



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.

These FAQs will be provided electronically only to save paper, and so you can search for a key term easily. We will be updating this document periodically.

If we have missed something, please get in touch with us at MARCH@nictu.hscni.net.

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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 NICTU on +44 (0)28 9615 1447.

2) How long is the MARCH trial recruiting for?

Recruitment to the trial will end on 31st October 2024.

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. 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?

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

SITE SET-UP

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

Yes, trial documents need to be localised prior to use at your site.

6) 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.

7) 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.

SCREENING

8) 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 (Screening, Eligibility, Approached, Randomised) to understand why patients are not recruited. Please return your completed screening log via MACRO by the **1st Friday of the month**.

9) 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).

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.

10) 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 confirmation of eligibility of potential patients do need to be listed on the Delegation Log.

11) 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 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.

12) 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.

13) 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.

14) 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.

ELIGIBILITY

15) What is the process to confirm patient eligibility?

Eligibility must be confirmed by a medically qualified person listed on the Delegation Log and it must be signed off 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.

16) 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.

17) 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.

18) 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.

19) Is the pregnancy test detailed in the eligibility confirmation essential?

Yes, a pregnancy test for all women with child-bearing potential (aged 15-55 years) is required in order to confirm eligibility. MARCH is a CTIMP and this test is important for ensuring the safety of patients enrolled into the trial.

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.

20) 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.

CONSENT

21) Who can consent patients for enrolment into MARCH?

The Principal Investigator (PI) (or designee) is responsible for ensuring that informed consent for trial participation is given by each patient or a legal representative. An appropriately trained doctor or nurse may take consent.

22) 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.

23) Does the main consent form mention the SWAT?

Yes, the SWAT is mentioned in the information sheet and consent form. It states that we are looking at different methods of following up with patients on the study. It is not included as a separate consent as everyone who has given consent to continue is included in the SWAT. People will not know what group they have been randomised to, so they will receive different follow up according to the internal randomisation. We are looking at how best to communicate with the patients and to improve the return of study questionnaires.

24) Does the witness have to be on the Delegation Log?

No, the witness could be another member of staff.

25) 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, or a person nominated by the healthcare provider.

26) If a Personal Legal Representative cannot be contacted can an API consent on behalf of the patient?

No, only an independent medical consultant responsible of the care of the patient can perform that role.

27) Is there a timeline for consent?

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

28) 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.

RANDOMISATION

29) 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.

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

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

31) 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.

32) 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.

MUCOACTIVE TREATMENT AT SCREENING/ENROLMENT:

33) 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 carbocysteine 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).

CO-ENROLMENT

34) 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.

INTERVENTIONS

35) 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.

36) 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.

37) 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.

38) Are study mucoactives being provided?

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

39) 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.

40) Does it matter what nebuliser device is used for delivery of hypertonic saline?

No, you can use whichever nebuliser system is normally in use in your ICU.

41) 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).

42) 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.

43) 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.

44) 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.

45) 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.

46) If a patient has completed 48 hours of unassisted breathing should their study mucoactive no longer be given?

No, 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.

47) 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.

48) 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.

49) 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).

50) 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.

51) 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.

52) 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.

53) 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.

DATA COLLECTION

54) Can we access training on MACRO?

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

55) 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 separate trial coordinated by a different Clinical Trials Unit, you will need to attend training provided by NICTU.

56) 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.

57) 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.

58) 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.

59) 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 it is submitted within the required 24-hour timeframe. Signatures can follow if that is not possible in advance.

60) 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).

61) How is 'successful unassisted breathing' defined?

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

62) 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.

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

Yes, this is possible.

64) 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.

65) 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.

66) 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.

67) 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 treatment, and if so, how many sessions that day.

68) Is bronchial lavage or bronchoscopy a secondary outcome and do these need reporting

No, these procedures do not need reporting.

SAMPLE COLLECTION

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

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

70) 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.

MISCELLANEOUS

71) 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.

72) 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.

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

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

74) We have a suspected protocol breach, what should we do?

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

If the deviation is classified as a potential 'serious breach', 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.

75) 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.

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

- 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.

77) Can Co-PIs report on AEs, for example where a team member works part-time and there is a risk of the AE not being reported within 24hrs?

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