MARCH

Mucoactives in Acute Respiratory failure: Carbocisteine and Hypertonic saline

Mucoactives in Acute Respiratory failure: Carbocisteine and Hypertonic saline (MARCH)

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NI C T U CLINICAL TRIALS UNIT

HSC Belfast Health and Social Care Trust

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Agenda: Site Initiation Visit Training

Part 1:	MARCH Study Overview
	Background and Trial Design; SWAT, Sample Study; Sites; Recruitment Targets
Part 2:	Mucoactive Management and Pharmacovigilance
Part 3:	Local Trial Management *(ex. Pharmacy Staff)*
	Patient Pathway and Screening Logs; Informed Consent; Randomisation System; Case Report Forms (eCRF); Study Withdrawal; Safety Outcome Reporting; Serious Breaches; Protocol Deviations; Monitoring; Sample Study; Training and Delegation Logs

NB SIV Training covers Protocol Version 2.0

General

- Introduction to trial team
- Enter name, role, organisation in the chat function
- Session recording
- Please contact the trial team for dates and times of upcoming sessions should other colleagues need to attend

Key Details

Main Contact
MARCH Trial Team
Northern Ireland Clinical Trials Unit (NICTU)
7 Lennoxvale, Malone Road, Belfast, BT9 5BY
Tel: +44 28 9615 1447
Email: MARCH@nictu.hscni.net

Funder:	National Institute for Health Research HTA Programme (CI: Connolly)
Sponsor:	Belfast Health and Social Care Trust
CI:	Prof Danny McAuley
Co-CI:	Dr Bronwen Connolly, b.connolly@qub.ac.uk, 028 9097 6047
Trial Manager:	Dr Naomi Dickson
Trial Coordinators:	Dr Jennifer Bell, Ms Judith McCrory

Study Oversight and Support

Trial Steering Committee
Prof Leanne Aitken
Prof James Chalmers (Chair)
Dr Bronwen Connolly (Co-CI)
Ms Chantal Davies (PPI)
Dr Abdel Douiri (Statistician)
Ms Rebecca Langley (PPI)
Prof Danny McAuley (CI)
Prof Alistair Nichol

Data Monitoring and Ethics Committee
Prof Julian Bion (Chair)
Dr Michelle Kho
Prof John Norrie

Patient and Family Advisory Group
Goutam Das
Chantal Davies
Fransceso Palma
Gordon Stumey
Rebecca Langley
Barry Williams

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Mucoactives in Acute Respiratory failure: Carbocisteine and Hypertonic saline

Background and Trial Design

Invasive Mechanical Ventilation

- Artificial airway
- Removal of body's own humidification system
- Impaired mucociliary clearance
- Altered secretion rheology
- Risk of aspiration
- Ventilator-associated infection
- Pre-existing infection diagnosis

Usual Airway Clearance Management

Key techniques

- Suctioning
- Humidification
- Isotonic saline instillation
- Respiratory physiotherapy techniques
- **May be supplemented by mucoactives**

Key features

- Patient-centred approach
- Individualised assessment to determine clinical need
- Tailored treatment
- Evaluation using objective and subjective markers
- **Mucoactives typically commenced for thick, difficult to clear, secretions**

Connolly et al, 2020, Physiotherapy, 108, 78-87

Use in Clinical Practice

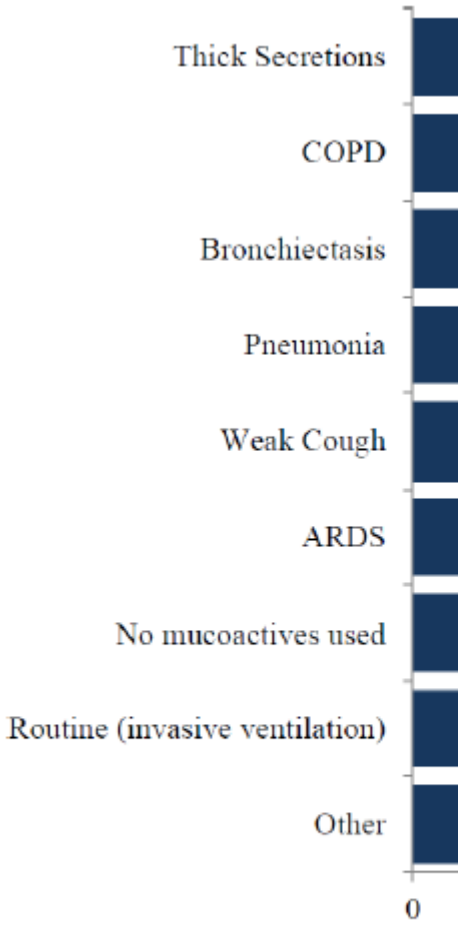

Figure 1 Usual indication for

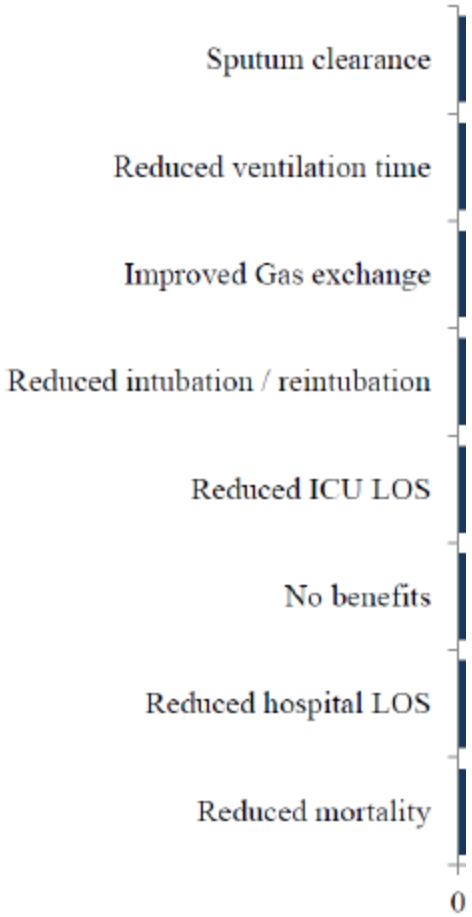

Figure 2 Expected clinical ben

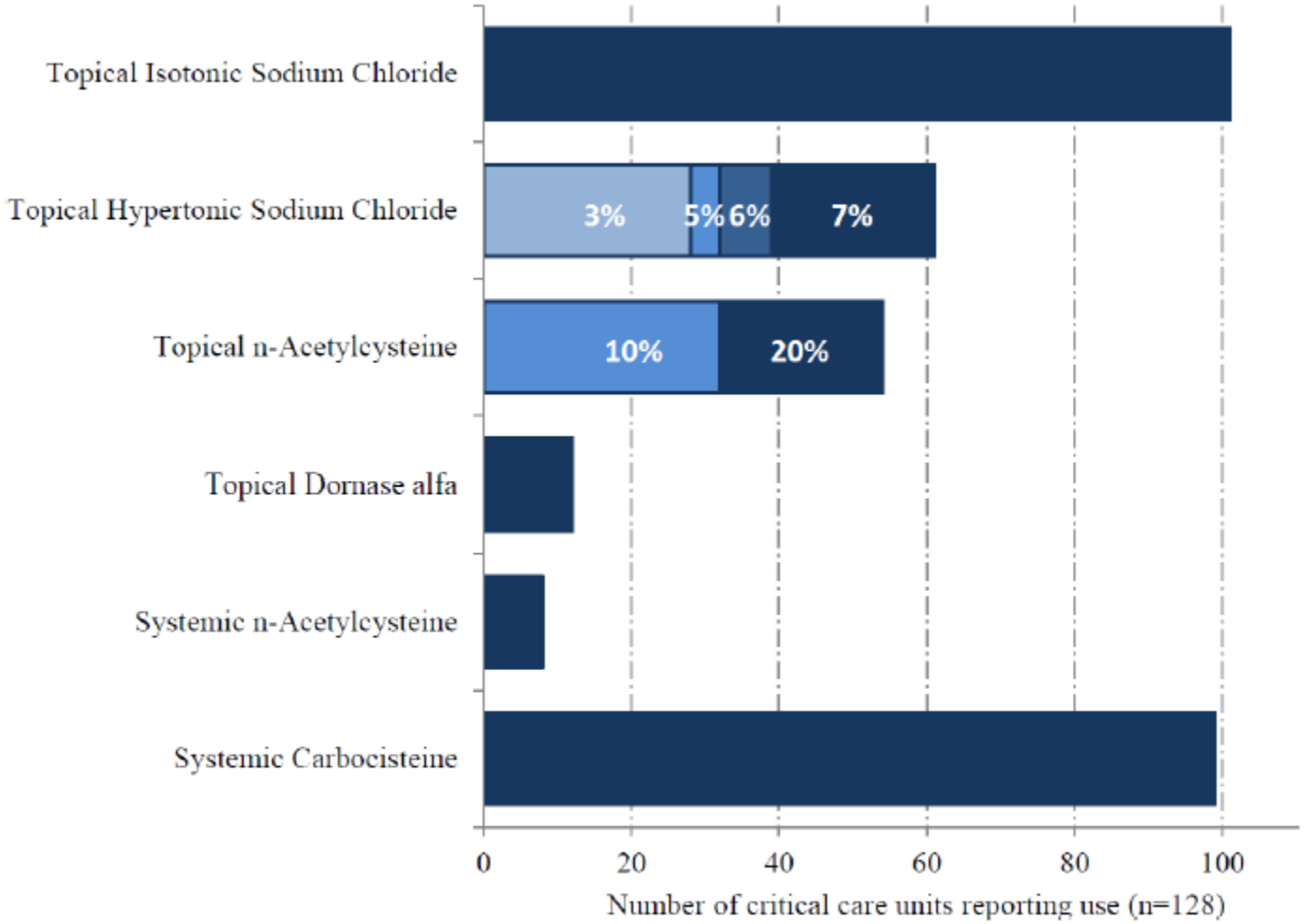

Figure 5 Topical and systemic mucoactive agents in use.

Borthwick et al, 2020, Peer J, 8:e8828 https://peerj.com/articles/8828

Mucoactive agents for acute respiratory failure in the critically ill: a systematic review and meta-analysis

Rohan Anand [1] Daniel F McAuley,[1] Bronagh Blackwood,[1] Chee Yap,[1] Brenda ONeill,[2] Bronwen Connolly,[1,3,4] Mark Borthwick,[5] Murali Shyamsundar,[1] John Warburton,[6] David van Meenen,[7] Frederique Paulus,[7] Marcus J Schultz,[7,8,9] Paul Dark,[10] Judy M Bradley[1]

- No effect on duration of mechanical ventilation, mortality, hospital stay, and ventilator-free days
- Effect on reducing ICU length of stay
- Varying quantities of data, often with high risk of bias and heterogeneity, and low certainty
- Not all commonly used mucoactives had evidence to support or refute use e.g. carbocisteine; others had low quality evidence e.g. HTS

Anand et al, 2020, Thorax, 75, 623-631

Mucoactives

- Empirical use, and minimal evidence of effectiveness
- Wide variability in prescription practices across ICUs and clinicians
- No national guidelines to inform clinical practice
- Decision-making around use based on
  - Local availability
  - Personal preference
  - Prior experience

Aim

To determine whether use of mucoactives in critically ill patients with acute respiratory failure improves outcomes and is cost effective compared to usual care

Overview

2x2 factorial RCT; open label, unblinded

1956 patients

40-50 UK ICUs

Trial Design

2x2 factorial RCT

Group 1 (n=489)	Group 2 (n=489)	Group 3 (n=489)	Group 4 (n=489)
Carbocisteine	Hypertonic saline	Carbocisteine and Hypertonic saline	No mucoactive
+	+	+	+

Usual airway clearance management; suctioning, heated humidification, respiratory physiotherapy +/- isotonic saline

Primary outcome: Duration of mechanical ventilation

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 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 clinician believes that participation in the trial would not be in the best interests of the patient

*use of isotonic ('normal') saline nebulisers is considered usual airway clearance management and not mucoactive treatment; therefore any patient receiving isotonic saline nebulisers is eligible for enrolment

COVID-19

- COVID-19 not a specific exclusion criterion

- All patients with suspected or confirmed COVID-19 meeting MARCH inclusion criteria can be considered for participation
  - Enter onto screening log
  - Eligibility based on local physician decision
    - if excluded note reason on screening log
  - If randomised, excluded from the sample study (no blood or sputum samples)

Co-enrolment

- Eligible for co-enrolment on discussion with trial team
- CTU should be informed if co-enrolment is being considered
- Case-by-case basis adopting national critical care approach
- Details of co-enrolment with studies should be documented in the eCRF (MACRO)
- Sites will be updated of any co-enrolment agreements

Study Interventions and Comparator

	Study IMP	IMP administration
Intervention 1	Carbocisteine (Capsules, syrup or sachet)	750 mg three times daily, for up to 28 days, delivered systemically, plus usual airway clearance management. *NB Patients extubated on Day 27 or Day 28 will receive the study mucoactive until Day 29 or Day 30 respectively (until primary outcome achieved – see next slide).*
Intervention 2	Hypertonic saline (6 or 7% concentration)	4 ml four times daily, for up to 28 days, delivered via nebulisation, plus usual airway clearance management. *NB Patients extubated on Day 27 or Day 28 will receive the study mucoactive until Day 29 or Day 30 respectively (until primary outcome achieved – see next slide).*
Intervention 3	Carbocisteine and hypertonic saline	As described in intervention 1 and 2, plus usual airway clearance management.
Comparator	No mucoactive	Usual airway clearance management including suctioning, heated humidification, and respiratory physiotherapy; isotonic saline may also be used depending on clinical preference.

Study Interventions and Comparator

	Study IMP	IMP administration
Intervention 1	Carbocisteine (Capsules, syrup or sachet)	750 mg three times daily, for up to 28 days, delivered systemically, plus usual airway clearance management. *NB Patients extubated on Day 27 or Day 28 will receive the study mucoactive until*
Comparator	No mucoactive	Usual airway clearance management including suctioning, heated humidification, and respiratory physiotherapy; isotonic saline may also be used depending on clinical preference.

- Importance of **comparator group to** MARCH
- Non-use of mucoactives part of current UK practice
- Avoid use of hypertonic saline and carbocisteine in comparator group
- Use of non-study mucoactives recorded and monitored by CTU/ TMG.

Primary Outcome: duration of mechanical ventilation (hours)

- Time from randomisation until first successful unassisted breathing (defined as maintaining unassisted breathing at 48 hours or death)
- ‘COVenT’ core outcomes for trials of interventions intended to modify the duration of mechanical ventilation

Blackwood et al, *Critical Care Medicine* 2019; 47(10): 1324-31

Primary Outcome: duration of mechanical ventilation (hours)

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

Secondary Outcomes

In hospital

Outcome	Measurement tool, definition, method	Censorship
Extubation	Time from randomisation to first successful extubation (success defined as remaining free from endotracheal or tracheostomy tubes at 48 hours)	60 days
Re-intubation	Event of reintubation of endotracheal tube after a planned extubation (censored at hospital discharge); excludes temporary reinsertion of endotracheal tube for procedures only.	60 days
Respiratory physiotherapy input	Occurrence and frequency of airway clearance sessions	ICU discharge, death, or Day 28, whichever occurs first
Antibiotic usage	Dose of individual agents	ICU discharge, death, or Day 28, whichever occurs first

Secondary Outcomes

In hospital

Outcome	Measurement tool, definition, method	Censorship
Duration of ICU and hospital stay	Time from randomisation until patient first leaves the relevant facility or dies	6 months
All-cause mortality	Confirmation and cause of death	6 months
Safety	1. Clinically important upper gastrointestinal (GI) bleeding due to peptic ulceration confirmed on upper GI endoscopy 2. Bronchoconstriction requiring nebulised bronchodilators 3. Ventilator or circuit dysfunction with respiratory deterioration 4. Hypoxaemia during nebulisation	Censored at ICU discharge, death, or Day 28 whichever occurs first.
Hospital resource use	Number of days at level of care 0/1/2/3	6 months

Secondary Outcomes


Follow-up

Outcome	Measurement tool, definition, method	Time-point
Health-related quality of life	EQ-5D-5L	Consent to continue, 60 days, 6 months
All-cause mortality	Confirmation and cause of death	60 days and 6 months
Health service use since hospital discharge	Categories: care at hospital, emergency, GP surgery. Health clinical or other community setting, health care at home, medication.	6 months

Study Within A Trial

Aim

To determine if promoting group identity improves questionnaire return rate at 6 months

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?

MARCH Trial SWAT

ALL MARCH TRIAL PARTICIPANTS AFTER ICU DISCHARGE

Self-Categorisation
Theory-
interve

SWAT enrolment and post-hospital discharge data collection managed by NICTU

KEY INPUT FROM SITES:
Tracking date of hospital discharge and timely data entry on eCRF

2 WEEKS			
60 DAYS	wording	wording	standard wording
6 MONTHS	Follow-up letter with trial wording, and Qs	Follow-up letter with trial wording, and Qs	Follow-up letter with standard wording, and Qs

utcomes
eturn rates
r 6 month Q
ost per
additional Q
returned
3. Measure of
group ID

Sample Study

- Biological samples (sputum and blood) will be collected at sites giving agreement and infrastructure in place to support
  - Sample collection at Day 0, 3, and 7
  - If no Day 0 sample, then no need for Days 3 and 7
  - Patients with suspected or confirmed COVID-19 disease **will not** have samples collected
  - Investigator Site File will include sample study guidelines
  - Technician contact: John Conlon (QUB) j.conlon@qub.ac.uk

Sample Study

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Sample Handling Guidelines:

Blood and Sputum

Summary

Biological samples (sputum and blood) will be collected at MARCH study 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 this Sample Handling Guideline. If samples (either blood, sputum, or both) for mechanistic studies cannot be collected this will **not be recorded as a protocol deviation**.

Queen's University Belfast (QUB) will be responsible for managing the samples for the MARCH study and will liaise with each site regarding provision of materials for sample acquisition and tracking.

MARCH Study Timeline and Key Milestones

31st Jan 2022;
Further 15 sites open

30th Oct 2024;
1956 patients recruited

May-July	Aug-Oct	Nov-Jan	Feb-Apr	May-July	Aug-Oct	Nov-Jan	Feb-Apr	May-July	Aug-Oct	Nov-Jan	Feb-Apr	May-July	Aug-Oct	Nov-Jan	Feb-Apr	May-July
2021	2021	2021/2	2022	2022	2022	2022/3	2023	2023	2023	2023/4	2024	2024	2024	2024/5	2025	2025
																Database lock
														Follow up		
				Main Study												
		Internal Pilot														
Trial Set Up																
Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1
Year 1				Year 2				Year 3				Year 4				Year 5

1st Nov 2021
Open for recruitment;
15 sites open

30th April 2022;
40 sites open

Green light
152 - 203 patients recruited
by 30th April 2022

NB: Actual internal pilot dates February 2022 to July 2022 (but no overall extension to trial timeline)

Internal Pilot (6 months: Feb 22 – July 22)

- **NIHR Recruitment Progression Criteria**

	RED	AMBER	GREEN
% Threshold	<40	40-74	75-100
Recruitment rate/site/month	<0.6	0.6-<1.1	1.1-1.5
No. of Sites Open	<12	12-22	23-30
Total no. of participants recruited	<81	81-151	152-203

MARCH Study Sites

- 65 (and counting!) ICUs across all 4 nations
- Variation in ICU size and speciality
- Phased opening
  - 30 sites for inclusion in the pilot study
- NIHR funding for translation of patient- and family-facing materials
  - Thank you for responses so far to assist

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Mucoactive Management and Pharmacovigilance

MARCH - Type A CTIMP Study

- MHRA Clinical Trial Authorisation (CTA) under the notification scheme for Type A CTIMPs
  - Risks are no higher than that of standard medical care
  - Products used within licensed range of indications
  - Risk adapted pragmatic approach to IMP management using routine ICU stock
- Investigational Medicinal Products (IMPs)
  - Carbocisteine capsules (375mg), or 250 mg/5ml syrup, or 750 mg/10ml oral solution in sachet
  - Hypertonic saline 6% or 7% inhalation solution
- Reference safety information
  - Carbocisteine - Section 4.8 of SPC for **Mucodyne 375mg capsules** (date 18/03/2021)
  - Hypertonic saline – Side effects as listed in **Mucoclear 6%** inhalation solution Product Instructions for Use Leaflet or PIL (as of 31/07/2018)

Study Mucoactive Administration (1)

- Products will be used within terms of marketing authorisation/ established clinical practice
- Used from local site stock and usual site practice will be followed for the purchase, supply and administration
- Prescribed and dispensed in accordance with usual local site prescription practice
  - No additional labelling outside usual local records or practice
- Batch traceability and product recall processes will match standard hospital medicines management processes for licensed medicines

Study Mucoactive Administration (2)

- Patient enrolment and treatment allocation recorded in clinical notes
- Source document for IMP administration will be the inpatient medication administration record
- First dose of study mucoactive will be administered as soon as possible, ideally within 4 hours of randomisation
  - *Not protocol deviation*
- Subsequent doses given as per locally determined scheduled prescription
  - If a dose is not administered at the intended time, it may be administered subsequently but ***not within 1 hour of the next intended dose***

Study Mucoactive Administration (3)

- 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 extubation (or when unassisted breathing commences if extubated onto NIV) until the primary outcome of duration of mechanical ventilation (first successful unassisted breathing) is reached

Study Mucoactive Administration (4)

- NB Where extubation occurs on Day 27 or Day 28, mucoactives should continue to be administered until Day 29 or Day 30 respectively
  - Daily data collection and safety outcome reporting also continues for duration of study drug administration (until Day 29 or Day 30 for patients extubated on Day 27 or Day 28)

- 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*

Study Mucoactive Termination

- Study mucoactives (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

Study Mucoactive Compliance

- Nursing staff at the site will administer the study mucoactives
- The administration or omission of study mucoactives will be recorded in the case report form (CRF) ***(not a protocol deviation)***
- Adherence to usual airway clearance management will be monitored throughout the study
  - TMG will review sites that administer carbocisteine or hypertonic saline to participants randomised to usual airway clearance management group
- Administration of non-trial mucoactives will be recorded on the CRF ***(not a protocol deviation)***

Pharmacovigilance (1)

- MARCH population may naturally experience Adverse Events (AE) and Serious Adverse Events (SAE)
- Events that are **expected** in this population **do not** need to be reported as AEs
  - E.g. death, agitation, delirium, organ failure, nosocomial infections
- Events that are collected as **safety outcomes** for MARCH **do not** need to be reported as AEs
  - Clinically important upper GI bleeding; bronchoconstriction requiring nebulised bronchodilators; ventilator or circuit dysfunction with respiratory deterioration; hypoxaemia during nebulisation

Pharmacovigilance (2)

- Only SAEs that are related to the mucoactive should be reported i.e. **Serious Adverse Reactions (SAR**)
- SAE defined as related to the mucoactive if assessed as being possibly, probably, or definitely related to the mucoactive
- All SARs should be reported to the CTU within 24 hours of the investigator becoming aware of the event
- Reporting period for the trial begins upon administration of the mucoactive and ends at ICU discharge, death or Day 28 - whichever occurs first *(or up to Day 29 or Day 30 for patients extubated Day 27 or Day 28 respectively)*

Pharmacovigilance (3)

- 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

- CTU is responsible for reporting SUSARs to the Sponsor, REC, and MHRA within the required timelines:
  - Fatal or life-threatening: within 7 days of CTU's first knowledge of the event; follow-up information will be provided within an additional 8 days
  - All other SUSARs: reported to MHRA and REC within 15 days of knowledge of such an event

Pharmacy: Next Steps

- Pharmacy file to follow shortly and to be updated by site staff
  - Index
  - Contact Details – for NICTU, CI and Co-CI
  - Protocol
  - SIV Presentation Slides
  - Reference Safety Information for Mucodyne 375 mg Capsules and Hypertonic saline 6%
  - LIP Covering Letter
  - Risk Adaptions Document
  - Pharmacy Technical Review
- One Pharmacy representative to be listed on the Delegation Log
  - We require GCP certificate, CV & Protocol training

Any questions?

Discussion Point:

How will your site/team identify potentially eligible MARCH patients?

Inclusion criteria: *Presence of secretions that are difficult to clear with usual airway clearance management (as assessed by the treating clinical team)*

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Local Study Management

Screening and Recruitment Log

Screening

- All mechanically ventilated patients in the ICU screened daily for MARCH eligibility
  - Patients who meet inclusion criteria entered onto screening log in eCRF (MACRO) *(MS Excel provided for site use)*
  - Screening number SXXYYYY (XX - Centre No., Y - 0001, 0002 etc. generated on eCRF)
- Reasons patient is not recruited will be recorded on log
  - For CONSORT reporting
  - Recruitment monitoring and optimisation
  - Return eCRF MACRO Screening and Recruitment Log to NICTU by **1st Friday of every month** (MS Excel for local site use only)

Screening Log eCRF: The SEAR Framework

Screening: for all patients who meet the MARCH 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)**

Screening Log eCRF: The SEAR Framework

Eligibility: record if eligible/ineligible against 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

8. Provide physician reason *(Open text e.g. active peptic ulceration, COVID-19, asthma)*

Screening Log eCRF: The SEAR Framework

Exclusion Criteria Key	
1. Patient has a chronic respiratory condition requiring routine use of any mucoactive	5. Patient known to be pregnant
2. Patient has started mucoactive treatment more than 24 hours prior to trial enrolment	6. Patient previously enrolled in the MARCH trial
3. Patient has a known adverse reaction to either study mucoactive	7. Patient is a Prisoner
4. Treatment withdrawal is expected within 24 hours	8. The treating physician believes that participation in the trial would not be in the best in

Please enter ALL potentially eligible patients with ARF who meet the MARCH study inclusion criteria

Site No:		PI Name:									Site Name:		
				Exclusion									Approache
Screening ID	Patient Name	DOB	Screening Date	1	2	3	4	5	6	7	8	If 8 = yes, please specify physician reason:	Was patient's Personal Legal Representative (PerLR) or Professional Legal Representative (ProfLR) (if no PerLR available) provided with information about the study and asked for their consent?	If no, please provide a reason: If 'other' is selected please provide reason under 'Other Comments'

Guidance | Screening Log

Screening Log eCRF: The SEAR Framework

Approach

- Was patient's Personal Legal Representative (PerLR) or Professional Legal Representative (ProfLR; if no PerLR available) provided with information about the study and asked for their consent?
  - *If no, provide the reason (drop down and open text in 'Other comments')*

Randomised?

- If consent was provided, was the patient randomised?
  - *If no, provide the reason (open text in 'Other comments')*

- **Other Comments -** open text field on non-recruitment and other feedback
- **Non-English language PIS -** Please specify if used

Eligibility Confirmation

Before randomisation:

- Eligibility must be confirmed by a medically qualified person on the Delegation Log and signed off in patient's medical notes *(stickers provided which include the date and time)*
- Eligibility checklist completed in eCRF (MACRO)
- Pregnancy test for all women
  - Pregnancy test in females with child-bearing potential (aged 15-55 years)
- Reasons for ineligibility on eCRF Screening and Recruitment Log (MACRO)

Informed Consent Process (1)

- The Legal Representative (LR) of all patients who meet the inclusion and exclusion criteria for MARCH should be provided with information and consent form:
  - Translated information sheet and consent forms available
  - Record reason for non-approach on eCRF Screening and Recruitment Log

- Consent sought from a Personal Legal Representative (PerLR) or Professional Legal Representative (Prof LR) *(if PerLR not available)*
  - If consent not given, record the reason on eCRF

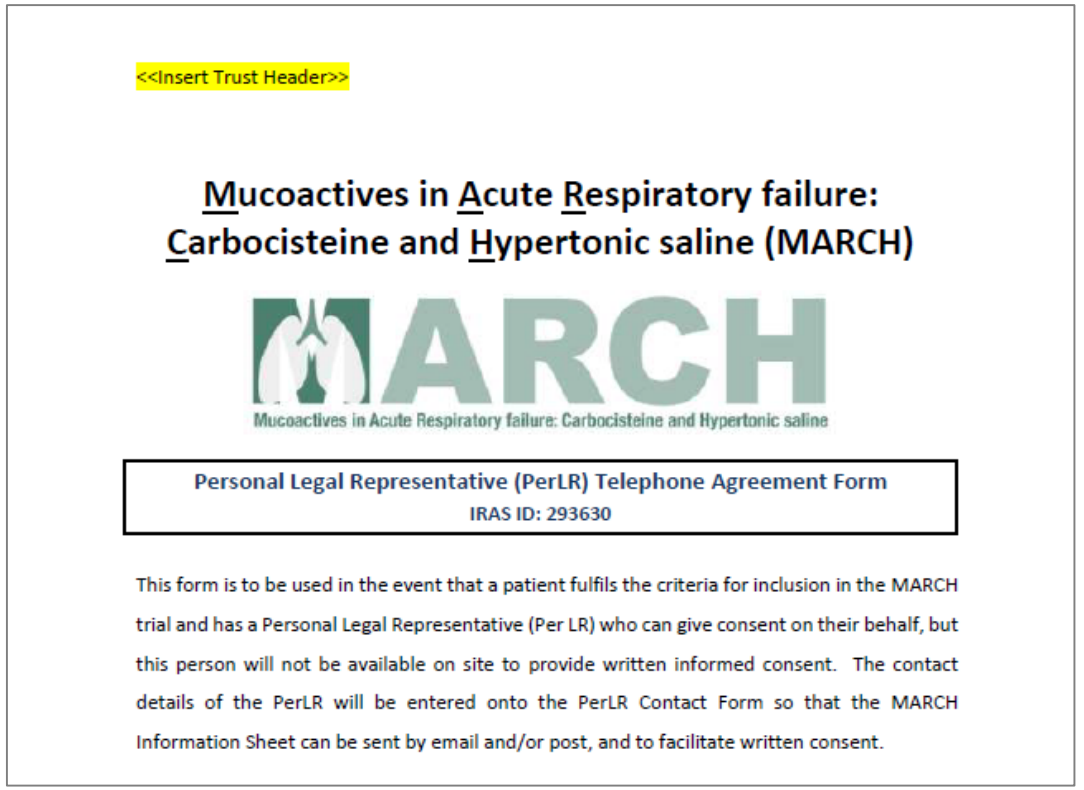
Informed Consent Process (2)

- Personal Legal Representative (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 (HRA 2020)
  - Relative/friend/partner
- The PerLR will be informed about the trial by the responsible clinician/research team and provided with a copy of the PerLR covering statement, information sheet (PIS) and consent form
- The PerLR will be asked to give an opinion as to whether the patient would be willing to participate in such medical research

Informed Consent Process (3)

Telephone Consent for PerLR

- Researcher may contact PerLR by telephone
- Verbal agreement recorded on form
- Signed by a second member of staff who witnessed the phone call
- Form filed in ISF and medical notes
- Written consent subsequently obtained if possible



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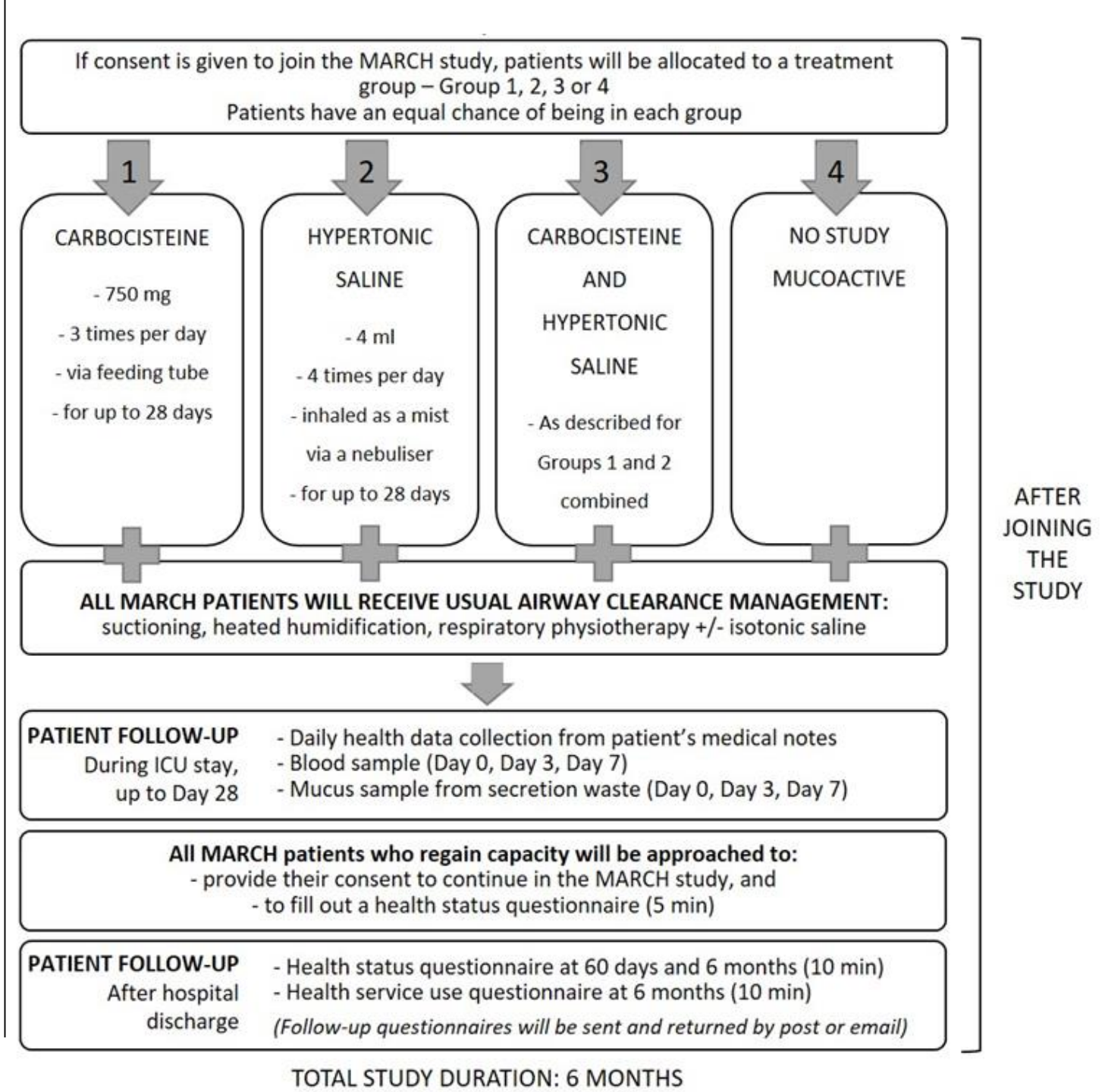
Personal Legal Representative (PerLR) Telephone Agreement Form

IRAS ID: 293630

This form is to be used in the event that a patient fulfils the criteria for inclusion in the MARCH trial and has a Personal Legal Representative (Per LR) who can give consent on their behalf, but this person will not be available on site to provide written informed consent. The contact details of the PerLR will be entered onto the PerLR Contact Form so that the MARCH Information Sheet can be sent by email and/or post, and to facilitate written consent.



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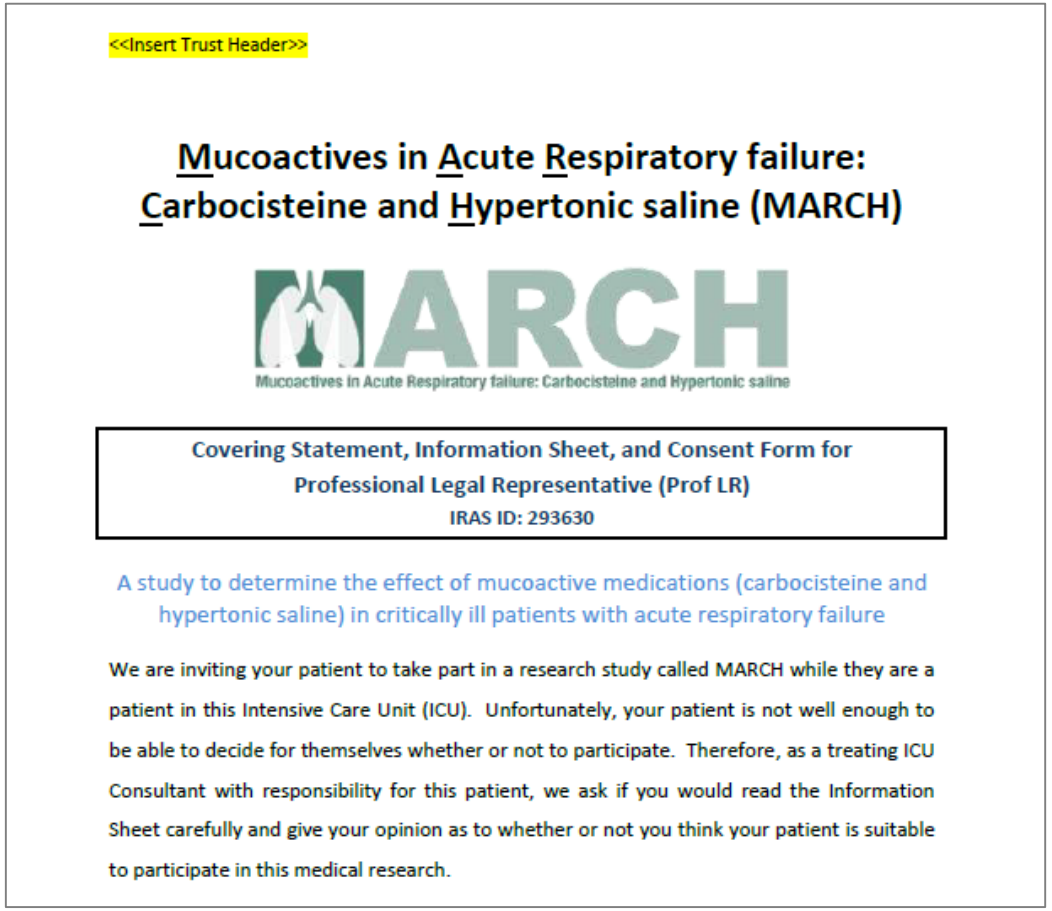
Patient Pathway Diagram in Information Sheet to facilitate informed consent discussions

Recommended by Patient and Family Advisory Group to support consent process

Informed Consent Process (4)

Professional Legal Representative

- If no PerLR available in person or by telephone
- The 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
  - If consent not given, record the reason on the eCRF



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Mucoactives in Acute Respiratory failure: Carbocisteine and Hypertonic saline (MARCH)

MARCH

Mucoactives in Acute Respiratory failure: Carbocisteine and Hypertonic saline

Covering Statement, Information Sheet, and Consent Form for Professional Legal Representative (Prof LR)
IRAS ID: 293630

A study to determine the effect of mucoactive medications (carbocisteine and hypertonic saline) in critically ill patients with acute respiratory failure

We are inviting your patient to take part in a research study called MARCH while they are a patient in this Intensive Care Unit (ICU). Unfortunately, your patient is not well enough to be able to decide for themselves whether or not to participate. Therefore, as a treating ICU Consultant with responsibility for this patient, we ask if you would read the Information Sheet carefully and give your opinion as to whether or not you think your patient is suitable to participate in this medical research.

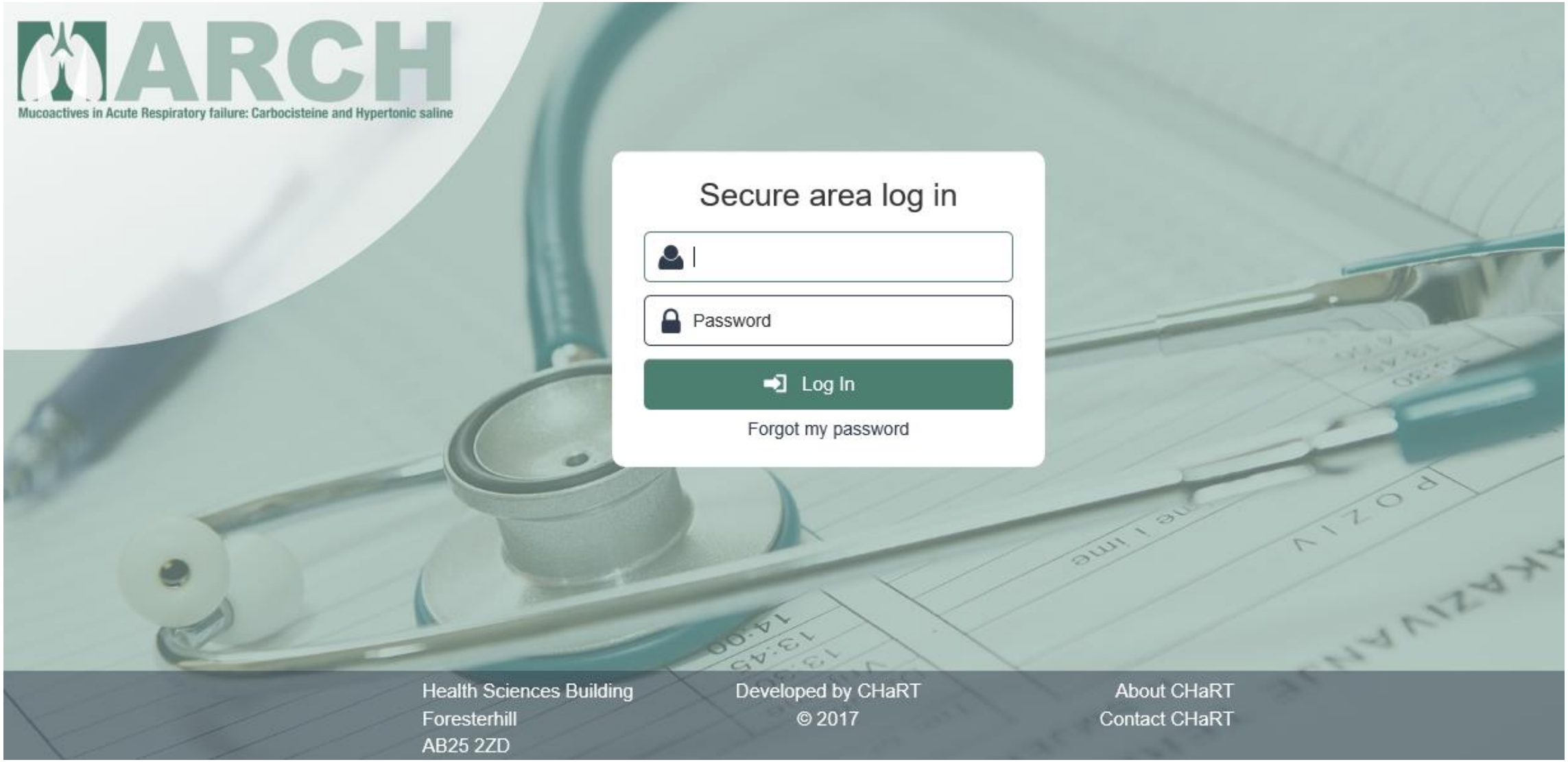
Informed Consent Process (5)

- Must be obtained from the patient's LR prior to conducting any trial specific procedures
- The informed consent form (ICF) must be signed and dated by the patient's LR and the study staff taking consent
- Original ICF:
  - To be retained in the Investigator Site File
- Copy of Information Sheet & ICF:
  - To be filed in the patient's medical notes
  - To be given to the LR
- GP Letter to be sent for enrolled patients

Randomisation System

- CHaRT Randomisation System (University of Aberdeen)
- Telephone and web-based systems (24/7)
- Eligible participants will be allocated to one of four treatment groups in a 1:1:1:1 ratio
- Randomisation stratified by recruitment centre
- Ensure internet browser is enabled for Internet Explorer v8 or above
- Randomisation notifications with treatment allocation sent to staff as per user requests
- User accounts, guide and training support provided by NICTU

https://w3.abdn.ac.uk/hsru/MARCH/Login/login.aspx



New Randomisation

Centre Number and Name — Please select...

Initials
Please enter initials using two letters.

Gender — Please select...

Date of Birth
(DD/MM/YYYY)

Screening Number
Please enter the screening number without the leading S. The screening number has six digits.

Has the participant been confirmed as eligible? — Please select...

Has informed consent been obtained? — Please select...

Review Data

MARCH

Mucoactives in Acute Respiratory failure: Carbocisteine and Hypertonic saline

Trial Data Collection

eCRF (MACRO)

eCRF (MACRO) for Trial Data Collection

- MACRO user ID and training for all staff using the database
  - Training sessions provided by Data Manager (Una Holmes)
  - Previous MACRO training provided by NICTU counts for MARCH

- Please log into MACRO soon after randomisation as possible to enter patient details and baseline data
  - No later than Day 7
  - Daily data collection - respiratory physiotherapy for usual airway clearance management (all groups), study mucoactives administration, non-study mucoactives administration, antibiotic usage

Data Collection (Day 0)

- Day 0 (Baseline) – Baseline data are collected in the 24 hours preceding randomization (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
- Demographic, clinical, data linkage/identifiers, trial process data
  - See protocol for details
- **Please be prompt with data entry**

ARCH

Mucoactives in Acute Respiratory failure: Carbocisteine and Hypertonic saline

Protocol Number: 20131DMcA-AS

Site Number:

Participant Study Number:

Patient Initials:

Ventilation Parameters (Day 0)

The recorded results for both total Respiratory Rate and Minute Volume must be from the SAME observation.

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

Plateau Pressure is equal to peak inspiratory pressure during pressure control mode ventilation. It is not possible to attain Plateau Pressure with pressure support ventilation.

Mode of ventilation

If other, please specify

Minute Volume (ml)

Tidal Volume (Minute Volume/Total Respiratory Rate

Total Respiratory Rate

Respiratory Compliance (ml/cmH2O)

Plateau Pressure (cmH2O)

Driving Pressure (cmH2O)

PEEP (cmH2O)

Was humidification used?

If yes, what type of humidification was used?

If other, please specify

Daily Data Collection (Day 1 to Day 28) (1)

- Day 1 is from the time of randomisation to the end of that calendar day
  - 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 should be recorded

- Daily data will be collected up to and including Day 28 (or up to 29 or 30 days for patients extubated on Day 27 or Day 28 respectively), or until the primary outcome is reached, or ICU discharge, or death

Daily Data Collection (Day 1 to Day 28) (2)

- Respiratory physiotherapy airway clearance management
- Administration of any non-trial mucoactive
- Study mucoactive administration
- Antibiotic usage
- Study mucoactive-related serious adverse event
- Safety outcomes

Other Data Collection (ICU/ hospital)

- Event-driven data 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

MARCH

Mucoactives in Acute Respiratory failure: Carbocisteine and Hypertonic saline

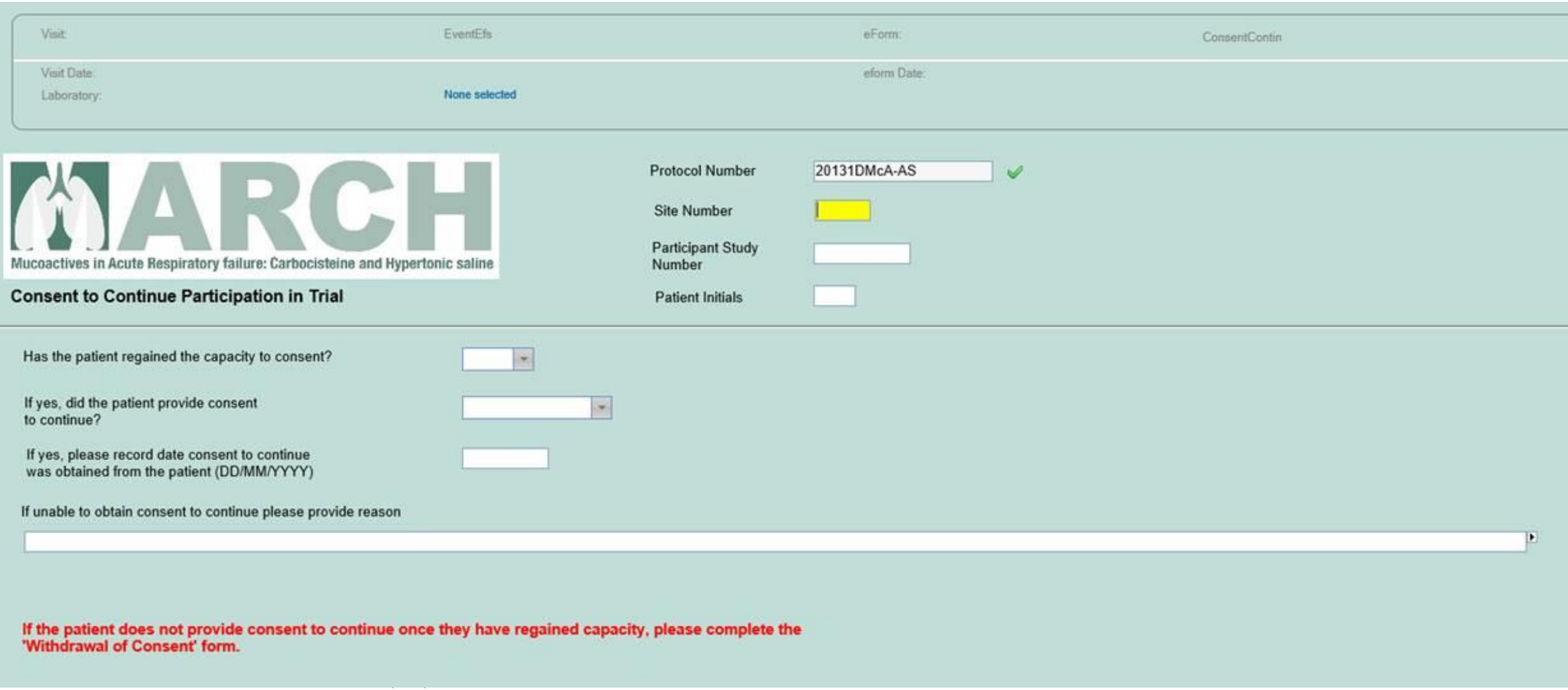
Follow-up Data Collection

Consent to Continue (1)

- Consent to continue will be sought after patient regains capacity
  - If patient does not give consent, permission to use data collected to that point will be requested

- If consent to continue is <u>not</u> obtained, the legal representatives' consent remains valid
  - Patient will be sent follow-up questionnaires - EQ-5D-5L and Health Services Use questionnaires
  - *Patient cannot be randomised into the SWAT*

Consent to Continue (2)



Consent to Continue (3)

- Ask patients to fill out an EQ-5D-5L Questionnaire
- Give patients a Health Service Use Diary and explain this is for patients to note health service use for 6 months following hospital discharge
- If consent to continue is obtained patients can be entered into the SWAT; to be eligible for the SWAT we require:
  - Consent to continue
  - Date of hospital discharge
  - PCD form return

Time-Critical Data Entry for SWAT

SWAT participants may receive a **thank you card** and **gift item** 2 weeks following hospital discharge if information on eCRF:

- Consent to continue
- Date of hospital discharge (on average 2 weeks from ICU discharge)

Please follow-up MARCH patients post-ICU discharge, to assist data collection for study duration (6 months)

Study Withdrawal (eCRF form)

- If patient or Legal Representative asks to withdraw consent, the researcher will determine which elements of the trial are to be withdrawn including:
  - Mucoative administration (if ongoing)
  - Data collection during hospital admission/ following hospital discharge
  - Confirmation of vital status
  - Use of samples/ data collected to date
- In event of withdrawal of consent anonymised data until point of withdrawal will be included unless explicitly stated otherwise (likewise samples)

MARCH

Mucoactives in Acute Respiratory failure: Carbocisteine and Hypertonic saline

Recording and Reporting of Adverse Events (TM03)

Recording and Reporting of Adverse Events (1)

- It is expected that many 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 AEs:
  - *E.g. 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:
  - *Clinically important upper GI bleeding, bronchoconstriction requiring nebulised bronchodilators, ventilator or circuit dysfunction with respiratory deterioration, and hypoxaemia during nebulisation*

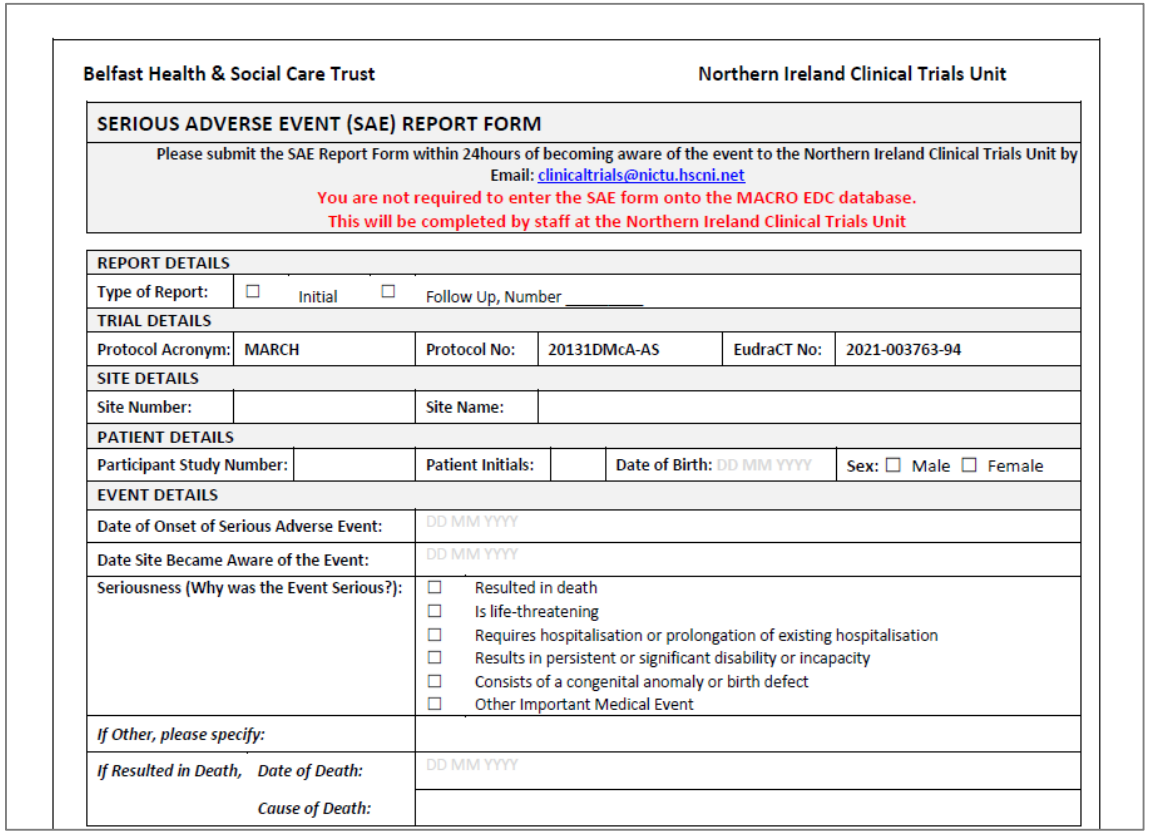
Recording and Reporting of Adverse Events (2)

- Responsibility for recording and reporting of Adverse Events – PI or medically qualified designee on Delegation Log

- Assessed for seriousness, causality, severity and expectedness
  - Protocol
  - Reference Safety Information
    - Carbocisteine - Section 4.8 of SPC for **Mucodyne 375mg capsules** (dated 18/03/2021)
    - Hypertonic saline – Side effects as listed in **Mucoclear 6%** inhalation solution Product Instructions for Use Leaflet or PIL (as of 31/07/2018)
  - SOP TM03 – Recording and Reporting of Adverse Events

Recording and Reporting of Adverse Events (3)

- Only AEs which are **serious and related** to the mucoactive should be reported
  - i.e. Serious Adverse Reactions (SAR)
- Use SAE Reporting Form
- SAE will be defined as related to the mucoactive if assessed as being **possibly, probably or definitely** related



Belfast Health & Social Care Trust — **Northern Ireland Clinical Trials Unit**

SERIOUS ADVERSE EVENT (SAE) REPORT FORM

Please submit the SAE Report Form within 24hours of becoming aware of the event to the Northern Ireland Clinical Trials Unit by Email: clinicaltrials@nictu.hscni.net

You are not required to enter the SAE form onto the MACRO EDC database.
This will be completed by staff at the Northern Ireland Clinical Trials Unit

REPORT DETAILS					
Type of Report:	☐ Initial ☐ Follow Up, Number _____				
TRIAL DETAILS					
Protocol Acronym:	MARCH	Protocol No:	20131DMcA-AS	EudraCT No:	2021-003763-94
SITE DETAILS					
Site Number:		Site Name:			
PATIENT DETAILS					
Participant Study Number:		Patient Initials:		Date of Birth: DD MM YYYY	Sex: ☐ Male ☐ Female
EVENT DETAILS					
Date of Onset of Serious Adverse Event:	DD MM YYYY				
Date Site Became Aware of the Event:	DD MM YYYY				
Seriousness (Why was the Event Serious?):	☐ 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 ☐ Other Important Medical Event				
If Other, please specify:					
If Resulted in Death, Date of Death:	DD MM YYYY				
Cause of Death:					

Recording and Reporting of Adverse Events (4)

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:

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 possible.
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.

*If assessed as **possibly, probably or definitely** related, the event is an Adverse Reaction (AR)

Recording and Reporting of Adverse Events (5)

The PI or designee should make an **assessment of severity** according to the following categories:

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

Recording and Reporting of Adverse Events (6)

The PI (or designee) should make an assessment of the **seriousness** on the basis that the event:

- 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

If the event is assessed as **possibly, probably or definitely** related to the mucoactive the PI (or designee) is required to make an assessment of **expectedness**

Recording and Reporting of Adverse Events (7)

Serious Adverse Reactions must be:

- Recorded in the patient's medical notes
- Documented on the AE form within the eCRF (MACRO)
- Recorded on the **paper** SAE reporting form:
  - to be signed by the PI or medical designee, and
  - submitted electronically to clinicaltrials@nictu.hscni.net within 24 hours of becoming aware of the SAE

The NICTU will confirm receipt by email and retain all documentation and correspondence related to the SAE

Urgent Safety Measures

An Urgent Safety Measure is information necessitating an immediate change to study procedures to protect participants from immediate harm

- Contact MHRA Safety Scientist (020 3080 646)
- The PI should also contact NICTU within 24 hours by email (clinicaltrials@nictu.hscni.net)
- The PI or designee should respond to queries from the Sponsor or Chief Investigator immediately to ensure adherence to reporting requirements to REC and MHRA
- Reference Section 16 of MARCH Protocol: Pharmacovigilance

Protocol Deviations/Serious Breaches

What is a Deviation?

- An incident which deviates from the normal expectation of a particular part of the trial process
- If a deviation from the protocol or GCP occurs during a trial, the PI must be notified, and it must be documented appropriately

What is a Serious Breach?

- A deviation from the protocol or GCP which is likely to effect to a significant degree:
  - the safety or physical or mental integrity of the subjects of the trial, or
  - the scientific value of the trial

Recording and Reporting Deviations

- Protocol or GCP deviations that occur at a site, that are **patient specific,** should be documented using the Protocol Deviation Form within the eCRF and recorded on the clinical trial database

- Protocol or GCP deviations that occur at a site, that are **non-patient specific**, should be documented at site using the Protocol Deviation Form within the Investigator Site File (ISF)

- Please submit to the CTU within 28 days of becoming aware (MARCH@nictu.hscni.net)

Recording and Reporting Serious Breaches

- If the deviation is classified as a *potential* 'Serious Breach' the PI should complete a 'Notification of Serious Breach of Trial Protocol or GCP' form and:
  - Contact the CI and/or Co-CI to discuss
  - Scan and email the form to the NICTU within 24 hours of becoming aware of the event

- The Sponsor and the trial management team will investigate reports of potential serious breaches and fully document any action taken

MARCH

Mucoactives in Acute Respiratory failure: Carbocisteine and Hypertonic saline

Investigator Site File and Essential Documents (TM02)

Investigator Site File (1)

- The NICTU has been delegated Trial Master File (TMF) set-up & maintenance by the Sponsor
  - Therefore, the Investigator Site File must be set-up according to NICTU SOP TM02
- The TMF holds all essential documents and the ISF at each site is a key component
- Inspections or audits of the TMF are used confirm compliance with regulatory requirements
- The PI is ultimately responsible for the set up and maintenance of all essential documents in the ISF but may delegate (Task 17/19) to a member of the research team who has documented SOP training

Investigator Site File (2)

- Each site will be provided with study supplies including an ISF following initiation
- Study team at the NICTU will assist in setting up of your ISF
- Each ISF has an index of essential documents
- Some essential documents may be located in other areas e.g. Pharmacy
  - Add a file note to explain where the document can be located
- ISF should be held in a secure location with restricted access
  - In a locked, fireproof filing cabinet
- This will be checked at monitoring/audit visits

Investigator Site File (3)

Table of Contents	
1.0	Sponsorship
2.0	Agreements
3.0	Regulatory Approvals (Clinical Trial Authorisation)
4.0	Ethics Approval (REC)
5.0	Research & Development
6.0	Protocol
7.0	Participant Information
8.0	Site Personnel and Training
9.0	Pharmacy/Investigational Medicinal Product
10.0	Screening and Recruitment
11.0	Data Collection
12.0	Laboratories
13.0	Pharmacovigilance
14.0	Monitoring, Audits and Inspections
15.0	Training and Procedural documents
16.0	General Correspondence
17.0	Other Trial Related Correspondence

- Index at the beginning of the file outlines the documents to be retained in the file and where these should be held
- Intended as a guide; if a document is not applicable to the MARCH trial this should be noted on the index

Investigator Site File (4)

Should be maintained on an ongoing basis throughout the trial

- All documents should legible, accurate, and signed and date as appropriate
- Previous versions of essential documents e.g. the protocol should be marked as superseded
- All filing should be completed in a timely manner and documents filed chronologically within each section
- Must be available for monitoring visits and audits

Once the trial is finished the PI is responsible for reviewing to ensure all essential documents are present

- Once close out activities completed the ISF can be archived - when advised by NICTU
- PI is responsible for archiving essential documents at the study site
- Sites follow local R&D SOP for archiving
- Change of PI – R&D office/PI need to notify NICTU

Retention of Trial Records

- The site PI:
  - Should maintain all trial records in the ISF according to GCP and applicable regulatory requirements
  - Is responsible for the archiving of essential documents in accordance with applicable regulatory requirements, Sponsor and local policies
  - Is responsible for allowing Sponsor access to archived data which can be audited by the Sponsor on request
  - Should notify the NICTU of planned PI changes during the study so an amendment may be progressed

Following confirmation from the Sponsor, the CTU will notify the PI when they are no longer required to maintain study documentation

Monitoring (1)

- Remote monitoring will take place throughout the study
- The first remote monitoring visit will be arranged after the randomisation of the first 1-2 participants
- An on-site monitoring visit will take place thereafter
- A remote monitoring close-out will be arranged at each site once the final participant recruited has completed all follow-up

Monitoring (2)

Monitoring visits will involve:

- Review of the Investigator Site File
- Review of Consent Forms and Eligibility Confirmation
- Review of CRF data and Source Data Verification (SDV)

Please ensure a team member is available to deal with queries, and the PI should be available at the end of the visit for a feedback meeting if possible

MARCH Trial Manual

- MACRO Electronic Data Capture (EDC) User Guide
- Randomisation Guidelines (telephone & web-based systems)
- Sample Handling Guideline
- Adverse Event Reporting Guideline
- Key Trial Terms
- Frequently Asked Questions (FAQs)
- NICTU SOP TM03 - Recording and Reporting of Adverse Events (V4.0 Final, 24/03/2016)
- NICTU SOP TM02 - Investigator Site File (ISF) and Essential Documents (V4.0 Final, 14/11/2016)

Site Set Up: Checklist

- ❑ Study Training Log
  - Protocol/SIV training required for **all staff** to go on Delegation Log (including Pharmacy staff)
  - MACRO training required for all those delegated Tasks 15/16/18

- ❑ SOP-Specific Training Logs
  - TM02 (ISF Maintenance & Archiving) required for all staff to be delegated Task 17 and/or 19
  - TM03 (AE/SAE Reporting) required for all staff to be delegated Task 12

- ❑ CVs
  - Electronic copies of wet-ink signed CVs dated within 1 year for all staff

- ❑ GCP Certificates
  - Dated within 3 years for all staff

- ❑ Delegation Log
  - Only add a start date when all training and documentation are confirmed as in place for those listed

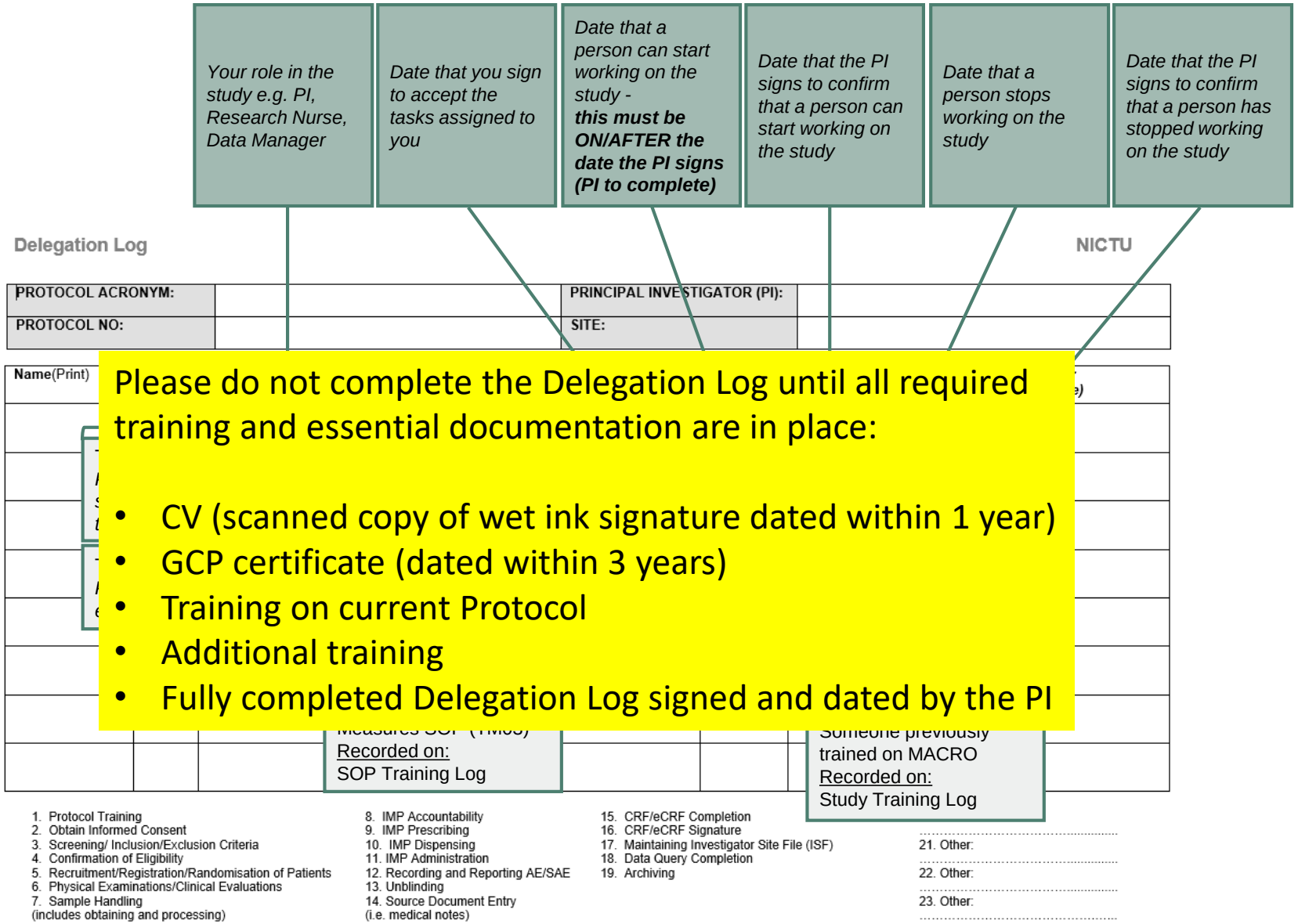
- ❑ Investigator Protocol Agreement (V2.0, 06/12/2022)

- ❑ Fully Executed Site Agreement and Local C&C

Before you start working on MARCH you will need:

- CV (scanned copy of wet ink-signed CV dated within 1 year prior to site opening)
- GCP (dated within 3 years)
- Training on the current Protocol
- Additional training*
- Fully completed Delegation Log signed & dated by the PI

If you make a mistake, put a single line through it, and initial & date it



When you update documents please send a copy to MARCH@nictu.hscni.net

Questions…

MARCH

Mucoactives in Acute Respiratory failure: Carbocisteine and Hypertonic saline

Thank you for attending

b.connolly@qub.ac.uk to contact Bronwen Connolly (CI)

028 9097 6047 / 07903 844833

MARCH@nictu.hscni.net to contact the MARCH Study Team

Naomi Dickson (Trial Manager)
Judith McCrory (Trial Coordinator)
Jennifer Bell (Trial Coordinator, part-time)
Cathy McMaster (Trial Administrator)
Una Holmes (Data Manager)

028 9615 1447

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NICTU CLINICAL TRIALS UNIT

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