The MARCH Trial
Mucoactives in Acute Respiratory failure:
Carbocisteine and Hypertonic saline

Mucoactive drugs for acute respiratory failure: A 2x2 factorial, randomised, controlled, open-label, Phase 3, pragmatic, clinical and cost effectiveness trial with internal pilot

Health Economic Analysis Plan

Protocol /Study number:	20131DMcA-AS
Trial registration number:	ISRCTN17683568
Funder and number	Health Technology Assessment Programme; NIHR130454
Sponsor:	Belfast Health and Social Care Trust
REC and number:	Yorkshire & The Humber - Leeds East Research Ethics Committee; 21/YH/0234
Protocol version:	Final 4.0 02/12/2024
HEAP version:	Final 3.0 14/01/2025
Author:	Ashley Agus
Chief Investigator:	Danny McAuley
Co-Chief Investigator:	Bronwen Connolly

Contents

Introduction

The MARCH trial is a 2x2 factorial, randomised, controlled, open-label, Phase 3, pragmatic, clinical and cost effectiveness trial with internal pilot to determine whether mucoactives (carbocisteine and hypertonic saline) in critically ill patients with acute respiratory failure (ARF) reduce duration of mechanical ventilation. Although mucoactives are unlikely to impact on mortality, a reduction in the duration of mechanical ventilation may reduce ventilator-associated co-morbidities and hospital service resource use compared to usual care. The cost of a Level 3 (Intensive Care Unit, ICU) bed day in critical care in the UK (based on 2 to 6 organs being supported) is approximately £2600 [1]. If the use of mucoactives results in patients coming off mechanical ventilation one day earlier and stepping down to a lower level of care, this could save more than £900 per patient with ARF (based on a Level 2 (High Dependency Unit) bed day cost of £1700) [1]. This is a conservative estimate of the economic saving because the patient's overall hospital length of stay might also be reduced.

Method

We will assess the cost-effectiveness of the interventions in Table 1 at 6 months via a cost-utility analysis embedded in the MARCH trial. Current guidelines for conducting [2, 3, 4] and reporting [5] economic evaluations will be followed. The analysis of costs will be performed from the perspective of the National Health Service (NHS) and Personal Social Services (PSS). Discounting will not be required for the analysis as the time horizon does not exceed one year.

Table 1 MARCH trial treatment arms.

Intervention A	Carbocisteine: 750 mg three times daily, for up to 28 days, delivered systemically, plus usual airway clearance management.
Intervention B	Hypertonic saline: 4 ml of 6 or 7% concentration, delivered via nebulisation, four times daily, for up to 28 days, plus usual airway clearance management.
Intervention AB	Carbocisteine and hypertonic saline (as described in A and B), plus usual airway clearance management.
Usual Care 0	Usual airway clearance management including suctioning, heated humidification (either active heated humidification devices, or passive heat and moisture exchangers), and respiratory physiotherapy; use of isotonic saline may also be used depending on clinician preference

Measurement of health care resource use and costs

Hospital resource use data will be collected prospectively using the case report form during the participants' primary admission to ICU. Length of stay for the primary critical care admission will be calculated from the date of randomisation to the date of critical care discharge or date of death if this occurs within critical care. General hospital ward length of stay will be calculated from the date of critical care discharge to the date of hospital discharge or date of death if this occurs on the ward. Data on any readmissions to ICU will be obtained from the Intensive Care National Audit and Research Centre (ICNARC) for participants at ICUs which participate in the Casemix Programme (CMP) and from the Scottish Intensive Care Society Audit Group (SICSAG) via the Electronic Data Research and Innovation Service (EDRIS) for those participants in Scottish ICUs.

Cost for critical care will be calculated for each participant's critical care admission using the Healthcare Resource Group (HRG) code corresponding to each critical care admission and any readmission during the primary hospital admission. These will be provided by ICNARC for participants at CMP sites. The HRG codes represent the highest level of complexity, based on the total number of organs supported during the admission.. Since Scotland has not fully adopted the HRG methodology we will apply the modal HRG code observed for the critical care admissions of participants at the CMP sites to the critical care admissions of the Scottish participants. An approach used previously in a similar population [9].

Intervention costs will be calculated using data collected from the CRF. Ward stay costs will be calculated by multiplying the number of ward days during the primary hospital admission by the unit cost associated with rehabilitation for respiratory disorders.

Participants' use of health and social care service from hospital discharge to 6 months post randomisation will be measured using a postal questionnaire. Telephone completion will also be used for non-responders. Participants will be provided with a health service log booklet at hospital discharge to keep track of their health service use and to facilitate questionnaire completion. Mortality status will be confirmed prior to participant contact by contacting GPs. Individual-level resource use will be combined with unit costs to estimate costs for each participant. Unit costs will be obtained from publicly available sources; NHS Reference Costs,

Unit Cost of Health and Social Care from Personal Social Services Research Unit and the Drug Tariff.

Measurement of health outcomes

Utilities for the calculation of quality adjusted life years (QALYs) will be obtained using the EQ-5D-5L [6] administered at consent to continue, 60 days and 6 months post randomisation via a postal questionnaire. Telephone completion will be used for non-responders. The EQ-5D-5L is a generic preference-based measure of health-related quality of life (HRQoL), which provides a description of health using five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each with 5 levels of severity. Responses will be converted into utility scores using the UK tariff recommended by NICE at the time of analysis: this is currently a model developed by Hernández Alava et al [7]. QALYs will be calculated using the area under the curve method. As patients are critically ill at baseline, an EQ-5D-5L utility score of zero will be assumed, in keeping with other studies in the critical care setting [8-11].

Analysis of costs and outcomes

Descriptive statistics (mean, standard error, 95% confidence interval) will be used to summarise (by each treatment arm) the health service use (during primary hospital admission and after discharge until 6 months), the associated costs, EQ-5D-5L scores and QALYs. Death will not be treated as a censoring event and so periods after death will be counted as observations with known outcome, an approach used previously in similar patient populations [8-10]. This means that for participants who have died in hospital, resource use and costs after hospital discharge until 6 month follow up will be considered to be zero.

Missing data

Missing data have the potential to introduce bias into trial results as participants with incomplete health economic data may be systematically different from those with complete data [12]. Therefore, for the cost-effectiveness analysis missing health economic data will be multiply imputed with chained equations and predictive mean matching using the 'mi impute chained command' in Stata. This assumes that data are missing at random. A regression model will be specified to predict the missing data and selected variables will be entered into

the model as predictors e.g. treatment group, baseline characteristics. The number of imputed datasets generated will be similar to the maximum percentage of incomplete cases observed in the data [13].

Cost-effectiveness analyses

Recommendations have recently been published [14] on methods for analysing economic evaluations of full factorial trials and we will use these to guide the analyses. In keeping with this guidance, we will treat each option within the factorial design as mutually exclusive options (A, B, AB or 0 as per Table 1) i.e. we will not assume important interactions exist between the factors. Although no interactions are anticipated between carbocisteine and hypertonic saline in the analysis of clinical endpoints, it is possible that interactions may occur in terms of costs and QALYs. Regression analysis with an interaction term and adjusting for baseline characteristics will be used on the multiply imputed datasets to estimate Total Costs, QALYs and net monetary benefit (NMB)[1] over the 6 month time horizon for each of the four treatment options. Incremental Costs, QALYs, NMBs and the incremental cost-effectiveness ratios (ICERs)[2] of each option relative to the next best option will also be calculated. NICE's [2] cost-effectiveness threshold of £20,000 per additional QALY will be used to identify which of the four treatments has the highest NMB and is therefore the optimal choice i.e. best value for money.

Uncertainty in the health economic data will be explored by non-parametric bootstrapping drawing 1000 samples of the same size as the original sample with replacement [15]. The resulting 1000 replicates will be plotted on the cost-effectiveness plane [16] and used to construct a cost-effectiveness acceptability curve [17] showing the probability of each option having the highest NMB at different levels of WTP per QALY.

Sensitivity analysis

Sensitivity analyses will be performed to explore impact on cost effectiveness of variations in key parameters and will include exploring the impact of; regression analysis without an

[1] Net monetary benefit is calculated as NMB=WTP*mean QALYs-mean Costs, where WTP is the decision maker's maximum willingness-to-pay per QALY

[2] Incremental cost effectiveness ratio is calculated as ICER= difference in mean Costs / difference in mean QALYs between a pair of treatments.

interaction term and plausible departures from the missing at random assumption of multiple imputation (performed using pattern-mixture models [18]).

Draft tables are presented in the Appendix.

References

1. Department of Health. Reference Costs 2020–21, Department of Health, 2021.
2. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual.2022. Online https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation [last accessed 07/03/2023]
3. Drummond MF, Schulper MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Fourth Edition. Oxford: Oxford University Press, 2015
4. Glick HA, Doshi JA, Sonnad SS, Polsky D. Economic evaluation in clinical trials. Second Edition. Oxford: Oxford University Press OUP, 2014
5. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, Caulley L, Chaiyakunapruk N, Greenberg D, Loder E, Mauskopf J, Mullins CD, Petrou S, Pwu RF, Staniszewska S; CHEERS 2022 ISPOR Good Research Practices Task Force. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement: Updated Reporting Guidance for Health Economic Evaluations. Value Health. 2022 Jan;25(1):3-9.
6. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version ofEQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20(10):1727-36. doi: 10.1007/s11136-011-9903-x
7. Hernández Alava, M., Pudney, S. & Wailoo, A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. *PharmacoEconomics* 2023;41, 199–207
8. Agus A, Hulme C, Verghis RM, McDowell C, Jackson C, O'Kane CM, Laffey JG, McAuley DF. Simvastatin for patients with acute respiratory distress syndrome: long-term outcomes and cost-effectiveness from a randomised controlled trial. Crit Care. 2017 May 17;21(1):108.
9. Agus A, McNamee JJ, Jackson C and McAuley DF. Extracorporeal carbon dioxide removal compared to ventilation alone in patients with acute hypoxaemic respiratory failure: cost-utility analysis of the REST RCT
10. Agus A, Phair G, Page V, et al. Simvastatin for the prevention and treatment of delirium in critically ill, mechanically ventilated patients (MoDUS): a cost-effectiveness analysis. The Lancet Respiratory Medicine, Volume 6, Issue 3, e9-e10.
11. Walsh TS, Stanworth S, Boyd J et al. The age of blood. Evaluation (ABLE) randomised controlled trial: description of the UK-funded arm of the international trial, the UK cost–utility analysis and secondary analyses exploring factors associated with health-related quality of life and health-care costs during the 12-month follow-up. *Health Technol Assess*. 2017; **21**: 1-118

12. Faria R, Gomes M, Epstein D, White IR. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. Pharmacoeconomics. 2014 Dec;32(12):1157-70. doi: 10.1007/s40273-014-0193-3.
13. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. Stat Med 2011;30:377–99.
14. Dakin H, Gray A. Economic evaluation of factorial randomised controlled trials: challenges, methods and recommendations. Stat Med. 2017 Aug 15;36(18):2814-2830. doi: 10.1002/sim.7322. Epub 2017 May 3. PMID: 28470760; PMCID: PMC5599939.
15. Briggs AH, O'Brien BJ,Blackhouse G. Thinking outside the box: recent advances in the analysis and presentation of uncertainty in cost-effectiveness studies. Annu Rev Public Health. 2002;23:377-401.
16. Black WC. The CE plane: a graphic representation of cost-effectiveness. Med Decis Making. 1990;10(3):212-214.
17. Fenwick E, Claxton K, Sculpher MJ. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Econ 2001;10:779–87
18. Leurent B, Gomes M, Faria R, Morris S, Grieve R, Carpenter JR. Sensitivity Analysis for Not-at-Random Missing Data in Trial-Based Cost-Effectiveness Analysis: A Tutorial. Pharmacoeconomics. 2018 Aug;36(8):889-901. Erratum in: Pharmacoeconomics. 2019 Mar 9.

Appendix

Draft tables

Table 2 Units costs in 2020/2021 Great British pounds (GBP, £)

Resource item	Unit Cost (£)	Source and details
Carbocisteine		NHS Drug Tariff
Hypertonic saline		NHS Drug Tariff
Level 3 day		NHS Reference Costs
Level 2 day		NHS Reference Costs
Level 1 day		NHS Reference Costs
Level 0 / Ward day		NHS Reference Costs
Ambulance		NHS Reference Costs
Emergency department attendance, not admitted		NHS Reference Costs
Emergency department attendance, admitted		NHS Reference Costs
Hospital Outpatient attendance		NHS Reference Costs
GP surgery consultation		Unit Costs of Health and Social Care
GP phone consultation		Unit Costs of Health and Social Care
GP home consultation		Unit Costs of Health and Social Care
GP out of hours consultation		Unit Costs of Health and Social Care
GP nurse surgery consultation		Unit Costs of Health and Social Care
GP nurse phone consultation		Unit Costs of Health and Social Care
District nurse visit		Unit Costs of Health and Social Care
Specialist nurse visit		Unit Costs of Health and Social Care
Social worker visit		Unit Costs of Health and Social Care
Physiotherapist visit		Unit Costs of Health and Social Care

Occupational therapist visit		Unit Costs of Health and Social Care
Dietitian visit		Unit Costs of Health and Social Care
Counsellor visit		Unit Costs of Health and Social Care
Homecare worker		Unit Costs of Health and Social Care

Table 3 Table 1 Number (%) of participants with complete health economic data by type and treatment group

	Carbocisteine (n=)		**Hypertonic saline (n=)**		**Carbocisteine & Hypertonic saline (n=)**		**Usual care (n=)**	
Data type	Complete (%)	Incomplete (%)	Complete (%)	Incomplete (%)	Complete (%)	Incomplete (%)	Complete (%)	Incomplete (%)
Health service								
Primary hospital admission (Randomisation to hospital discharge)								
Discharge to 6 months								
Randomisation to 6 months								
EQ-5D-5L								
60 days								
6 months								
QALYs at 6 months								

Table 4 Total costs (UK £) by type and treatment group over 6 months (observed cases, without imputation of missing data).

	Carbocisteine (n=)		Hypertonic saline (n=)		Carbocisteine & Hypertonic saline (n=)		Usual care (n=)	
Service Costs	Obs	Mean (95% CI)	Obs	Mean (95% CI)	Obs	Mean (95% CI)	Obs	Mean (95% CI)
Primary ICU stay								
Other ICU readmission days								
Wards days								
Total primary admission costs								
Intervention								
Health service use discharge to 6 months								
Total health care costs over 6 months								

Obs= Observed number of cases; N (%) = number of participants using the service; n=number randomised; CI= confidence intervals

Table 5 Regression analysis with an interaction term, including imputation of missing values and adjustment for baseline characteristics

	Total Costs/ Participant	Total QALYs/ Participant	NMB/ Participant	Cost per QALY		
				Versus Usual Care	Versus Carbocisteine	Versus Hypertonic saline
Main effect Carbocisteine (SE)						
Main effect Hypertonic saline (SE)						
Interaction Carbocisteine X Hypertonic saline (SE)						
Constant term (SE)						
Predicted mean outcome						
Carbocisteine (SE)						
Hypertonic saline	(SE)					
Carbocisteine & Hypertonic saline (SE)						
Usual care (SE)						