTS

12.1 Participant Assessments

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)

See Section 10 (Outcome measures) for further details of the above items for data collection.

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)

12.2 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

12.2.1 Study Instruments for Participant Follow-Up

12.2.1.1 EuroQol-5 Dimension-5 Level (EQ-5D-5L)

The EQ-5D-5L is a generic preference-based measure of health, which provides a description of health using five dimensions (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression) each with five levels of severity. Responses can be converted to an overall utility score and used for the calculation of quality adjusted life years (QALYs). Respondents are also asked to place their health on a visual analogue scale (VAS) where 0 represents the worst imaginable health state and 100 the best imaginable health state. It is recommended by NICE for use in economic evaluations[34].

12.2.1.2 Health and Social Care Service Use Questionnaire

A health service use questionnaire and diary have been developed specifically for the trial. The questionnaire will include the minimum set of core resource use items recently recommended for UK economic evaluations[30]. These include:

- Hospital care: Number of inpatient or day-case hospital admissions; length of stay; number of hospital outpatient appointments
- Emergency care: Number of visits to Emergency Departments; number of admissions to hospital, after a visit to the Emergency Department
- Care at a GP surgery, health clinic, or other community setting: Number of appointments; type of professional seen
- Health care at home: Number of health care professional visits at home; type of health care professional seen at home
- Medication: Name/class of medication. Oxygen use will also be recorded.

The health service use diary will be given to patients at the point of consent to continue to record their health service use prospectively. The questionnaire will then be completed at 6 months after randomisation.

12.3 Process Evaluation

A process evaluation may be conducted to explore the process of implementation of the intervention that may enhance interpretation of the trial findings[41]. For example, these may include determining patient eligibility (e.g. determining difficulty in clearing secretions with usual airway clearance management), delivering the mucoactive intervention, and collection of outcome data. Any process evaluation undertaken will follow MRC guidance[41].

12.4 Mechanistic Studies

Biological samples (sputum and blood) will be collected at a sample of sites giving agreement, and with any necessary infrastructure in place to support. Patients with suspected or confirmed COVID-19 disease will not have samples collected.

Biological samples will be collected by trained staff and processed according to the Sample Processing Guideline. If samples for mechanistic studies cannot be collected this will not be recorded as a protocol deviation. In summary, samples will be labelled with the patient's unique Participant Study Number. After any local processing, samples will be stored at –80 °C until transfer to Queen's University Belfast, where samples will be further stored at –80 °C until analysis, and beyond study completion. As new scientific data become available, this resource of stored samples can be used to

investigate if this new data is relevant to acute respiratory failure. All necessary ethical approvals for analyses of samples, or any future study, will be secured prior to any investigation being conducted.

12.4.1 Sputum Samples

Sputum samples will be collected as follows by trained staff and processed according to the Sample Processing Guideline. If endotracheal aspirate samples for mechanistic studies cannot be collected this will not be recorded as a protocol deviation.

- Baseline (Day 0): sufficient quantity to conduct subsequent analyses
- Day 3: sufficient quantity to conduct subsequent analyses
- Day 7: sufficient quantity to conduct subsequent analyses

Day 3 and 7 samples will only be obtained if the patient is still invasively mechanically ventilated.

12.4.2 Blood Sampling

Blood samples (where possible) will be collected by trained staff and processed according to the Sample Processing Guideline. If blood samples for mechanistic studies cannot be collected this will not be recorded as a protocol deviation.

- Baseline (Day 0): up to 30 ml
- Day 3: up to 30 ml
- Day 7: up to 30 ml

Day 3 and 7 samples will only be obtained if the patient is still invasively mechanically ventilated.

12.5 Long-Term Follow-Up

Consent will be obtained to contact patients for long-term follow-up to characterise recovery trajectories following critical illness; data acquisition will align with specific core outcome sets for long-term follow-up after acute respiratory failure[42] and physical rehabilitation in critical illness[43]. All necessary ethical approvals for any future follow up study, will be secured prior to being conducted.

13 DATA COLLECTION and MANAGEMENT

13.1 Data Collection

To ensure accurate, complete, and reliable data are collected, the CTU will provide training to site staff.

All data for an individual patient will be collected and recorded in source documents and transferred onto a bespoke, web-based, electronic 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 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.

13.2 Data Quality

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 Standard Operating Procedures (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.

A DMEC will be convened for the study to carry out reviews of the study data at staged intervals during the study.

13.3 Data Management

Following the entry of patient data into the study database, the data will be processed as per the CTU SOPs and the study specific Data Management Plan (DMP). Data queries will be generated electronically for site staff to clarify data or provide missing information. The designated site staff will be required to respond to these queries. All queries will be responded to or resolved within the study database and amended in the study database.

14 STATISTICAL CONSIDERATIONS

14.1 Sample Size

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[4,44] with a minimal clinically important difference of 1 day[45], 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[46]. 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%[36,47-50], 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[51]

14.2 Data Analysis

14.2.1 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. Trial results will be reported in accordance with Consolidated Standards of Reporting Trials guidance (CONSORT)[52]. 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.

14.2.2 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 and interquartile ranges for continuous data; and frequencies and proportions for categorical data (including binary data).

Primary outcomes for the randomised groups will be compared using a Cox proportional hazards model including site and adjusting for age and illness severity (APACHE II). For this analysis, no interaction between interventions will be assumed. Comparison for other continuous outcomes will use analysis of covariance to adjust for baseline characteristics and covariates. Comparison for binary outcomes will use logistic regression. 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. Since the primary outcome is duration of mechanical ventilation until first successful unassisted breathing or death, we will report the primary

analysis overall and with sensitivity analyses for survivors and non-survivors. Bearing in mind that the crude comparison between the survivors in each randomised group may give rise to biased outcome comparisons, we will consider using a 'survivor average causal effect' (SACE) analysis as a sensitivity analysis for the primary outcome[53]. This will allow us to estimate the effect of each treatment on the outcome among the sub-population that would have survived regardless of which treatment they were allocated to (given that we expect that all deaths will be due to factors other than the trial treatment). Mortality will also be presented as a secondary outcome.
We will include a variety of sensitivity and secondary analyses that will handle death in alternative ways. These will include a time-to-event analysis for the time from randomisation to the "event" of first successful unassisted breathing (with censoring of deceased patients at the time of death, along with censoring of those who withdraw or are lost to follow-up for other reasons); and secondary outcome analysis of deaths while on mechanical ventilation.

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. Further details and a full description of the analyses will be given in the Statistical Analysis Plan.

14.3 Health Economics Evaluation

We will undertake a full health economic evaluation. Although mucoactives are unlikely to impact on mortality, a reduction in the duration of mechanical ventilation this may reduce ventilator-associated co-morbidities and hospital service resource use compared to usual care. The cost of a Level 3 (ICU) bed day in critical care in the UK (based on 2 to 6 organs being supported) is approximately £1680[54]. If the use of mucoactives results in patients coming off mechanical ventilation one day earlier and stepping down to a lower level of care, this could save more than £500 per patient with ARF (based on a Level 2 (High Dependency Unit) bed day cost of £1136)[54]. This is a conservative estimate of the economic saving because the patient's overall hospital length of stay might also be reduced.

We will assess the cost-effectiveness of the treatment in the three IMP groups compared with usual care at 6 months via a cost-utility analysis. We will follow NICE methodological guidance in taking the perspective of the NHS and personal social services for the analysis[55]. The cost per quality adjusted life year (QALY) gained and the net benefit for each of the treatments compared to usual care will be estimated. Recommendations have recently been published[56] on methods for analysing economic evaluations of factorial trials and we will use these to guide the analyses. However, our analyses will likely involve an inside-the-table analysis, treating the four options in the factorial design as mutually exclusive treatments. Economic outcomes will then be estimated and presented separately for each treatment option so that the effect of any interactions can be seen directly. Regression analysis with an interaction term will be performed as a robustness check and allow control for baseline covariates. Health service use will be measured from baseline to 6 months via the CRF and the study-specific questionnaire described in Section 12.2.

EQ-5D-5L responses at the time of consent to continue (in lieu of a baseline measure), 60 days, and 6 months will be converted into utility scores using the UK tariff recommended by NICE at the time of the analysis; this is currently the Crosswalk Value Set[57]. QALYs will be calculated using the utilities and the area under the curve method. Uncertainty in the data will be summarised in cost-effectiveness acceptability curves showing probability of the treatment strategies being cost-effective at different threshold levels of willingness-to-pay per QALY. Sensitivity analysis will be performed to explore

impact on cost effectiveness of variations in key parameters. Further details and full descriptions of analyses will be given in the Health Economics Analysis Plan.

14.4 Additional Analysis

Exploratory analyses for the primary outcome will be reported using interaction tests (treatment group by subgroup) and 99% confidence intervals for the following subgroups:

i) Baseline APACHE
ii) Baseline PF ratio
iii) Pre-existing chronic respiratory condition prior to randomisation
iv) Neurological diagnosis prior to randomisation
v) Admission diagnostic categories; pulmonary vs. non-pulmonary
vi) Receiving antibiotics for pulmonary infection at randomisation

14.5 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.

15 STUDY WITHIN A TRIAL

We plan to include the following Study Within A Trial (SWAT) embedded within the trial. This SWAT is registered on the Northern Ireland Methodology Hub's SWAT Repository (SWAT 51, Lead Contact: Agus, https://go.qub.ac.uk/SWAT-SWAR).

This SWAT will assess the effect on the 6-month follow-up questionnaire return rates of a Self-Categorisation Theory intervention to actively promote group identity in trial participants. According to Self-Categorisation Theory[58], if a person identifies as a member of a particular group they are more likely to cooperate and pursue the joint interests of the group. By applying this theoretical framework to clinical trials, it may be possible to influence participant retention. Retaining patients in clinical trials in order to obtain follow up after their treatment has finished is a significant challenge[59] and one that has been relatively under-examined in methodology research[60]. High levels of attrition can introduce bias and reduce the generalisability of a trial's results. Retention is particularly difficult in critical care trials[61,62] for many reasons. This may be due to patients' poor health status, or because they are recruited onto trials where the intervention may have occurred early during their illness course and ICU admission, and when they do not fully understand the importance of assessing their outcomes several months after discharge from ICU. We aim to actively promote group identity for randomly selected patients in the MARCH trial using theory-informed study materials consisting of an adapted trial logo, thank you cards, promotional items, and letters. We will also prospectively record the resource use associated with delivering the SWAT (e.g. additional study materials, promotional items, and trial team time input).

We have worked closely with our Patient and Family Advisory Group to discuss the nature and content of the SWAT study materials with particular emphasis on how to increase the salience of the MARCH trial as a "group" and how to encourage participants to feel part of this group.

Research Question
What is the effect on 6-month follow-up questionnaire return rates of a Self-Categorisation Theory-based intervention to actively promote group identity in trial participants?

Hypothesis
A Self-Categorisation Theory-based intervention to actively promote group identity in trial participants will improve rates of return of 6 month follow-up questionnaires

Participants
MARCH participants who have regained capacity, given consent to continue participation in the main trial, and who have been discharged from hospital.

Consent
Separate consent will not be required for SWAT participation.

Interventions and comparator
Participants will be randomised to one of three arms (Table 5) comprising two SWAT group identity intervention arms (S1 and S2) and one control arm (S3). S1 and S2 will receive the same correspondence but S2 will also receive a promotional item (e.g. reusable coffee cup or water bottle). Patients allocated to the SWAT control arm will receive the standard trial follow-up correspondence.

Table 5. SWAT arms and schedule of events

Time point	SWAT group identity intervention arm 1 (S1)	SWAT group identity intervention arm 2 (S2)	SWAT control arm (S3)
2 weeks post discharge	Thank you card incorporating theory-informed wording and adapted trial logo	Thank you card and promotional item incorporating theory-informed wording and adapted trial logo	Nothing
60 days post randomisation	Letter and questionnaire incorporating theory-informed wording and adapted trial logo	Letter and questionnaire incorporating theory-informed wording and adapted trial logo	Letter and questionnaire incorporating standard trial follow-up wording and standard trial logo
6 months post randomisation	Letter and questionnaires incorporating theory-informed wording and adapted trial logo	Letter and questionnaires incorporating theory-informed wording and adapted trial logo	Letter and questionnaires incorporating standard trial follow-up wording and standard trial logo

Outcomes

The primary outcome will be the return rates for the 6-month questionnaires. We will compare the combination of S1 and S2 versus S3 to assess the impact of increasing the salience of the MARCH trial as a "group" on the return rate. We will also compare S1 versus S2 to assess the additional impact of sending a promotional item on the return rate.

Secondary outcomes will include:

i) Group identification scores; measured using the single-item social identification instrument[63], and another study specific question asking about group membership. We will compare the combination of S1 and S2 versus S3 to assess the impact of increasing the salience of the MARCH trial as a "group" on group identification. We will also compare S1 versus S2 to assess the additional impact of sending a promotional item on group identification

ii) Cost per additional questionnaire returned

iii) Total costs associated with embedding the SWAT in the MARCH trial

Randomisation

Participants will be randomised (1:1:1) to S1, S2, or S3. The randomisation process will be separate from the main trial randomisation. The trial statistician will generate the randomisation sequence, which will be accessed by a member of the trial team at the CTU on confirmation of a participants' regained capacity, consent to continue participation in the main trial, and hospital discharge. This should be done within 2 weeks of hospital discharge.

We intend to include as many of the MARCH trial participants in the SWAT as possible, but if randomisation to the SWAT does not occur this will not be a protocol deviation from the MARCH trial, and these non-SWAT participants will receive the standard follow-up correspondence as per the SWAT control group in accordance with the MARCH trial protocol. Further details and full descriptions of analyses will be given in the SWAT Analysis Plan.

16 PHARMACOVIGILANCE

16.1 Adverse Event (AE) / Serious Adverse Event (SAE) Reporting

As the MARCH study is recruiting a population that is already in a life-threatening situation, it is expected that many of the participants will experience adverse events (AEs) and serious adverse events (SAEs).

Events that are expected in this population do not need to be reported as adverse events (AEs). Examples include death, agitation, delirium, organ failure and nosocomial infections.

Events that are collected as safety outcomes for the MARCH study do not need to be reported as AEs, including clinically important upper GI bleeding, bronchoconstriction, ventilator or circuit dysfunction with clinical deterioration, and hypoxaemia during nebulisation.

Only SAEs that are related to the mucoactive should be reported (i.e. serious adverse reaction (SAR)). A SAE will be defined as related to the mucoactive if assessed as being possibly, probably or definitely related to the mucoactive (Section 16.4).

All SARs should be reported using the SAE Reporting Form. SARs should be reported to the CTU within 24 hours of the investigator becoming aware of the event, by email to clinicaltrials@nictu.hscni.net. All SARs should also be reported on the AE Form within the CRF.

The reporting period for the trial begins upon administration of the mucoactive and ends upon termination of the mucoactive. Termination of the mucoactive will usually occur at Day 28 (or when the primary outcome is reached), ICU discharge, or death, whichever comes first. Additional termination criteria for the study mucoactives are listed in Section 9.6. (Where unassisted breathing occurs on Day 27 or Day 28, SAR reporting will continue up to Day 29 and Day 30 respectively).

16.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are considered to be related to the mucoactive and are unexpected, i.e. their nature or severity is not consistent with the reference safety information. The reference safety information is the Summary of Product Characteristics (SPC) for carbocisteine and the Product Instructions for Use Leaflet (PIL) for hypertonic saline.

The CTU is responsible for reporting SUSARs to the Sponsor, REC and MHRA within the required timelines as per the regulatory requirements. A fatal or life threatening SUSAR must be reported within 7 days after the CTU has first knowledge of such an event. Relevant follow up information will be sought and communicated within an additional 8 days. All other SUSARs will be reported to MHRA and REC within 15 days after the knowledge of such an event.

16.3 Definition of Adverse Events

The European Clinical Trials Directive 2001/20/EC and applicable clinical trial regulations set out the legal requirements for adverse event recording, management and reporting of clinical trials.

The MHRA Good Clinical Practice Guide 2012 provides the definitions given in Table 6.

Table 6. Terms and Definitions for Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product, which is related to any dose administered to that participant.
Unexpected Adverse Reaction (UAR)	An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the Summary of Product Characteristics (SPC) or Investigator's Brochure (IB) for that product.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the Summary of Product Characteristics (SPC) for that product • in the case of any other investigational medicinal product, in the Investigator's Brochure (IB) relating to the trial in question.
Serious Adverse Event (SAE); Serious Adverse Reaction (SAR); or Unexpected Serious Adverse Reaction	Respectively, any adverse event, adverse reaction or unexpected adverse reaction that: • results in death • is life-threatening • requires hospitalisation or prolongation of existing hospitalisation* • results in persistent or significant disability or incapacity • consists of a congenital anomaly or birth defect 'Important medical events' may also be considered serious if they jeopardise the subject or require an intervention to prevent one of the above consequences. The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

*Hospitalisation is defined as an inpatient admission regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

16.4 Assessment of Causality

The PI or designee should make an assessment of causality, i.e. the extent to which it is believed that the event may be related to the mucoactive (Table 7).

Table 7. Categories of causality for adverse events

Category	Definition
Definitely*	Temporal relationship of the onset, relative to administration of the product, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.
Probably*	Temporal relationship of the onset of the event, relative to the administration of the product, is reasonable and the event is more likely explained by the product than any other cause.
Possibly*	Temporal relationship of the onset of the event, relative to administration of the product, is reasonable but the event could have been due to another, equally likely cause.
Unlikely	Temporal relationship of the onset of the event, relative to administration of the product, is likely to have another cause which can by itself explain the occurrence of the event.
Not Related	Temporal relationship of the onset of the event, relative to administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event.

* Where an event is assessed as possibly, probably or definitely related, the event is an AR.

16.5 Assessment of Severity

The PI or designee should make an assessment of severity according to the following categories (Table 8).

Table 8. Categories of severity for adverse events

Category	Definition
Mild (Grade 1)	A reaction that is easily tolerated by the trial participant, causing minimal discomfort and not interfering with every day activities.
Moderate (Grade 2)	A reaction that is sufficiently discomforting to interfere with normal everyday activities.
Severe (Grade 3)	A reaction that prevents normal everyday activities.
Life Threatening (Grade 4)	A reaction that has life threatening consequences; urgent intervention indicated.
Death (Grade 5)	A reaction that results in death.

16.6 Assessment of Seriousness

The PI or designee should make an assessment of seriousness on the basis that it:

- Resulted in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is any other important medical event(s) that carries a real, not hypothetical, risk of one of the outcomes above

16.7 Assessment of Expectedness

The PI or designee is required to make an assessment of expectedness if the event is possibly, probably or definitely related to the mucoactive.

16.8 Recording and Reporting Urgent Safety Measures

The Sponsor and investigator may take appropriate urgent safety measures to protect clinical trial participants from any immediate hazard to their health and safety. The investigator may implement urgent safety measures without prior approval from the REC or MHRA.

When a PI becomes aware of information that necessitates an urgent safety measure, they should phone the MHRA Clinical Trials helpline (020 3080 6456) and discuss the issue with a safety scientist or medical assessor immediately after an urgent safety measure has been implemented.

The PI or designee should report the urgent safety measure to the CTU immediately, by email to clinicaltrials@nictu.hscni.net.

The CTU will report the urgent safety measure to the Chief Investigator and to the Sponsor immediately, using the dedicated email address: clinical.trials@belfasttrust.hscni.net.

The CI will notify the MHRA and the REC providing full details of the information they have received and the decision-making process leading to the implementation of the urgent safety measure within 3 days.

The PI or designee should respond to queries from the Sponsor or Chief Investigator immediately to ensure the adherence to reporting requirements to REC and MHRA.

17 DATA MONITORING

17.1 Data Access

The agreement with each PI will include permission for trial related monitoring, audits, ethics committee review and regulatory inspections, by providing direct access to source data and trial related documentation. Each patient's confidentiality will be maintained and their identity will not be made publicly available, to the extent permitted by the applicable laws and regulations.

17.2 Monitoring Arrangements

The CTU will be responsible for trial monitoring. The frequency and type of monitoring (on site and/or remote) will be detailed in the monitoring plan and agreed by the Sponsor.

Before the trial starts at a participating site, training will take place to ensure that site staff are fully aware of the trial protocol and procedures. Checks will take place to ensure all relevant essential documents and trial supplies are in place. Monitoring during the trial will check the accuracy of data entered into the CRF against source documents, adherence to the protocol, procedures and GCP, and the progress of patient recruitment and follow up.

The PI or designee should ensure that the monitor can access all trial related documents (including source documents) that are required to facilitate the monitoring process. The extent of source data verification (SDV) will be documented in the monitoring plan.

18 REGULATIONS, ETHICS AND GOVERNANCE

18.1 Regulatory and Ethical Approvals

The trial will comply with the principles of GCP, the requirements and standards set out in the UK policy framework for health and social care research and the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol will be approved by a Research Ethics Committee (REC) flagged for reviewing research involving adults lacking capacity. A clinical trial authorisation (CTA) will be obtained from the Medicines for Healthcare products Regulatory Agency (MHRA) under the notification scheme for Type A CTIMPs before the start of the trial.

The trial protocol is prepared in compliance with the SPIRIT 2013,statement[64], and the trial will be registered at https://www.isrctn.com/ and the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database before randomisation of the first patient. Should the trial require any major modifications during its course in response to the COVID-19 pandemic or other extenuating circumstances, the CONSERVE 2021 statement (CONSORT and SPIRIT Extension for RCTs Revised in Extenuating Circumstances) will also be applied.

18.2 Ethical Considerations

This study is recruiting in a population that is in a life-threatening situation and their vulnerability is fully appreciated. Every effort will be undertaken to protect their safety and well-being, in line with the Medicines For Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, and the UK policy framework for health and social care research.

18.3 Protocol Compliance

The investigators will conduct the study in compliance with the protocol given approval/favourable opinion by the REC and the MHRA.

A protocol deviation is defined as an incident which deviates from the normal expectation of a particular part of the trial process. Any deviations from the protocol will be fully documented.

A serious breach is defined as a deviation from the trial protocol or GCP which is likely to effect to a significant degree:
(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

The PI or designee is responsible for ensuring that any potential serious breaches are reported directly to the CTU within one working day using the dedicated email address (clinicaltrials@nictu.hscni.net).

The CTU will notify the CI and Sponsor immediately to ensure adherence to reporting requirements to REC and MHRA where a serious breach has occurred.

Protocol compliance will be monitored by the CTU to ensure that the trial protocol is adhered to and that necessary paperwork (e.g. CRFs and patient consent forms) is being completed appropriately.

18.4 Protocol Amendments

All protocol amendments will be undertaken in accordance with the regulatory requirements. Substantial changes to the protocol will require REC and MHRA approval prior to implementation, except when modification is needed to eliminate an immediate hazard to patients.

18.5 Good Clinical Practice

The trial will be carried out in accordance with the principles of the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines (www.ich.org). All members of the trial team will be required to have completed GCP training.

18.6 Indemnity

The BHSCT will provide indemnity for any negligent harm caused to patients through the Clinical Negligence Fund in Northern Ireland. Queen's University Belfast will provide indemnity for negligent and non-negligent harm caused to patients by the design of the research protocol.

18.7 Patient Confidentiality

In order to maintain confidentiality, all CRFs, questionnaires, study reports and communication regarding the study will identify the patients by their unique participant study number and initials only. Patient confidentiality will be maintained at every stage and their identity will not be made publicly available, to the extent permitted by the applicable laws and regulations.

18.8 Record Retention

The site PI will be provided with an ISF by the CTU and will maintain all trial records according to GCP and the applicable regulatory requirements. The PI is responsible for the archiving of essential documents at their sites in accordance with the requirements of the applicable regulatory requirements, Sponsor and local policies. The PI has a responsibility to allow Sponsor access to archived data and can be audited by the Sponsor on request. Following confirmation from the Sponsor the CTU will notify the PI when they are no longer required to maintain the files. If the PI withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept responsibility and this must be documented in writing to the CTU and Sponsor.

The TMF will be held by the CTU within the BHSCT and the essential documents that make up the TMF will be listed in a SOP. On completion of the trial, the TMF and study data will be archived by the CTU according to the applicable regulatory requirements and as required by the BHSCT as Sponsor.

18.9 Competing Interests

The research costs are funded by the NIHR Health Technology Assessment Programme.

The CI and members of the TMG have no financial or non-financial competing interests and the members of the DMEC and TSC will be asked to confirm that they have no conflict of interest. In the event that a DMEC or TSC member reports a conflict of interest, advice will be sought from the Sponsor.

Professor Danny McAuley is noted as a NIHR Scientific Director

19 DISSEMINATION/PUBLICATIONS

19.1 Publication Policy

The study will be reported in accordance with the CONSORT guidelines and the TIDieR checklist and guide[27,52]. If necessary, the CONSERVE statement[65] will also be applied in the event that the COVID-19 pandemic or any other extenuating circumstances require major modifications to the trial during its course.

We will publish our trial protocol and statistical analysis plan to ensure transparency in our methodology. The study findings will be presented at national and international meetings with abstracts on-line. Presentation at these meetings will ensure that results and any implications are rapidly disseminated to the wider UK intensive care community. This will be facilitated by our investigator group which includes individuals in executive positions in the UK Intensive Care Society, the NIHR Critical Care National Specialty Group, and the UK Critical Care Research Group, as well as other specialist multi-professional bodies.

In accordance with the open access policies proposed by the NIHR we plan to publish the clinical findings of the trial as well as a separate paper describing the cost-effectiveness in the NHS setting in high quality peer-reviewed open access (e.g. including via Pubmed Central) journals. This will secure a searchable compendium of these publications and make the results readily accessible to the public, health care professionals and scientists. A final report will also be published in the NIHR HTA journal.

We will actively promote the findings of the study to journal editors and opinion leaders in critical care to ensure the findings are widely disseminated (e.g. through editorials and conference presentations) and are included in future guidelines. Due to limited resources, it will not be possible to provide each patient with a personal copy of the results of the trial. However, upon request, patients involved in the trial will be provided with a lay summary of the principal study findings. We will also work with our Patient & Family Advisory Group, PPIE co-applicants, and PPIE members of our Trial Steering Committee (should they be willing to contribute) to produce lay summaries, and determine a dissemination strategy of these, for circulation via relevant patient and family support networks.

The most significant results will be communicated to the wider public through media releases. An on-going update of the trial will also be provided on the CTU website.

19.2 Authorship Policy

Authorship will be determined according to the internationally agreed criteria for authorship (www.icmje.org).

19.3 Data Access/Sharing

Following publication of the primary and secondary outcomes there may be scope to conduct additional analyses on the data collected. In such instances formal requests for data will need to be made in writing to the CI or Co-CI via the CTU, who will discuss this with the Sponsor. The study will comply with the good practice principles for sharing individual participant data from publicly funded clinical trials[66,67] and data sharing will be undertaken in accordance with the required regulatory requirements. In the event of publications arising from such analyses, those responsible will need to provide the CI and Co-CI with a copy of any intended manuscript for approval prior to submission.

20 REFERENCES

1. Vincent JL, de Mendonca A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Critical Care Medicine* 1998;26(11):1793-800. doi: 10.1097/00003246-199811000-00016
2. Narendra DK, Hess DR, Sessler CN, et al. Update in Management of Severe Hypoxemic Respiratory Failure. *Chest* 2017;152(4):867-79. doi: 10.1016/j.chest.2017.06.039
3. Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *Journal of the American Medical Association* 2016;315(8):788-800. doi: 10.1001/jama.2016.0291
4. Harrison D. Patient characteristics by days of Level 3 care, days of Level 3 or Level 2 care and age during 2012. *Case Mix Programme Database* 2014; Intensive Care National Audit & Research Centre (ICNARC).
5. Konrad F, Schreiber T, Brecht-Kraus D, et al. Mucociliary Transport in ICU Patients. *Chest* 1994;105(1):237-41. doi.org/10.1378/chest.105.1.237
6. Connolly B, Barclay M, Blackwood B, et al. Airway clearance techniques and use of mucoactive agents for adult critically ill patients with acute respiratory failure: a qualitative study exploring UK physiotherapy practice. *Physiotherapy* 2020;108:78-87. doi: 10.1016/j.physio.2020.06.003
7. Borthwick M, McAuley D, Warburton J, et al. Mucoactive agent use in adult UK Critical Care Units: a survey of health care professionals' perception, pharmacists' description of practice, and point prevalence of mucoactive use in invasively mechanically ventilated patients. *PeerJ* 2020;8:e8828. doi: 10.7717/peerj.8828
8. Balsamo R, Lanata L, Egan CG. Mucoactive drugs. *European Respiratory Review* 2010;19(116):127-33. doi: 10.1183/09059180.00003510
9. Anand R, McAuley DF, Blackwood B, et al. Mucoactive agents for acute respiratory failure in the critically ill: a systematic review and meta-analysis. *Thorax* 2020;75(8):623-31. doi: 10.1136/thoraxjnl-2019-214355
10. Lu X, Ma Y, He J, et al. N-acetylcysteine for adults with acute respiratory distress syndrome: A meta-analysis of randomized controlled trials. *Hong Kong Journal of Emergency Medicine* 2019;26(5):288-98. doi: 10.1177/1024907918794559
11. Tarrant BJ, Maitre CL, Romero L, et al. Mucoactive agents for adults with acute lung conditions: A systematic review. *Heart & Lung: The Journal of Cardiopulmonary and Acute Care* 2019;48(2):141-47. doi: 10.1016/j.hrtlng.2018.09.010
12. Wong H, Anderson G, Shyamsundar M. Mucoactive agent use in acute respiratory distress synrdome - audit of practice in a Regional Intensive Care Unit. *Journal of the Intensive Care Society* 2018;20(2):Supplement 1-253. doi: 10.1177/1751143719835452
13. Reay H, Arulkumaran N, Brett S. Priorities for Future Intensive Care Research in the UK: Results of a James Lind Alliance Priority Setting Partnership. *Journal of the Intensive Care Society* 2014;15(4):288-96. doi:10.1177/175114371401500405
14. Tatham KC, McAuley DF, Borthwick M, et al. The National Institute for Health Research Critical Care Research Priority Setting Survey 2018. *Journal of the Intensive Care Society* 2020;21(3):198-201. doi: 10.1177/1751143719862244
15. Monthly Critical Care Beds and Cancelled Urgent Operations (MSITREP) Data, England, July 2019.Prepared by the Government Statistical Service, https://www.england.nhs.uk/statistics/wp-content/uploads/sites/2/2019/09/July-19-Monthly-SitRep-SPN-2ojbog.pdf
16. Blackwood B, Ringrow S, Clarke M, et al. A Core Outcome Set for Critical Care Ventilation Trials. *Criticial Care Medicine* 2019;47(10):1324-31. doi: 10.1097/CCM.0000000000003904
17. British National Formulary; available at https://bnf.nice.org.uk/. Accessed 11/09/19.

18. Bradley JM, Anand R, O'Neill B, et al. A 2 × 2 factorial, randomised, open-label trial to determine the clinical and cost-effectiveness of hypertonic saline (HTS 6%) and carbocisteine for airway clearance versus usual care over 52 weeks in adults with bronchiectasis: a protocol for the CLEAR clinical trial. *Trials* 2019;20(1):747. doi: 10.1186/s13063-019-3766-9
19. Carpagnano GE, Resta O, Foschino-Barbaro MP, et al. Exhaled Interleukine-6 and 8-isoprostane in chronic obstructive pulmonary disease: effect of carbocysteine lysine salt monohydrate (SCMC-Lys). *European Journal of Pharmacology* 2004;505(1):169-75. doi: 10.1016/j.ejphar.2004.10.007
20. MRC/DH/MHRA Joint Project Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products. Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf. 2011.
21. Australian TPIft, New Zealand Intensive Care Society Clinical Trials Group AHSCCSCN, Group tICCT. Effect of Stress Ulcer Prophylaxis With Proton Pump Inhibitors vs Histamine-2 Receptor Blockers on In-Hospital Mortality Among ICU Patients Receiving Invasive Mechanical Ventilation: The PEPTIC Randomized Clinical Trial. *Journal of the American Medical Association* 2020;323(7):616-26. doi: 10.1001/jama.2019.22190
22. Vargas M, Chiumello D, Sutherasan Y, et al. Heat and moisture exchangers (HMEs) and heated humidifiers (HHs) in adult critically ill patients: a systematic review, meta-analysis and meta-regression of randomized controlled trials. *Critical Care* 2017;21(1):123. doi: 10.1186/s13054-017-1710-5
23. Cocks K, Torgerson DJ. Sample size calculations for pilot randomized trials: a confidence interval approach. *Journal of Clinical Epidemiology* 2013;66:197-201. doi: 10.1016/j.jclinepi.2012.09.002
24. Avery KNL, Williamson PR, Gamble C, et al. Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies. *BMJ Open* 2017;7(2):e013537. doi: 10.1136/bmjopen-2016-013537
25. Levels of Adult Critical Care, Second Edition, Consensus Statement. Intensive Care Society. Available at https://www.ics.ac.uk/ICS/Guidelines/PDFs/Levels_of_Care_25_3_21.aspx?WebsiteKey=10967510-ae0c-4d85-8143-a62bf0ca5f3c. 2021.
26. Felton T, Pattison N, Fletcher S, et al. Co-enrolment to UK Critical Care Studies – A 2019 update. *Journal of the Intensive Care Society* 2020;Published Ahead of Print. doi: 10.1177/1751143720971542
27. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *British Medical Journal* 2014;348:g1687. doi: 10.1136/bmj.g1687
28. Anand, R, Norrie, J, Bradley, JM, et al. Fool's gold? Why blinded trials are not always best. *British Medical Journal* 2020;368:l6228. doi: 10.1136/bmj.l6228
29. Moustgaard H, Clayton GL, Jones HE, et al. Impact of blinding on estimated treatment effects in randomised clinical trials: meta-epidemiological study. *British Medical Journal* 2020;368:l6802. doi: 10.1136/bmj.l6802
30. Thorn JC, Brookes ST, Ridyard C, et al. Core Items for a Standardized Resource Use Measure: Expert Delphi Consensus Survey. *Value in Health* 2018;21(6):640-49. doi: 10.1016/j.jval.2017.06.011
31. van Meenen DMP, van der Hoeven SM, Binnekade JM, et al. Effect of On-Demand vs Routine Nebulization of Acetylcysteine With Salbutamol on Ventilator-Free Days in Intensive Care Unit Patients Receiving Invasive Ventilation: A Randomized Clinical Trial. *Journal of the American Medical Association* 2018;319(10):993-1001. doi: 10.1001/jama.2018.0949
32. Dixon B, Smith RJ, Campbell DJ, et al. Nebulised heparin for patients with or at risk of acute respiratory distress syndrome: a multicentre, randomised, double-blind, placebo-controlled

phase 3 trial. *The Lancet Respiratory Medicine* 2021;9(4):360-72. doi: 10.1016/S2213-2600(20)30470-7
33. Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomised Trials. *PLOS Medicine* 2010;7(3):e1000251. doi: 10.1371/journal.pmed.1000251
34. Wilson C, Rooshenas L, Paramasivan S, et al. Development of a framework to improve the process of recruitment to randomised controlled trials (RCTs): the SEAR (Screened, Eligible, Approached, Randomised) framework. *Trials* 2018;19(1):50. doi: 10.1186/s13063-017-2413-6
35. Health Research Authority Consent and Participant Information Guidance. Available at http://www.hra-decisiontools.org.uk/consent/docs/Consent%20and%20PIS%20Guidance.pdf. 2020.
36. McAuley DF, Laffey JG, O'Kane CM, et al. Simvastatin in the Acute Respiratory Distress Syndrome. *New England Journal of Medicine* 2014;371(18):1695-703. doi: 10.1056/NEJMoa1403285
37. Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome. The Acute Respiratory Distress Syndrome Network*. *New England Journal of Medicine* 2000;342(18):1301-08. doi: 10.1056/nejm200005043421801
38. Smith FG, Perkins GD, Gates S, et al. Effect of intravenous β-2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial. *The Lancet* 2012;379(9812):229-35. doi: 10.1016/S0140-6736(11)61623-1
39. Papazian L, Forel JM, Gacouin A. Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome. *New England Journal of Medicine* 2010;363:1107-16. doi: 10.1056/NEJMoa1005372
40. Craig T, Duffy M, McDowell C, et al. A Randomized Clinical Trial of Hydroxymethylglutaryl–Coenzyme A Reductase Inhibition for Acute Lung Injury (The HARP Study). *American Journal of Respiratory and Critical Care Medicine* 2011;183(5):620-26. doi: 10.1164/rccm.201003-0423OC
41. Moore GF, Audrey S, Barker M, et al. Process evaluation of complex interventions: Medical Research Council guidance. *British Medical Journal* 2015;350:h1258. doi: 10.1136/bmj.h1258
42. Needham D, Sepulveda K, Dinglas V, et al. Core Outcome Measures for Clinical Research in Acute Respiratory Failure Survivors. An International Modified Delphi Consensus Study. *American Journal of Respiratory and Critical Care Medicine* 2017;196(9):1122-30. doi: 10.1164/rccm.201702-0372OC
43. Connolly B, Denehy L, Hart N, et al. Physical Rehabilitation Core Outcomes In Critical illness (PRACTICE): protocol for development of a core outcome set. *Trials* 2018;19(1):294. doi: 10.1186/s13063-018-2678-4
44. Walsh TS, Kydonaki K, Antonelli J, et al. Staff education, regular sedation and analgesia quality feedback, and a sedation monitoring technology for improving sedation and analgesia quality for critically ill, mechanically ventilated patients: a cluster randomised trial. *The Lancet Respiratory Medicine* 2016;4(10):807-17. doi: 10.1016/S2213-2600(16)30178-3
45. Perkins G, D., Mistry D, Gates S, et al. Effect of Protocolized Weaning With Early Extubation to Noninvasive Ventilation vs Invasive Weaning on Time to Liberation From Mechanical Ventilation Among Patients With Respiratory Failure: The Breathe Randomized Clinical Trial. *Journal of the American Medical Association* 2018;320(18):1881-88. doi: 10.1001/jama.2018.13763
46. McGlothlin A, Lewis R. Minimal Clinically Important Difference: Defining What Really Matters to Patients. In. JAMA Guide to Statistics and Methods. Eds Edward H. Livingston, Roger J. Lewis. JAMAevidence. 2019.
47. Gordon AC, Mason AJ, Thirunavukkarasu N, et al. Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial. *Journal of the American Medical Association* 2016;316(5):509-18. doi: 10.1001/jama.2016.10485

48. Gordon AC, Perkins GD, Singer M, et al. Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis. *New England Journal of Medicine* 2016;375(17):1638-48. doi: 10.1056/NEJMoa1609409
49. Mouncey PR, Osborn TM, Power GS, et al. Trial of Early, Goal-Directed Resuscitation for Septic Shock. *New England Journal of Medicine* 2015;372(14):1301-11. doi: 10.1056/NEJMoa1500896
50. Young D, Lamb SE, Shah S, et al. High-Frequency Oscillation for Acute Respiratory Distress Syndrome. *New England Journal of Medicine* 2013;368(9):806-13. doi: 10.1056/NEJMoa1215716
51. McAlister FA, Straus SE, Sackett DL, et al. Analysis and Reporting of Factorial Trials: A Systematic Review. *Journal of the American Medical Association* 2003;289(19):2545-53. doi: 10.1001/jama.289.19.2545
52. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. *British Medical Journal* 2010;340:c869. doi: 10.1136/bmj.c869
53. Chiba Y, Taguri M, Uemura Y. On the Identification of the Survivor Average Causal Effect. *Journal of Biometrics and Biostatistics* 2011;2:5. doi: 10.4172/2155-6180.1000e104
54. NHS Improvement Reference Costs: National Schedule of Reference Costs. *Available at https://improvementnhsuk/resources/reference-costs/#rc1718*
55. NICE PMG9 Guide to the methods of technology appraisal 2013. *Available at https://wwwniceorguk/process/pmg9* 2013
56. Dakin H, Gray A. Economic evaluation of factorial randomised controlled trials: challenges, methods and recommendations. *Statistics in Medicine* 2017;36(18):2814-30. doi: 10.1002/sim.7322
57. van Hout B, Janssen MF, Feng Y-S, et al. Interim Scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L Value Sets. *Value in Health* 2012;15(5):708-15. doi: 10.1016/j.jval.2012.02.008
58. Turner J. Introducing the problem: individual and group. Rediscovering the Social Group: A Self-categorization Theory. *Oxford: Blackwell* 1987.
59. Brueton VC, Tierney J, Stenning S, et al. Strategies to improve retention in randomised trials. *Cochrane Database of Systematic Reviews* 2013;(12):MR000032. doi: 10.1002/14651858.MR000032.pub2
60. Daykin A, Clement C, Gamble C, et al. 'Recruitment, recruitment, recruitment' – the need for more focus on retention: a qualitative study of five trials. *Trials* 2018;19(1):76. doi: 10.1186/s13063-018-2467-0
61. Agus A, Hulme C, Verghis RM, et al. Simvastatin for patients with acute respiratory distress syndrome: long-term outcomes and cost-effectiveness from a randomised controlled trial. *Critical Care* 2017;21(1):108. doi: 10.1186/s13054-017-1695-0
62. Agus A, Phair G, Page VJ, et al. Simvastatin for the prevention and treatment of delirium in critically ill, mechanically ventilated patients (MoDUS): a cost-effectiveness analysis. *The Lancet Respiratory Medicine* 2018;6(3):e9-e10. doi: 10.1016/S2213-2600(18)30070-5
63. Postmes T, Haslam SA, Jans L. A single-item measure of social identification: reliability, validity, and utility. *British Journal of Social Psychology* 2013;52(4):597-617. doi: 10.1111/bjso.12006 [published Online First: 2012/11/06]
64. Chan A-W, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *British Medical Journal* 2013;346:e7586. doi: 10.1136/bmj.e7586
65. Orkin AM, Gill PJ, Ghersi D, et al. Guidelines for Reporting Trial Protocols and Completed Trials Modified Due to the COVID-19 Pandemic and Other Extenuating Circumstances: The CONSERVE 2021 Statement. *JAMA* 2021;326(3): 257-65. doi:10.1001/jama.2021.9941
66. Tudur Smith C, Hopkins C, Sydes M, et al. Good Practice Principles for Sharing Individual Participant Data from Publicly Funded Clinical Trials. *Trials* 2015;16(Suppl 2):O1. doi: 10.1186/1745-6215-16-S2-O1

67. Tudur Smith C, Nevitt S, Appelbe D, et al. Resource implications of preparing individual participant data from a clinical trial to share with external researchers. *Trials* 2017;18(1):319. doi: 10.1186/s13063-017-2067-4