<<Insert Trust Header>>

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

Covering Statement, Patient Information Sheet, and Consent to Continue Form

IRAS ID: 293630

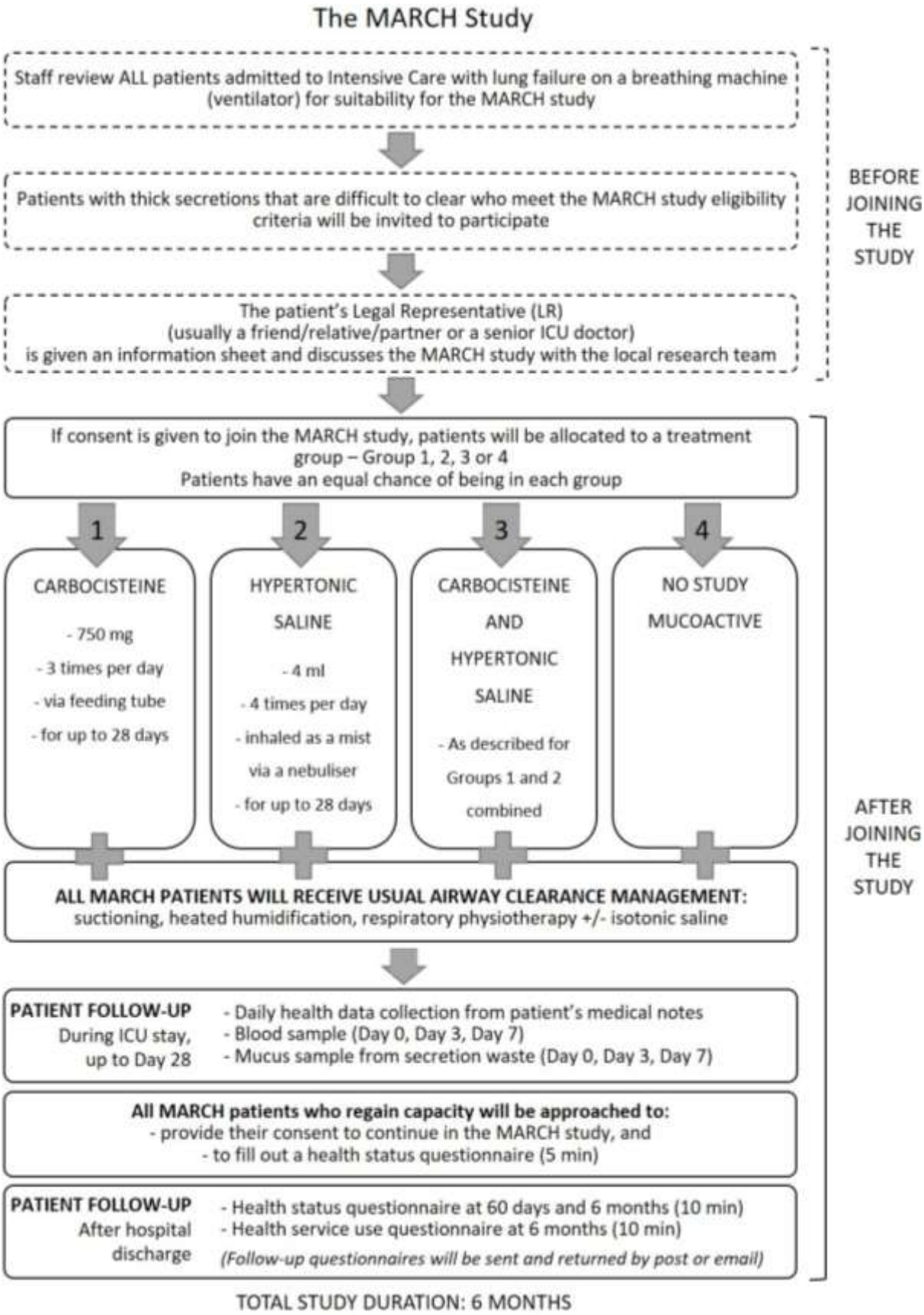
A study to determine the effect of mucoactive medications (carbocisteine and hypertonic saline) in critically ill patients with acute respiratory failure

You are being invited to continue to take part in a research study called MARCH. When you were in the intensive care unit (ICU), your lungs were not working properly. This condition is known as lung failure or acute respiratory failure. The doctors put you on a breathing machine (a ventilator) to ensure you were getting enough oxygen in your blood. When you were in ICU and were not well enough to make a decision for yourself, your relative/friend/partner or senior ICU doctor gave consent on your behalf to take part in the MARCH study. We now want to ask you to decide for yourself if you want to continue in the MARCH study.

Before you decide whether you will continue in the MARCH study, it is important for you to understand why the research is being done and what it involves. Please take time to read the following information carefully and discuss it with your doctor and other people if you wish, before you decide whether or not you want to continue in the MARCH study.

If you have any questions now or at any time in the future, please feel free to contact a member of your local research team (details at the end of this Information Sheet).

Thank you for considering your ongoing participation in the MARCH study


The MARCH Study
Staff review ALL patients admitted to Intensive Care with lung failure on a breathing machine (ventilator) for suitability for the MARCH study
Patients with thick secretions that are difficult to clear who meet the MARCH study eligibility criteria will be invited to participate
The patient's Legal Representative (LR) (usually a friend/relative/partner or a senior ICU doctor) is given an information sheet and discusses the MARCH study with the local research team
BEFORE JOINING THE STUDY
If consent is given to join the MARCH study, patients will be allocated to a treatment group – Group 1, 2, 3 or 4
Patients have an equal chance of being in each group
1
CARBOCISTEINE
- 750 mg
- 3 times per day
- via feeding tube
- for up to 28 days
2
HYPERTONIC SALINE
- 4 ml
- 4 times per day
- inhaled as a mist via a nebuliser
- for up to 28 days
3
CARBOCISTEINE AND HYPERTONIC SALINE
- As described for Groups 1 and 2 combined
4
NO STUDY MUCOACTIVE
ALL MARCH PATIENTS WILL RECEIVE USUAL AIRWAY CLEARANCE MANAGEMENT:
suctioning, heated humidification, respiratory physiotherapy +/- isotonic saline
PATIENT FOLLOW-UP
During ICU stay, up to Day 28
- Daily health data collection from patient's medical notes
- Blood sample (Day 0, Day 3, Day 7)
- Mucus sample from secretion waste (Day 0, Day 3, Day 7)
All MARCH patients who regain capacity will be approached to:
- provide their consent to continue in the MARCH study, and
- to fill out a health status questionnaire (5 min)
PATIENT FOLLOW-UP
After hospital discharge
- Health status questionnaire at 60 days and 6 months (10 min)
- Health service use questionnaire at 6 months (10 min)
(Follow-up questionnaires will be sent and returned by post or email)
AFTER JOINING THE STUDY
TOTAL STUDY DURATION: 6 MONTHS

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

What is the purpose of the study?

When patients are critically ill, one of the main complications is called 'acute respiratory failure'. This is when a patient's illness causes their lungs to fail to work (lung failure). Patients need to be admitted to the Intensive Care Unit (ICU) and often need to have a breathing machine, or ventilator, to help them breathe and ensure that enough oxygen gets into their blood.

However, one problem that can occur as a result of being on a ventilator, is difficulty clearing secretions (mucus, or sputum) from the lungs. This can happen for many reasons. Lack of the body's own natural moisture in the airways can make the secretions become very thick and dry. The breathing tube from the ventilator can also make coughing up secretions more difficult. Patients may also feel too sleepy from their medication to cough by themselves. Not being able to clear secretions from the lungs can make breathing harder, and this may result in developing a lung infection (called ventilator-associated pneumonia).

To reduce the problem of thick secretions, the air coming from the ventilator can have moisture added to it (humidification). Other treatments can include using a suction tube to remove secretions via the breathing tube. Physiotherapists may also use techniques to help clear secretions. In some cases, medications called 'mucoactives' may be prescribed for patients. However, even though mucoactives are commonly used in patients with lung failure in the ICU, we do not know if these medications really help patients when they have thick secretions that are difficult to clear.

What are mucoactives?

Mucoactives are medications that work to help clear secretions from the airways. Different mucoactives work in different ways. Two examples of mucoactives are 'Carbocisteine' and 'Hypertonic saline'. Carbocisteine can help by changing the thickness and stickiness of

secretions, which may help clear mucus from the lungs. It is given to patients in the ICU whilst they are on a breathing machine, in either liquid form or as powder dissolved in water, via the patient's feeding tube. Hypertonic saline is salty water that is delivered into the airways via a device called a nebuliser, which turns the salty water into a mist. The mist may stimulate coughing to help clear thick secretions from the lungs. The process takes approximately 5-10 minutes.

Carbocisteine and hypertonic saline are commonly given to patients with long-term respiratory conditions such as bronchiectasis or cystic fibrosis, as they have been shown to be helpful. We carried out a survey of UK ICUs and found that about one-third of patients on a breathing machine (ventilator) with lung failure were receiving a mucoactive, and carbocisteine and hypertonic saline were the most commonly used. However, we do not know for certain if these medications work in patients admitted to the ICU with lung failure.

What outcomes will be measured as part of the MARCH Study?

The purpose of the MARCH study is to investigate whether using one, or both, of these mucoactives (carbocisteine and hypertonic saline), really helps patients when they have difficulty clearing secretions, and if as a result, this means patients spend less time on the breathing machine (ventilator). We will also determine whether these mucoactives can improve other important outcomes for patients during their ICU stay, such as being taken off the breathing machine (ventilator) and having the breathing tube removed (extubation), the need to have the breathing tube put back in (reintubation), and how long patients stayed in the ICU and in hospital. We will record whether patients experience any side effects from use of these mucoactives.

We will ask patients to complete a brief questionnaire to tell us how they feel about their quality of life (at discharge from ICU, and after 2 months and 6 months). We will contact your GP before sending you the 2 and 6 month follow-up questionnaires. We will record whether any patients died. Additionally, we will look at treatment costs. Mucoactives such as hypertonic saline and carbocisteine are generally not very expensive. However, if they are prescribed unnecessarily for a large number of patients, this could be very costly overall

for the NHS. We will ask patients to fill out a questionnaire at 6 months about their health care use, to know if there are any differences between the study treatment groups. We will also take samples of airway secretions and blood from patients to allow us to determine biologically, the ways in which these mucoactives might work, to improve lung failure treatments for patients in the future.

Why have I been invited to take part?

The ICU doctors found that you had lung failure when you were admitted to the ICU, and whilst you were on the breathing machine (ventilator), you had difficulty clearing secretions from your lungs. When you were in ICU, your relative/friend/partner or a senior ICU doctor was provided with information about the MARCH study and gave their consent for you to participate in the study. They gave their consent when you were not well enough to make this decision yourself. The research is being done because the ICU doctors do not know whether mucoactives will help patients with lung failure recover more quickly. Therefore, we are inviting you to give consent to continue to take part in this study to help us find out whether mucoactives are beneficial for patients with lung failure and difficulty clearing secretions. We plan to recruit up to 2000 patients to join the study, from around 40 hospitals across the UK.

Do I have to continue to take part?

No. It is up to you to decide whether or not you continue to take part in the study. If you do decide to continue, you will be given this Information Sheet to keep and will be asked to sign a consent form, called the study 'consent to continue' form. You are still free to withdraw at any time and without giving a reason. If you decide not to take part, the standard of care you receive will not be affected.

What does participation in the MARCH study involve?

After your relative/friend/partner or doctor gave consent for you to take part in the study, you were put into one of four different groups, by chance. This means your relative/friend/partner or doctor could not choose the treatment group, so the study

treatments can be compared fairly. You had an equal chance (1:1:1:1) of being in one of the four groups. When you received the study treatment, the doctors and nurses looking after you knew which group you were in. This type of study is called a randomised controlled trial and it ensures that the treatments are compared fairly. The treatments received by each group are as follows:

Group 1: Carbocisteine (750 mg, three times daily) plus usual airway clearance management (described below).

Group 2: Hypertonic saline (4 ml, four times daily) plus usual airway clearance management.

Group 3: Carbocisteine (750 mg, three times daily) and hypertonic saline (4 ml, four times daily) plus usual airway clearance management.

Group 4: Usual airway clearance management (including suctioning, heated humidification, respiratory physiotherapy, +/- isotonic saline). No mucoactive medication.

If you were in a group with mucoactive medication, you were given this daily, for the duration of your stay in intensive care up to a maximum of 28 days (or up to 29 or 30 days if your breathing tube was removed on Day 27 or Day 28 respectively).

Your medical notes have been reviewed by the doctors and nurses for the MARCH study, to find out if the treatment that you received had any effect. The study team reviewed your progress on a daily basis whilst you were in ICU. Samples of airway secretions (mucus) and blood were also taken whilst you were in ICU to allow the study team to determine the ways in which mucoactives might work to improve your condition. Mucus samples were taken from the breathing tube you already had in place to help your breathing, as part of routine care to clear your lungs. Blood samples were taken from lines that you already had in place to ensure that taking these samples did not cause any additional pain or discomfort. The blood and mucus samples were taken to help understand the ways in which mucoactives might work biologically, to improve lung failure.

We will also contact your GP to let them know of your participation in the study. After discharge from hospital, we will follow-up on your medical status either by telephone,

contact with your GP, or review of your health care record, up to 6 months following treatment. We may also use NHS Digital if available in your region, to confirm your medical status. If you move house during the 6-month follow-up period, please let us know by contacting the Northern Ireland Clinical Trials Unit either by post or email, using the contact details provided later in this Information Sheet.

What will happen to me if I continue to take part?

If you decide to continue to take part in the MARCH study, we ask you to do the following:

1. Return two short questionnaires about your health at 2 months and 6 months after your discharge from hospital. Each questionnaire should take approximately 10 minutes to complete.
2. Keep a diary to record any contact you have had with health services after you leave hospital. This will help you to complete a short questionnaire about your use of health services during the six months after you leave hospital. The questionnaire should take no more than 15 minutes to complete, depending on how much contact you have had with health services.

How will my samples be stored?

The samples taken will be stored in anonymised format at Queen's University Belfast. Samples are always stored according to appropriate regulations. We would like to store your samples indefinitely. However if you do not want this, it does not affect your participation in the study and any samples will be disposed of. The reason we want to store samples is that if new information or techniques are discovered in the future, this will allow us to use the samples stored to investigate if this information is important for patients who have lung failure. Future tests may involve genetic analysis. We may share samples with other investigators or commercial organisations in the UK or internationally, to help understand lung failure and improve treatments in the future. If this happens the samples shared would be anonymous and external investigators or organisations would not be able to identify you. The anonymised data collected as part of the study may also be used to understand the sample analyses. If future studies are to be carried out on the stored samples, the investigators will obtain Ethics Committee approval as required.

What are the possible benefits and disadvantages of taking part?

Taking part in this study may contribute to improved treatment of patients with lung failure in the future. Possible disadvantages of taking part are completing the questionnaires required at 2 months and 6 months after you leave hospital. However, these questionnaires are sent to you in the post or via email, to make it more convenient for you to complete them.

When you were in the ICU, you may have experienced some side effects from receiving one or either of the mucoactives. Like all medicines, carbocisteine can cause side effects, although not everybody gets them. There have been a very small number (approximately 1%) of reports of gastrointestinal bleeding occurring during treatment with carbocisteine, although these are reported from all patients receiving carbocisteine, not just patients in the ICU. You would not have been eligible for the trial if your doctors identified you as someone with an existing condition that could have placed you at higher risk of gastrointestinal bleeding, such as an active stomach ulcer. Patients in the ICU are routinely given other medications to protect against gastrointestinal bleeding, and all patients in the trial are closely monitored for any signs of gastrointestinal bleeding. A small number of people have reported other side effects including allergic reactions, vomiting, skin rashes, and allergies. While in ICU, the doctors monitored your response to the medication, including any side effects. If any side effects occurred, the doctors will have decided whether it was appropriate to continue the medications.

In a small number of people, nebulised hypertonic saline may cause chest tightness. This typically lasts a very short time and is quickly and easily detected by your doctor and bedside nurse. If this happened, you may have been given additional therapy called a bronchodilator – this is a medication that relieves chest tightness. Similarly, a small number of people may experience a brief drop in oxygen levels during nebulisation of hypertonic saline. Again, if this happened, your doctor and bedside nurse will have detected this from your monitors, and given you additional oxygen until your levels returned to normal.

We are following patients up to 6 months to collect data on health status that will help us determine the cost and benefits of mucoactives delivered whilst in the ICU. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

What if something goes wrong?

If you have any concerns about any aspect of this study, you should contact the local Principal Investigator (contact details below), who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the normal NHS Complaints Procedure.

If something does go wrong and you are harmed due to someone's negligence, then you may have grounds for legal action against your NHS Trust, but you may have to pay the legal costs.

Would my taking part in this study be kept confidential?

Any information which is collected about you during the course of the study will be kept strictly confidential and will only be seen by staff involved in the study from the NHS Trust, the Trial Co-ordinating centre (Northern Ireland Clinical Trials Unit), Belfast Health and Social Care Trust, Queen's University Belfast, and people from regulatory authorities who ensure that studies such as this are carried out correctly. All of them have a duty of confidentiality to you as a research participant.

In addition, information held and maintained by central UK NHS bodies, and organisations contracted to provide services to the NHS, may be used to access data collected routinely during your stay in hospital and to ascertain your long-term health status. In this instance your NHS number/hospital number, date of birth and postcode, may be used and held by the Trial Co-ordinating Centre (Northern Ireland Clinical Trials Unit), all other personal data will remain anonymised. This information will be used only for this study and will not be given to anyone else.

Because we may need to contact you after you leave hospital, the Trial Co-ordinating Centre (Northern Ireland Clinical Trials Unit) will need to keep records of your name, address, and other contact details such as telephone number and email address.

You have the right to see your personal health information related to the research study, but you will not be able to review some parts of the information until after the study has finished. When any information from the study is published it will not contain any personal information and it will not be possible to identify any individual participant.

The data from this study will be kept for at least twenty-five years after its conclusion and may be used in other research studies, and data may be retained by Belfast Health and Social Care Trust and Queen's University Belfast. If it is used in this way all personal identifiers will be removed and it will not be possible to identify any individual.

What will happen to the results of the research study?

Recruitment is due to commence November 2021 and the study is expected to take 4-5 years. It is envisaged that publication of the results will follow shortly after this, through medical journals, websites, press releases, and via appropriate patient charities and support groups. At this point we will be happy to forward a summarised version of the principal findings of the results of the study at your request. This can be requested through the Trial Co-ordinating Centre (Northern Ireland Clinical Trials Unit), whose contact details can be found at the end of this Information Sheet.

Who is organising and funding the study?

MARCH is being organised by a group of clinicians (including physiotherapists, doctors, nurses, and pharmacists) and scientists led by Dr Bronwen Connolly, a Senior Lecturer in Critical Care at Queen's University Belfast and Professor Danny McAuley, a Consultant in Intensive Care Medicine at the Royal Hospitals, Belfast, Northern Ireland. MARCH is funded by the National Institute for Health Research Health Technology Assessment Programme. The sponsor of the study is the Belfast Health and Social Care Trust. The study sponsor is

the organisation responsible to ensure the study is carried out to a high standard to safeguard patient rights and safety, and the quality of the research data.

Who has reviewed the study?

This research has been reviewed and given a favourable opinion by an independent group of people, called a Research Ethics Committee (REC), to protect your safety, rights, well-being, and dignity. The Ethics Committee is completely independent from the study team. The study has also been reviewed by the regulatory body, the Medicines and Healthcare Products Regulatory Agency (MHRA).

What happens if I have any questions, concerns or complaints about the study?

If you have any questions about your participation in this study or concerns about the way it has been carried out, you should contact the local Principal Investigator or a member of the research team (contact details below).

What happens if I don't want to carry on with the study?

You are free to withdraw your consent to participate at any time and without giving a reason. This will not affect the standard of care you receive. You have the right to request samples collected as part of this study to be destroyed and no further laboratory analysis to be performed. Your study doctor can take you out of the study at any time if it is in your best medical interests to stop your participation.

If you have any questions that remain unanswered, the study doctor or research nurse will be happy to answer these for you. If you require any further information, you may contact the local Principal Investigator or the Trial Co-ordinating Centre (Northern Ireland Clinical Trials Unit) as below.

Where can I access information and support following ICU discharge?

ICU Steps is a registered charity, run by former intensive care patients and relatives, with the aim to improve the care and support available to patients recovering from critical illness. https://icusteps.org/

In the event that you become distressed during or after participating in the research, please contact ICU Steps. The website provides information to support recovery, and links to online and face-to face support groups throughout the UK. You can message ICU Steps via the website or leave a voicemail on 03003020121 if you want to talk to someone about your experiences.

Thank you for taking the time to read this Information Sheet

Contact Details

Principal Investigator: *Update with local details*

Name: «name»

Address: «address»

Telephone: «telephone»

Chief Investigator:

Name: Dr Bronwen Connolly

Address: «address»

Telephone: «telephone»

Chief Investigator:

Name: Prof Danny McAuley

Address: «address»

Telephone: «telephone»

MARCH Trial Co-ordinating Centre:

Address: «address»

Telephone: «telephone»

Complaints/concerns: *Update with details for local complaints department and/or Patient Advice and Liaison Service.*

Name: «name»

Address: «address»

Telephone: «telephone»

Transparency Statement

Belfast Health and Social Care Trust is the sponsor for this study. The study sponsor is the organisation responsible to ensure the study is carried out to a high standard to safeguard patient rights and safety, and the quality of the research data.

How will we use information about you?
We will need to use information from you, from your medical records, your GP, NHS Digital, national clinical audit databases, central UK NHS bodies, and organisations contracted to provide services for the NHS for this research project.

This information will include your initials, NHS/ Hospital number, name, contact details (including email), and national clinical audit database number. People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?
- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
- If you choose to stop taking part in the study, we would like to continue collecting information about your health from central NHS records, your hospital, your GP, or national clinical audit databases. If you do not want this to happen, tell us and we will stop.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you. We can provide a list of the type of information we are collecting, upon request.
- If you agree to continue to take part in this study, you will have the option to take part in future research using your data saved from this study.

Where can you find out more about how your information is used?
You can find out more about how we use your information
- at www.hra.nhs.uk/information-about-patients/
- www.belfasttrust.hscni.net/about/access-to-information/data-protection/
- by asking one of the research team
- by sending an email to the MARCH study team: MARCH@nictu.hscni.net, or
- by ringing us on <<telephone>>

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

Regarding patient (please write patient's name here):_____

Please initial each box

1. I confirm that I have received a personal copy of the Information Sheet for the above study. I have read and understood the information, and have had the opportunity to ask questions and discuss the study. ☐

2. I understand that my participation is voluntary and that I am free to withdraw my consent at any time, without giving any reason and without my medical care or legal rights being affected. ☐

3. I understand that sections of my medical notes may be inspected by responsible individuals from the NHS Trust, the Trial Co-ordinating Centre, Belfast Health and Social Care Trust, or regulatory authorities, where it is relevant to taking part in this research. I give permission for these individuals to have access to my records. I agree to information related to this research being retained at the NHS Trust, the Study Co-ordinating Centre, Belfast Health and Social Care Trust, and Queen's University of Belfast. ☐

4. I understand that the Trial Co-ordinating Centre will keep records of my name and contact details and may access information held by other central UK NHS bodies and organisations contracted to provide services to the NHS to access data collected routinely during my hospital stay, to facilitate follow up and to ascertain my long-term health status. ☐

5. I agree to any biological samples that have been already collected to be analysed and the data generated from these analyses to be used. ☐

6. I agree to my samples being stored indefinitely so they can be used in future research in the event of new scientific research or techniques becoming available with regards to lung failure. ☐

7. I agree to my anonymised data being kept for at least 25 years after the study conclusion and it being used in other research studies, and I understand that they will not be personally identified. ☐

8. I understand anonymised samples taken during this study may be shared with external non-NHS organisations to undertake future analyses, including genetic analysis, transfer abroad, and commercial research. *(Optional)* ☐

9. I understand that my data will be shared in an anonymised format in publications, at conferences, and in research data-sharing repositories, and I understand that I will not be personally identified. ☐

10. I agree to be followed-up by the research team to assess my medical status. ☐

11. I agree to my GP being contacted by the research team to advise my doctor about my participation in the study. ☐

12. I agree to be contacted by the research team as part of the long-term follow up to the MARCH study. ☐

13. I agree to continue to take part in the MARCH study. ☐

Name of patient	**Signature**	**Date (dd/mm/yy)**

Name of person taking consent	**Signature**	**Date (dd/mm/yy)**