MARCH

Mucoactives in Acute Respiratory failure: Carbocisteine and Hypertonic saline

# Frequently Asked Questions (FAQs)

This FAQs document is a quick reference guide for the core MARCH site trial team. Please also refer to the current versions of the Protocol and SIV training slides.

We will be updating this document periodically. If we have missed something, please get in touch with us at MARCH@nictu.hscni.net.

## Contents:

## GENERAL QUERIES

**1) Who is coordinating the MARCH trial?**

The MARCH trial is coordinated by the Northern Ireland Clinical Trials Unit (NICTU). If you need to contact the trial team, please email: MARCH@nictu.hscni.net or for urgent enquiries phone the NICTU office on +44 (0)28 9615 1447.

**2) What is the recruitment target for each site?**

The recruitment target for each site is 1-2 participants per month.

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## NIHR ASSOCIATE PRINCIPAL INVESTIGATOR (API) SCHEME

**3) Is MARCH registered with the NIHR Associate PI Scheme?**

Yes. The MARCH trial is registered with the NIHR Associate Principal Investigator (API) Scheme. It is a valuable opportunity to obtain accreditation for contributions to working on the MARCH trial for those who do not have research as a core part of their role. Please contact the trial team if we can assist with any specific MARCH-related queries in relation to this.

For further API Scheme information and applications, please click here: https://www.nihr.ac.uk/health-and-care-professionals/career-development/associate-principal-investigator-scheme.htm.

**4) Can a site have more than one API trainee working on the study simultaneously?**

Yes, sites can have more than one API at a time. The maximum number will depend on PI capacity.

**5) Should I list my role as 'Associate PI' on the Delegation Log?**

No, please list your job role on the Delegation Log. This will ensure that the Delegation Log remains correct once your 6-month API tenure has ended, and will help us monitor that you have been delegated tasks appropriately.

**6) Who will countersign my completed API Checklist on behalf of the study team?**

At the end of your tenure as an API, please forward your completed checklist to the MARCH study mailbox (MARCH@nictu.hscni.net) for review and signature by the Trial Manager.

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## SITE SET-UP

**7) Do the trial documents (PIS, consent forms etc.) need to be localised?**

Yes, trial documents need to be updated with your Trust header and contact details prior to use at your site.

**8) Is there a minimum number and make-up of research team members required to open a site?**

Yes. As a minimum, we require the site PI, lead physiotherapist and/or research nurse, and a pharmacy representative to be listed on the Delegation Log, having completed all necessary training and submitted all required documents.

**9) What documents and/or training is required for research team members for opening a site?**

The following are required:

1. CV (scanned copy of wet ink signature dated within 1 year)

2. GCP certificate (dated within 3 years)
3. Training on current protocol
4. Additional training (as required for delegated tasks – e.g. MACRO training for data entry; NICTU SOP TM03 for safety reporting; NICTU SOP TM02 for maintenance of the Investigator Site File)
5. Fully completed Delegation Log signed and dated by the PI

Please do not add a start date to the Delegation Log until you have completed all appropriate training. Contact the trial team for any queries or assistance.

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## SCREENING

### 10) How do we record screening data for MARCH?

Screening data are collected for the MARCH trial using the Screening and Recruitment Log. Microsoft Excel logs can be filled out locally prior to data entry onto MACRO, or data entered directly into the database if preferred. We are using the SEAR Framework (Screened, Eligible, Approached, Randomised) to understand why patients are not recruited. Please return your screening data via MACRO by the **1st Friday of the month**.

### 11) Who can identify potential MARCH patients?

Any member of the clinical or research teams can identify potentially eligible patients for the MARCH trial e.g. bedside nurse, physiotherapist, ward round team, research nurse.

The key eligibility criterion for patients to enter the MARCH trial is the presence of secretions that are difficult to clear with usual airway clearance management. Patients may become eligible at any time during their ICU admission. If a patient is identified as being potentially eligible, then the local research team should be contacted to review the patient and undertake formal screening and confirmation of eligibility (by a qualified medic on the Delegation Log). Patients who have already been screened for MARCH, but not randomised (for whatever reason), can be rescreened if they still meet inclusion/exclusion criteria.

Please make sure that your wider team of clinical colleagues are aware of the trial, and how to contact your research team. We have provided promotional materials to support this process (poster for staff areas; bedside information for the trial; short PowerPoint presentation to explain the trial; MARCH stickers). Please let us know if you haven't yet received these, or have any suggestions on what would help with this process at your site.

### 12) Do clinicians who identify potentially eligible patients need to be on the Delegation Log?

No, any clinician can identify a potentially eligible patient, and these clinicians do not need to be listed on the Delegation Log.

Members of the research team who subsequently undertake formal screening and/or confirmation of eligibility of potential patients, do need to be listed on the Delegation Log. NB eligibility can only be confirmed by a physician.

### 13) What training do medics need to confirm eligibility?

We require a CV, GCP and documentation of protocol training. Once the core team have been trained at SIV, the PI or those delegated the task of protocol training (Task 1) on the Delegation Log are permitted to train other colleagues locally. Local protocol training needs to be documented on the Study Training Log, and all documentation returned to NICTU before additional people are added to the Delegation Log.

**14) Is there a specific timescale from ICU admission/meeting eligibility criteria to randomisation?**

No, there is no specific timeframe between becoming eligible and being randomised. Patients may become eligible at any time-point during their ICU admission. We would encourage sites to start the screening and consent process as soon as possible.

**15) Can a patient previously recruited to the trial be recruited to the trial again if they are readmitted to hospital?**

No, previous enrolment in the trial is an exclusion criterion.

**16) What happens if a potentially eligible patient is prescribed a mucoactive agent?**

Our exclusion criteria exclude participants who have commenced mucoactive treatment more than 24 hours prior to trial enrolment. This offers a 24-hour window to identify and enrol patients who have started a mucoactive agent.

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## ELIGIBILITY

**17) What is the process to confirm patient eligibility?**

Eligibility must be confirmed by a medically qualified person (i.e. a physician) listed on the Delegation Log prior to randomisation, and it must be documented in the patient's medical notes. We will provide stickers to include the date and time of eligibility confirmation. The screening log and eligibility checklist in the eCRF should also be completed.

**18) Are ACCP colleagues permitted to confirm eligibility?**

No, as per the MARCH protocol, only medically qualified doctors may document confirmation of eligibility. This task (Task 4) on the CTU Delegation Log should only be assigned to medically qualified personnel. We recommend training additional doctors on the study to be added to the Delegation Log for the purposes of eligibility confirmation at your site.

**19) Can more than one reason be entered on the CRF for ineligibility?**

Yes, more than one reason for ineligibility can be entered on the CRF.

**20) Are patients with suspected or confirmed COVID-19 disease eligible for MARCH?**

Yes, patients with suspected or confirmed COVID-19 disease are eligible. Any patient with suspected or confirmed COVID-19 will not undergo collection of biological samples.

**21) Do patients have to receive a specific amount of usual airway clearance management before eligibility?**

No, there is no specific amount or duration of usual airway clearance management (suctioning, humidification, respiratory physiotherapy, use of normal saline). As soon as any member of the clinical or research team identifies that a patient has secretions that are difficult to clear with usual airway clearance management, then they are potentially eligible for the trial and can undergo formal screening.

**22) Is completion of a pregnancy test required to confirm eligibility?**

Yes. This is required in the MARCH trial to adhere to regulations, and detailed in our protocol, as MARCH is a CTIMP and carbocisteine is contraindicated in the first trimester. A urine or blood pregnancy test in females with child-bearing potential (aged 15-55 years) is required prior to enrolment, and pregnant patients will be excluded.

Following further confirmation locally, where there is a biological reason that precludes potential for pregnancy e.g. menopause, hysterectomy, then a pregnancy test is not required. However, this must be clearly documented in the notes for monitoring purposes such that we have confirmation around the issue of pregnancy. Clinical judgement based on clinical presentation and history of the patient is not sufficient to exclude pregnancy, and therefore a test is still required for all other patients as detailed above.

In many ICUs, it is routine clinical practice to complete a pregnancy test on all women of childbearing age who are admitted to ICU. There is no requirement for an additional pregnancy test, beyond what would normally be conducted, to be performed for the MARCH trial.

In the event that a pregnancy test is not performed prior to randomisation of a patient of childbearing potential, this would be considered a Protocol Deviation and should be reported as such via the MACRO database. Please complete a test as soon as possible.

**23) Are pregnancy tests provided for the trial?**

No, we are not providing these as in many ICUs pregnancy tests are routinely performed on all women of childbearing age.

**24) Is a patient eligible if they have issues with enteral absorption e.g. NG tube on free drainage?**

Whilst this is not specifically an exclusion criterion, if the patient were to be randomised into a treatment arm which included carbocisteine then absorption of the drug would be an issue so these patients would not be considered eligible. Likewise, if there is enteral feeding access in situ, delivery of carbocisteine is not possible.

**25) Is there a definition of Acute Respiratory Failure for the purposes of the trial?**

No, we do not protocolise acute respiratory failure (ARF) in MARCH, so there is no need for reference to any blood gas or ventilatory parameters etc. Whether or not a patient has ARF is based on clinical assessment by the local research team.

**26) Is a patient receiving N-Acetylcysteine (NAC) for treatment of overdose eligible for participation?**

If otherwise eligible, patients being administered NAC for overdose would not be excluded. Whereas, if receiving NAC for secretion management, these patients would be excluded.

**27) Is a patient receiving hyoscine/ atropine/ glycopyrronium eligible for participation?**

These drugs are not mucoactives, but are typically used to dry excess secretions. Any patients receiving any of these agents (if otherwise eligible) may be enrolled into the MARCH study. However, where patients are still receiving these at the time of enrolment, please consider locally whether they could be stopped - as the action of hyoscine/atropine/glycopyrronium is opposite to the purpose of a mucoactive, clinical assessment would be advised to determine appropriateness of the patient receiving both.

**28) Is there a definition of 'thick secretions' in the protocol?**

No, we do not provide a definition of thick secretions. As soon as a patient is flagged by any member of the research team as having secretions that are difficult to clear using normal airway clearance management, this is the point at which they should be formally screened for eligibility.

**29) If a patient is currently receiving one of the interventions, can they be considered for inclusion in the trial?**

If a patient has a pre-existing chronic respiratory condition and is receiving routine use of any mucoactive, including either carbocisteine or hypertonic saline, then they are **NOT** eligible for inclusion in the trial (refer to the latest protocol for further details).

If a patient is currently receiving one of the study mucoactives, but this was commenced within 24 hours, then the patient is still **potentially eligible**. Commencement of any mucoactive treatment more than 24 hours prior to trial enrolment is an exclusion criterion (refer to the latest protocol for further details).

**30) If patient is transferred from another hospital ventilated are they excluded, given we may not be able to confirm treatment history?**

We have not defined a maximum time between a patient becoming eligible and randomisation, so as long as baseline data is available these patients would not be excluded.

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## CONSENT

**32) Who can take consent from the participant or their legal representative?**

Any member of staff who is GCP trained, suitably qualified and experienced, and has been delegated this duty on the Delegation Log.

**33) Can the physician in charge of a participant request their withdrawal from the study?**

No, only the Legal Representative (either personal or professional) who provided consent, or the participant themselves once capacity has been regained, may withdraw consent from trial participation. If the physician in charge of the patient does not want to comply with treatment allocation, the participant should remain in the trial. Any missed doses of IMP should be recorded in the CRF. Likewise, administration of non-trial mucoactives should be documented. Please let us know if this is an issue at your site.

**34) Are patient-related documents available in non-English languages?**

Yes, patient documents (the Consent to Continue and Personal Legal Representative information sheet and consent forms and the EQ-5D-5L questionnaire) are available in Arabic, Bengali, Chinese (simplified script), Polish, Punjabi and Urdu. If there are any other languages that are common at your site and you think it would be helpful to have patient documents in that language please notify the study team at NICTU.

**35) Does the witness for consent via telephone have to be on the Delegation Log?**

No. The witness may be a member of the site study team or other site medical staff. They will need to hear the full conversation i.e. the information given and the representative agreeing to consent.

**36) If we cannot get a Personal Legal Representative to provide consent on behalf of the patient, can we use a Professional Legal Representative?**

Yes, a Professional Legal Representative (ProfLR) may be approached to give consent if no Personal Legal Representative is 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 i.e. they must not be on the Delegation Log.

**37) If the Personal Legal Representative indicates that they are not in a position to consider participation of their relative/friend/partner in the study, can we approach a Professional Legal Representative?**

No, we would not advise defaulting to obtain ProfLR consent instead. Where a Personal Legal Representative (PerLR) is available to approach, this should be the first line of consent, and their decision respected. Please record the reason for non-eligibility in the database.

**38) Is there a timeline for consent?**

No, there is no timeline for consent and MARCH is not a time-sensitive intervention.

**39) Can the Participant Information Sheet and Consent Form be emailed to Personal Legal Representatives?**

Yes, but please subsequently follow-up by sending it to the legal representative via post, or provide directly if possible e.g. during a hospital visit to obtain written consent.

**40) What happens if I am unable to seek Consent to Continue for a participant who has regained capacity before they are discharged?**

In cases where it has not been possible to ask the patient for consent to continue, the consent of the legal representative (either personal or professional) remains valid. This is not considered a protocol deviation. These participants will be sent standard follow-up communication. Any attempt to approach the patient for consent to continue, whilst still in hospital, must be documented in the patient's notes. There is no need to pursue the patient for consent to continue beyond the point of hospital discharge. Please record the reason why consent to continue was not obtained.

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## RANDOMISATION

**41) Who will be able to access the randomisation system?**

We will set-up all members of the team who are on the MARCH Delegation Log to receive randomisation notifications with the treatment allocation included. All those on the Delegation Log who are assigned the task of randomising patients (Task 5) will be provided with the 'Randomise' functionality on the web-based system.

If there are any changes to the MARCH trial team at your site, please let us know as soon as possible and we will add or remove colleagues from the randomisation system.

**42) How do I access the web-based randomisation system?**

You can access the randomisation system using the following link: Login (abdn.ac.uk). Please save the randomisation system link to your browser or desktop for ease of access if you are randomising patients.

**43) What do I do if I have forgotten my username or password?**

You should have received your username from ChaRT at study set up, so please check your email. Please contact MARCH@nictu.hscni.net if you require your credentials to be re-sent. If you have forgotten your password, please click the password reset button on the CHaRT log in page.

You can also access the telephone randomisation system by dialling the following number: 0800 2802307.Your Trial ID Code is 219XX – where XX is your centre number.

**44) Where can I access help with the randomisation system?**

Please refer to the User Guides for the Telephone and Web Randomisation systems. These are included as hard copies in your Trial Manual, and electronically at the time of opening to recruitment. The guideline for the web randomisation system is also available electronically within the CHaRT system. Please click the help button to access.

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## CO-ENROLMENT

**45) Can patients be co-enrolled into other critical care trials?**

Co-enrolment will be reviewed on a case-by-case basis in accordance with NIHR-supported, national co-enrolment guidelines for critical care trials. Please let NICTU know about any other critical care studies you are currently involved in.

Details of co-enrolment with studies should be documented in the eCRF, and sites will be regularly updated with a current list of studies for which co-enrolment agreements are in place with MARCH.

Please contact the MARCH trial team if you have a potential MARCH patient that is currently enrolled in another ICU clinical trial for which there is currently no co-enrolment agreement in place.

**46) Are MARCH participants co-enrolled into the conservative care arm of UK-ROX more likely to trigger safety outcomes?**

For the purposes of MARCH, we would advise reporting any episode of desaturation over and above what would normally be targeted for that patient, and where that resulted in requiring an increase in FiO2.

**47) What are the arrangements for co-enrolment between MARCH and sites running the Cysteamine Domain of REMAP-CAP?**

Due to biological similarities between the Cysteamine and Carbocisteine interventions, is it not possible to co-enrol these patients. Therefore, for management of patients eligible for both MARCH and the Cysteamine Domain of REMAP-CAP, the following approach was agreed between the respective trial teams:

- Suspected/confirmed COVID patients should be enrolled into the Cysteamine Domain of REMAP-CAP
- Non-COVID patients should be enrolled into MARCH
- Non-COVID patients enrolled into MARCH may be co-enrolled with REMAP-CAP domains *other* than the Cysteamine Domain
- Patients only eligible for MARCH (and not the REMAP-CAP Cysteamine Domain) may be enrolled into MARCH regardless of COVID status

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## INTERVENTIONS

**48) Is using instilled saline considered normal practice? Does it need to be recorded on the eCRF**

Yes, instillation of isotonic ('normal') saline is considered part of usual airway clearance management and it does not need to be recorded on the eCRF.

**49) Can physiotherapy students treat patients enrolled in the MARCH trial?**

Yes, students can be part of the treating clinical physiotherapy team. We would expect all local regular supervisory arrangements to be in place for senior staff supervising student clinicians.

**50) What are the doses of mucoactive agents being tested in MARCH?**

Carbocisteine: 750 mg three times daily, delivered systemically via capsules, syrup, or sachet formulation, according to local availability and practice.

Hypertonic saline: 6 or 7% concentration, 4 ml four times daily, delivered via nebulisation. Either concentration is acceptable, depending on what sites use locally in their normal practice.

**51) Are study mucoactives being provided?**

No, study mucoactives should be sourced from local site stock.

**52) Who can prescribe study mucoactives, and do they have to sign the Delegation Log?**

Study mucoactives can be prescribed and dispensed in accordance with usual local site prescription practices, and therefore whichever clinicians are within this remit. Clinicians prescribing study mucoactives do not need to be listed on the Delegation Log.

**53) Can 3% percent hypertonic saline be given to patients in the usual airway clearance management group if required?**

3% hypertonic saline would be classed as a non-trial mucoactive, and so if this was given to a patient in the usual airway clearance management group, we would ask for this to be recorded on the eCRF (delivery of a non-trial mucoactive).

**54) Our site regularly prescribes PRN salbutamol for patients receiving 7% hypertonic saline – should we continue to do this for the trial? It is only delivered if the patient develops bronchospasm.**

If it is usual practice for your site to have salbutamol prescribed PRN for these patients, then this can be continued for patients in the MARCH trial. If it is subsequently delivered to a patient who develops bronchoconstriction, then this would be reported as a safety outcome on the eCRF.

**55) Our site typically carries out a tolerability test for patients commenced on 7% hypertonic saline, whereby a dose is given followed by a period of monitoring for bronchoconstriction and need for bronchodilation – is this part of the protocol?**

No, a tolerability test is not part of the protocol. However, one of the safety outcomes being collected across all patients in the MARCH trial, is bronchoconstriction requiring nebulised bronchodilators (during or up to 30 minutes following nebulisation).

Therefore, a patient allocated to receive hypertonic saline in the MARCH trial should continue to receive their scheduled doses, as any episodes of bronchoconstriction requiring nebulised bronchodilators will be collected and reported.

**56) Is it a protocol deviation if carbocisteine or hypertonic saline are given to patients in the usual airway clearance management group?**

No, this is not a protocol deviation. However, we would request delivery of either of the study mucoactives to patients in the comparator (usual airway clearance management alone) group is recorded on the eCRF (non-trial mucoactive page). The CTU will monitor adherence in the comparator group and review with individual sites as needed. Likewise, if a non-allocated treatment is given to patients in the carbocisteine or hypertonic saline group, this should also be recorded on the eCRF.

**57) Is it a protocol deviation if a dose of study mucoactive is missed?**

No, this is not a protocol deviation. If a scheduled dose is missed, this can be delivered subsequently, but not within 1 hour of the next planned dose of study mucoactive.

**58) If a patient has completed 48 hours of unassisted breathing should their study mucoactive be terminated?**

It is not mandated in the protocol for a patient to continue the study mucoactive once 48 hours of unassisted breathing has been achieved (that marks the primary outcome of duration of mechanical ventilation). At that point, the patient is considered to have completed their intervention period in the trial.

Mucoactive treatment beyond the primary outcome is at the discretion of the local treating clinical team. If mucoactive treatment is continued beyond the primary outcome and it is not a clinical decision that has been recorded in the notes, then this represents a protocol deviation.

**59) If a patient is reintubated within the 48-hour window what happens?**

A patient reintubated within the 48-hour period will not achieve unassisted breathing and you should continue with the protocol.

**60) If a patient is subsequently reintubated after achieving the primary outcome, do they restart their allocated study mucoactive?**

No. If a patient is reintubated, they do not need to restart their allocated study mucoactive. Re-intubation should be recorded on the eCRF as one of the secondary outcomes we are collecting. Further delivery of any mucoactive treatment would be at the discretion of the local treating clinical team.

**61) If a patient is randomised to the comparator group (usual airway clearance management alone) and the treating clinician feels they need to receive a mucoactive, does this mean the patient needs to be withdrawn from the study?**

No, the patient does not need to be withdrawn from the study. However, details of any non-trial mucoactive administration should be recorded on the eCRF (non-trial mucoactive page).

**62) If the patient is extubated onto NIV, does this mark the beginning of unassisted breathing?**

No, unassisted breathing begins once the patient has completed their time on NIV. NIV counts as assisted breathing and contributes to the duration of mechanical ventilation. Unassisted breathing begins when there is no inspiratory or pressure support.

**63) Are high flow or CPAP classed as assisted breathing?**

No. High flow and CPAP are classed as unassisted breathing. If a patient is extubated onto high flow or CPAP, their period of unassisted breathing starts at that point.

**64) For the mucoactives, do they need specific temperature monitoring and storage assessments? Are accountability logs required?**

No. Local processes should be followed regarding mucoactive temperature monitoring and storage. No study-specific accountability logs are required.

**65) If a mucoactive cannot be given because a patient is not absorbing for any reason or is nil by mouth for a day or two, what should we do?**

That information should be captured on the case report form as a reason for omission of a dose of study mucoactive. The patient might be able to receive the dose again, in which case this would continue to be reported on the CRF.

**66) Is it necessary to continue the study mucoactives in situations where a participant's secretions become loose and easy to clear?**

Study mucoactives should be continued until the first termination criterion is met (Protocol Section 9.6). This is important to ensure a standard approach to mucoactive delivery within the study.

**67) Does it matter which type/manufacturer of nebuliser is used locally?**

We do not stipulate what type/manufacturer of nebuliser should be used for MARCH participants randomised to receive hypertonic saline, and there will be variability across sites with regard to this.

**68) What should I do if I notice a problem with the vent for a patient receiving hypertonic saline?**

Please liaise with your local technicians around checking that nebuliser circuits are in situ appropriately, and the specific manufacturer instructions for the make and model of ventilator in use with that patient. If an issue occurs with a MARCH patient, and this meets the definition of a safety outcome (ventilator or circuit dysfunction with respiratory deterioration, Protocol Section 10.3) then please report via the MACRO database.

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## DATA COLLECTION

**69) Can we access training on MACRO?**

Yes, MACRO training sessions can be provided by NICTU Data Manager, Una McShane. Please contact the NICTU to arrange this.

**70) Do we need additional MACRO training if we have received previous training?**

If your previous MACRO training was provided by NICTU, then you do not need to attend additional training. However, if your MACRO training was provided for a trial coordinated by a different Clinical Trials Unit, you will need to attend training provided by NICTU.

**71) Who do we contact if there problems with MACRO?**

Please contact the MARCH trial team at NICTU if you experience any difficulties with data entry using MACRO.

**72) Our research team do not work at weekends, can data collection be completed retrospectively on Monday for the preceding Saturday and Sunday?**

Yes, data collection can be completed retrospectively on a Monday for the previous weekend for any patients enrolled in MARCH.

**73) What adverse events are being collected for MARCH?**

Only Serious Adverse Events that are related to the mucoactive should be reported i.e. Serious Adverse Reactions (SAR).

Events that are **expected** in this population **do not** need to be reported as adverse events 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 adverse events.

**74) We have an SAE form to submit which isn't signed, but are approaching the 24 hour window – should we still submit the form?**

Yes, please still submit the SAE form so that the CTU is notified within the required 24-hour timeframe. Signatures can follow if that is not possible in advance.

**75) What is the primary outcome for the MARCH trial?**

The primary outcome for the MARCH trial is the duration of mechanical ventilation. This is defined as the time from randomisation until first successful unassisted breathing (defined as maintaining unassisted breathing at 48 hours or death).

**76) How is 'successful unassisted breathing' defined?**

Successful unassisted breathing is defined as no inspiratory support or extracorporeal lung support, maintained at 48 hours.

**77) What counts towards the 'duration of mechanical ventilation?**

Duration includes time receiving extracorporeal lung support, invasive mechanical ventilation, and non-invasive ventilation delivering volume or pressure support ventilation. Time receiving high-flow oxygen therapy and/or continuous positive airway pressure is excluded.

**78) Can a patient with a tracheostomy in situ, achieve successful unassisted breathing?**

Yes, this is possible.

**79) If a patient is extubated onto CPAP/high flow does that count as unassisted breathing? What would happen if a patient were extubated onto NIV?**

For patients who are extubated onto CPAP or high flow, their 48-hour period of unassisted breathing would start from the point of extubation; CPAP/high flow constitute unassisted breathing. For a patient extubated onto NIV, unassisted breathing would commence once the NIV had finished. The period of time on NIV counts towards the duration of mechanical ventilation.

**80) My patient receives overnight CPAP/BiPAP for sleep-disordered breathing, does this count as receiving assisted breathing?**

No. Any use of CPAP does not constitute assisted breathing. If a patient routinely requires nocturnal BiPAP support for sleep-disordered breathing, their period of unassisted breathing would commence once regular nocturnal settings had been reached and were in use.

**81) Are any positive pressure devices used as part of respiratory physiotherapy counted towards assisted breathing?**

No. Use of positive pressure devices as part of respiratory physiotherapy treatment is not considered as part of the duration of mechanical ventilation.

**82) Do we need to collect data on secretion status?**

No, we will not be collecting any data describing secretion status. A brief amount of data will be collected in the eCRF regarding respiratory physiotherapy input, namely whether the patient has received respiratory physiotherapy treatment, and if so, how many sessions that day.

**83) Is bronchial lavage or bronchoscopy a secondary outcome and do these need reporting?**

No, these procedures do not need reporting.

**84) Do I need to record data for all antibiotics administered?**

No, only antibiotics prescribed to treat a respiratory tract infection post-randomisation should be documented on MACRO, using the Antiobiotic Usage eForm. The Medical History eForm will capture antibiotics being administered for pulmonary infection in the baseline period (the 24 hours preceding randomisation).

**85) What do I do if my unit is not listed within the dropdown menu for ICNARC codes?**

In the 'Admission Details' eForm within the database, enter the patient's CMP number and select 'Other' to specify the associated hospital/unit name and ICNARC number manually.

**86) When does data collection for antibiotic usage and non-trial mucoactive administration stop?**

This data collection should start at randomisation and stop when a participant meets the primary endpoint.

**87) If the event-driven forms (e.g. the Protocol Deviation eForm) are not applicable to a participant, do I need to complete these?**

Yes, the overarching question (yes or no) should be selected for all event driven forms for completeness.

**88) Do safety outcomes need to be recorded for participants across all four treatment arms?**

Yes, as we need to ensure that the opportunity for reporting a safety outcome is equal across all participants. For example, a patient in the usual airway clearance management group could experience a safety outcome in response to any other nebulised medication they were receiving.

**89) If a patient recruited to MARCH has been transferred from ICU in another hospital, what should be recorded as the date and time of hospital and ICU admission?**

Please record the date and time that the patient was admitted to the recruiting hospital/ICU.

**90) How do I record plateau pressure and driving pressure?**

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. Driving pressure is a derived field on MACRO (calculated as plateau pressure – PEEP). Once values have been entered for plateau pressure and PEEP the driving pressure will automatically calculate.

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## SAMPLE COLLECTION

**91) Does my site have to participate in biological sample collection?**

No, collection of biological samples (blood and sputum) is not a prerequisite for participation in the main MARCH trial.

If you have local capacity to collect sputum samples only, as these require minimal processing, this is fine and we can provide you with labels and bags for storage.

**92) What happens if my site is participating in biological sample collection?**

If your site is participating in collection of biological samples (blood and sputum) you will have received a copy of the Sample Handling Guideline. This contains more detailed information about sample collection (in addition to the information in the main trial protocol) for sites to follow. We will be commencing with collection of blood samples from patients enrolled into the trial; collection of sputum samples will commence at a later stage, and we will update sites accordingly. If your site is participating in collection of biological samples, please note that it is not a protocol deviation if a sample cannot be collected on any of the designated collection days.

**93) Do staff who collect sputum samples have to be listed on the Delegation Log?**

No, staff who collect sputum samples e.g. bedside nursing staff, or physiotherapists, do not have be listed on the Delegation Log if this is part of their routine clinical duties. We would ask that staff not trained on the study liaise with the research team with regards to labelling, storage etc.

**94) Who do I contact for additional sample kits?**

Please contact Judit Barabas (Judit.Barabas@qub.ac.uk) at Queen's University Belfast to request additional kits or consumables. Judit Barabas is also the point of contact for sample shipping.

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## MISCELLANEOUS

**95) Is there a letter for GPs?**

Yes, we have created a template letter for sites to notify GPs of their patient's participation in the study.

**96) When should GP letters be sent, to confirm enrolment or after hospital discharge?**

GP letters can be sent at any time, at the time of enrolment or at hospital discharge, whichever is most convenient for your site.

**97) Should a GP letter be sent if the patient dies?**

No, a GP letter is not required to be sent if the patient dies.

**98) When and how should the Patient Contact Details form be returned to the NICTU?**

Please return this form as soon as possible after randomisation via post or encrypted email.

**99) We have a suspected serious breach of the Protocol, what should we do?**

If you suspect there may have been a serious breach of the study Protocol, or GCP, please contact the Chief Investigator or Co-Chief Investigator to discuss any concerns before reporting it.

The PI should complete and sign a 'Notification of Serious Breach of Trial Protocol or GCP' form, which should be scanned and emailed to the NICTU within 24 hours of becoming aware of the breach.

**100) If there is a change of Principal Investigator at my site, what action should I take?**

If there is a change of Principal Investigator at your site, you should notify the NICTU as soon as possible so that we can progress an amendment and advise you how to proceed.

**101) What do I have to do to support patient follow-up for MARCH?**

All follow-up activity post-hospital discharge will be managed centrally by the NICTU, though we would ask you to do the following to facilitate this process:

- Ask patients to provide Consent to Continue in the study, provide a Health Service Use Diary, and explain planned follow-up health questionnaires (6 weeks and 6 months)
- Provide patients with an EQ-5D-5L to complete at the time of Consent to Continue.
- Enter date of hospital discharge and Consent to Continue data on the eCRF in a timely fashion.

**102) Can medical doctors other than the PI report SAEs, for example where a team member works part-time and there is a risk of the SAE not being reported within 24hrs?**

Yes, as long as that task has been delegated to the team member on the Delegation Log.