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

Mucoactives in Acute Respiratory failure: Carbocisteine and Hypertonic saline

Covering Statement, Information Sheet and Consent Form for Personal Legal Representative (PerLR)

IRAS ID: 293630

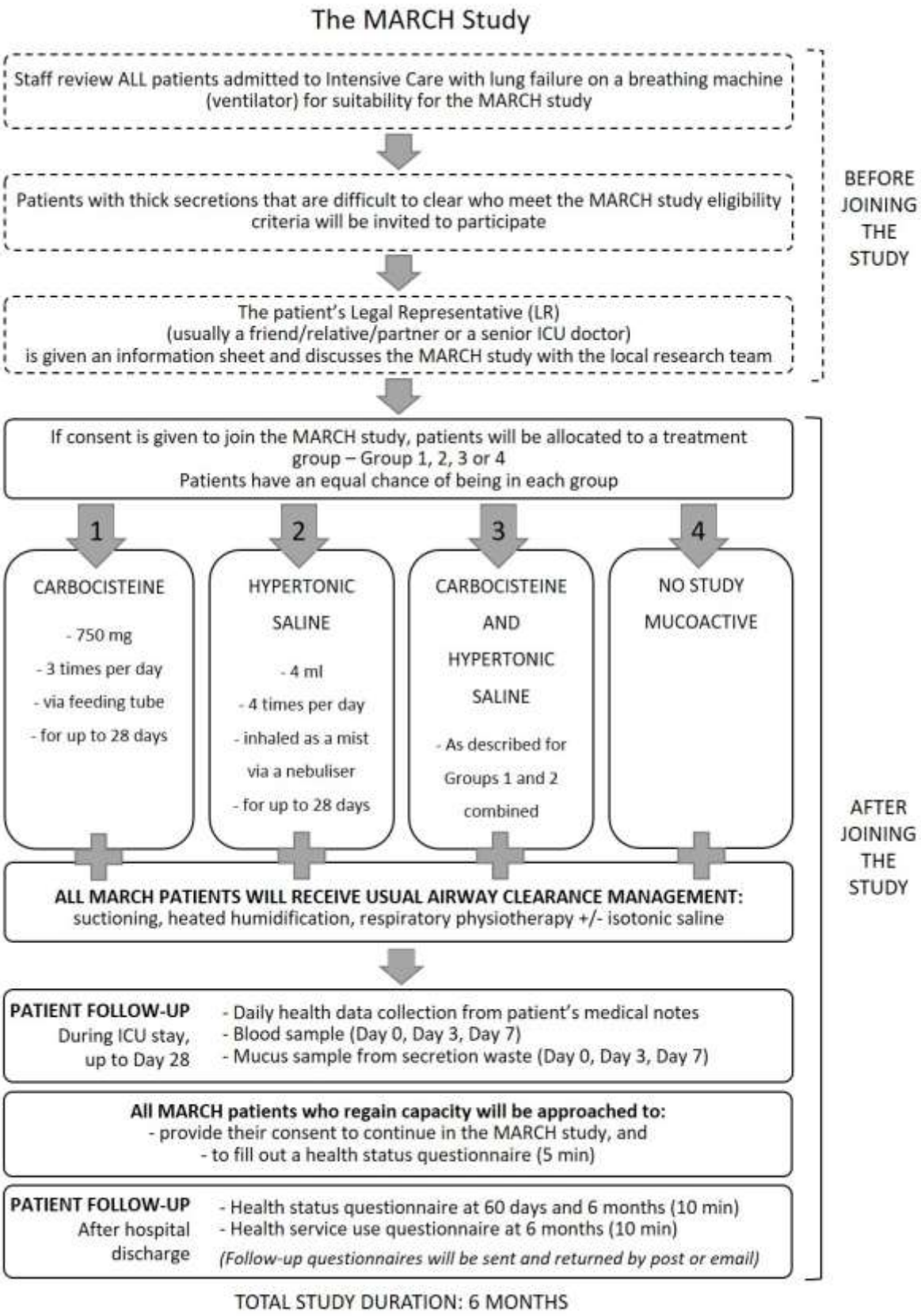
A study to determine the effect of mucoactive medications (carbocisteine and hypertonic saline) in critically ill patients with acute respiratory failure

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

When your relative/friend/partner has regained consciousness and has the ability to understand information about the purpose of this study, we will explain the study to them and seek their permission to continue in the research. Your relative/friend/partner's decision to continue in the study or withdraw will override the consent you have given.

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

Thank you for your time to consider 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 the 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 mucoactive medications 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 a liquid form or as a 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. This 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 with lung failure were receiving a mucoactive, and carbocisteine and hypertonic saline were 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 for the breathing tube to be 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 using these mucoatives.

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 relative/friend/partner's GP before sending their 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 has my relative/friend/partner been invited to take part?

The intensive care unit doctors found that your relative/friend/partner had lung failure when they were admitted to the ICU, and they now have difficulty clearing secretions from their lungs. Neither the researchers nor the intensive care unit doctors know whether mucoactives will help your relative/friend/partner recover more quickly. Therefore, we are inviting you to give consent for your relative/friend/partner to take part in this study to help us find out if mucoactives are beneficial for patients with lung failure who have difficulty clearing secretions. We plan to recruit up to 2000 patients to join the study, from around 40 hospitals across the UK.

Does my relative/friend/partner have to take part?

No. It is up to you to decide whether or not your relative/friend/partner takes part. If you do decide that they can take part, you will be given this Information Sheet to keep and will be asked to sign a study consent form. You are still free to withdraw your consent for your relative/friend/partner to take part, at any time and without giving a reason. If you decide that your relative/friend/partner should not take part, the standard of care they receive will not be affected.

What will happen to my relative/friend/partner if they take part?

Patients who are enrolled into the study will be put into one of four different groups, which is decided by chance. This means neither you nor the doctor treating your relative/ friend/partner can choose the treatment group, so the study treatments can be compared fairly. Patients have an equal chance (1:1:1:1) of being in one of the four groups. The treatments for 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.

When your relative/friend/partner is receiving the study treatment, the doctors and nurses looking after them will know which group they are in. This type of study is called a randomised controlled trial and it ensures that the treatment is compared fairly. If your relative/friend/partner is allocated to receive a mucoactive, they will be given this daily, for the duration of their stay in intensive care up to a maximum of 28 days (or up to 29 or 30 days if their breathing tube was removed on Day 27 or Day 28 respectively).

Your relative/friend/partner should not experience any pain or discomfort during the delivery of the mucoactive. Other than doses of mucoactives, your relative/friend/partner will receive the same care as other patients with lung failure.

Your relative/friend/partner's medical notes will be reviewed by the doctors and nurses, to find out if the treatment they are receiving has had any effect. The study team will review your relative/friend/partner's progress on a daily basis while in ICU.

Samples of your relative/friend/partner's airway secretions (mucus) and blood will also be taken to allow the study team to determine the ways in which mucoactive medications might work to improve patients' condition. Mucus samples will be taken from the breathing tube that your relative/friend/partner already has in place to help their breathing, as part of routine care to clear their lungs. Blood samples will be taken from lines that they already have in place. This will ensure that taking these samples does not cause them any additional pain or discomfort. The blood and mucus samples will be taken to help understand the ways in which mucoactives might work biologically, to improve lung failure.

We will contact the GP of your relative/friend/partner to let them know about their participation in the study. After discharge from hospital, we will follow-up the medical status of your relative/friend/partner either by telephone, contact with their GP, or review of their health care record, up to 6 months following treatment. We may also use NHS Digital if available in their region to confirm their medical status. If your relative/friend/partner moves house during the 6-month follow-up period, we will ask them to let us know by contacting the Northern Ireland Clinical Trials Unit either by post or email, using the contact details provided at the end of this Information Sheet.

How will my relative/friend/partner's samples be stored?

The samples taken from your relative/friend/partner will be stored in anonymised format at Queen's University Belfast. Samples are always stored according to appropriate regulations. We would like to store the samples indefinitely. However, if you do not believe your relative/friend/partner would want this, it does not affect their 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 your relative/friend/partner. 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 at 2 months and 6 months after your relative/friend/partner leaves hospital. However, these questionnaires are sent to them in the post or via email, to make it more convenient for them to complete.

While your relative/friend/partner is in the ICU, they may experience 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. Your friend/relative/partner would not have been eligible for the trial if your doctors identified them as someone with an existing condition that could have placed them 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 will closely monitor your relative/friend/partner's response to the medication, including any side effects. If any side effects occur, the doctors will decide whether it is appropriate to continue the medication.

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 the doctor and bedside nurse. If this happens to your relative/friend/partner, they may be 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 happens to your relative/friend/partner, their doctor and

bedside nurse will detect this from their monitors, and give them additional oxygen until their levels return 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 your relative/friend/partner 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 your relative/friend/partner is harmed due to someone's negligence, then they may have grounds for legal action against their NHS Trust, but they may have to pay their legal costs.

Would my relative/friend/partner taking part in this study be kept confidential?

Any information which is collected about your relative/friend/partner 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 will have a duty of confidentiality to your relative/friend/partner 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 relative/friend/partner's stay in hospital and to ascertain their long-term health status. In this instance your relative/friend/partner's 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 your relative/friend/partner after they leave hospital, the Trial Co-ordinating Centre (Northern Ireland Clinical Trials Unit) will need to keep records of their name, address, and other contact details such as telephone number and email address.

Your relative/friend/partner has the right to see their personal health information related to the research study, but they 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 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 to your relative/friend/partner at their 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 makes sure the research is conducted to a high standard to safeguard patient safety and 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 relative/friend/partner's 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 relative/friend/partner's 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 my relative/friend/partner to continue on the study?

You are free to withdraw your consent for your relative/friend/partner to participate at any time and without giving a reason. This will not affect the standard of care they receive. You have the right to request samples collected as part of this study to be destroyed and no further laboratory analyses to be performed. Your study doctor can take your relative/friend/partner out of the study at any time or stop their medication, if it is in their best medical interests. Your consent stands until such a time as your relative/friend/partner

can make a decision for themselves. They have the right to withdraw from the study without giving a reason and this will not affect their standard of care. They also have the right to withdraw samples collected.

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. For any updates on the progress of your relative/friend/partner during the study, please speak to a treating physician or a member of the research team.

How long can I think about my relative/friend/partner joining the study?

We are examining the effect of mucoactives started early once patients with lung failure have been identified as having difficulty clearing airway secretions from the lungs. You do not need to decide straight away and can take as much time as you need to make a decision.

Where can I or my relative/friend/partner 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 or your relative/friend/partner 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 your relative/friend/partner?

We will need to use information from your relative/friend/partner, your relative/friend/partner's medical records, your relative/friend/partner's 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 relative/friend/partner's 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 relative/friend/partner's records to make sure that the research is being done properly. People who do not need to know who your relative/friend/partner is, will not be able to see your relative/friend/partner's name or contact details. Your relative/friend/partner's data will have a code number instead.

We will keep all information about your relative/friend/partner 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 your relative/friend/partner took part in the study.

What are your choices about how your relative/friend/partner's information is used?

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

Where can you find out more about how your relative/friend/partner's 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 I am giving this consent based on what I believe would be my relative/friend/partner's wishes. In my opinion, they would be willing to participate in this study. ☐

3. I understand that my relative/friend/partner's participation is voluntary and that I am free to withdraw my consent for their participation at any time, without giving any reason and without their medical care or legal rights being affected. ☐

4. I understand that sections of my relative/friend/partner's medical notes may be inspected by responsible individuals from the NHS Trust, 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 their records for research related purposes only. I agree to information related to this research being retained at the NHS Trust, the Trial Co-ordinating Centre, Belfast Health and Social Care Trust, and Queen's University Belfast. ☐

5. I understand that the Trial Co-ordinating Centre will keep records of my relative/friend/partner's 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 their hospital stay, to facilitate follow up, and to ascertain their long-term health status. ☐

6. I agree to my relative/friend/partner having biological samples (blood and airway secretions) collected to be analysed and the data generated from these analyses to be used. ☐

7. I agree to my relative/friend/partner's 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. ☐

8. I agree to my relative/friend/partner's 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. ☐

9. 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)*. ☐

10. I understand that my relative/friend/partner's data will be shared in an anonymised format in publications, at conferences, and in research data-sharing repositories, and I understand that they will not be personally identified. ☐

11. I agree to my relative/friend/partner's GP being contacted by the research team to advise their doctor of their participation in the study. ☐

12. I agree to my relative/friend/partner being followed-up by the research team to assess their medical status. ☐

13. I agree to my relative/friend/partner to be contacted by the research team as part of the long-term follow up for the MARCH study. ☐

14. I agree to my relative/friend/partner taking part in the MARCH study. ☐

15. I understand that my relative/friend/partner's consent will override my consent, when they are able to give informed consent. ☐

I am the patient's:_____

(please write your relationship to the patient here)

Name of Personal Legal Representative	**Signature**	**Date (dd/mm/yy)**

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