The CLEAR trial: A 2x2 factorial randomised open label trial to determine the clinical and cost-effectiveness of hypertonic saline (HTS 6%) and carbocisteine for airway clearance versus usual care over 52 weeks in bronchiectasis

Health Economic Analysis Plan

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Introduction

Bronchiectasis (BE) caused by irreversible dilatation thickening and sac like formations in bronchial walls. BE not caused by cystic fibrosis has been considered an “orphan lung disease” due to perception that it was a rare disease. Greater numbers of patients are now diagnosed with BE with HRCT scans. Current estimates suggest 1 in 1000 people in the UK have BE. It is a debilitating illness with patients usually suffering from a persistent cough, chronic daily sputum expectoration, recurrent chest infections and a poor health-related quality of life. BE has been shown to be associated with significant mortality that displays a year on year increase of up to 3% per annum. Morbidity is also high and UK hospitals admission data found that BE was the primary diagnosis in 1 in 1800 admissions, with a 7-fold increase reported in hospital bed days needed for treating BE in the last eight years.

Mucus hypersecretion is a clinical feature of BE. Airway mucosal infection and/or inflammation associated with these diseases often gives rise to inflammatory products, including neutrophil-derived DNA and filamentous actin, in addition to bacteria, apoptotic cells and cellular debris that may collectively increase mucus production and viscosity. Mucoactive drugs potentially increase the ability to expectorate sputum and/or decrease mucus hypersecretion. Many mucoactive drugs are currently available and can be classified according to their mechanism of action. Mucoactive medications include expectorants, mucoregulators, mucolytics and mucokinetics.

The British Thoracic Society guidelines provide detail on the current standard of care for patients with BE and currently there is not enough evidence to recommend mucoactive agents as part of standard care. By developing our understanding of the specific effects of mucoactive agents, we may result in improved therapeutic use of these drugs. UK registry data demonstrates clearly that BE centres prescribe mucoactives but this is to a small proportion of the BE population and is not in line with current guidelines. Current guidelines both UK and elsewhere highlight the need for more research. There are no licenced medications in BE however a large number of clinical trials are currently ongoing in BE and so this situation is likely to change. This is balanced against evidence that adherence to therapies in BE is low and directly related to the number of prescribed medications. Furthermore, low adherence is linked to patient outcomes. Therefore, it is essential that only drugs demonstrated to be effective in

BE should be recommended. In the proposed study one of the medications is an oral medication (carbocisteine) and the other is an inhaled medication (HTS 6%).

Method

A within trial economic evaluation will assess the cost-effectiveness of the four treatment options in Table 1 at 52 weeks post-randomisation. A cost-utility analysis (CUA) will estimate the cost per quality adjusted life year. In addition, a cost-effectiveness analysis (CEA) consistent with the primary outcome measure will estimate the cost per exacerbation avoided. Current guidelines for conducting [1, 2, 3] and reporting [4] economic evaluations will be followed. Recommendations have recently been published [5] on methods for analysing economic evaluations of full factorial trials and we will use these to guide the analyses. 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 CLEAR trial treatment arms.

Intervention A	Standard care and twice daily nebulised Hypertonic Saline (6%) over 52 weeks;
Intervention B	Standard care and carbocisteine (750mg three times per day until visit 3 reducing to 750mg two times per day) over 52 weeks;
Intervention AB	Standard care and a combination of twice daily nebulised HTS (6%) and 750mg of carbocisteine three times per day until visit 3 reducing to 750mg twice per day) over 52 weeks;
Control 0	Standard care over 52 weeks.

Standard care= standard airway clearance management

Measurement of health and social care resource use and costs

Participants' use of health and social care resource use (both related and unrelated to their BE) will be collected from baseline to 52 weeks using a questionnaire and log developed specifically for the CLEAR study. At baseline participants will be asked about their service use in the previous four weeks so that baseline costs can be adjusted for in the analysis. Participants will be provided with a log at baseline, 2, 8 and 26 weeks to prospectively record their service use and record details of their prescribed medications (including antibiotics). The questionnaires will be completed at the baselines, 2, 8, 26 and 52 week visits with reference to the logs.

We will use the intervention-related resource data collected prospectively by the trial team to estimate the cost of the intervention. This will include drug usage, the cost of the nebuliser systems (including handsets, aerosol heads, controllers, cleaning aid) and any consumables required.

Individual-level service use will be combined with unit costs to estimate costs for each participant. Unit costs will be obtained from publicly available sources e.g. NHS Reference Costs, Unit Costs of Health and Social Care, NHS Drug Tariff. We will obtain the costs for the nebuliser system and consumables from PARI.

Measurement of health outcomes

The health outcome of interest for the CUA is the quality adjusted life year (QALY) calculated using responses on the EQ-5D-5L [6] at baseline, 2, 8, 26 and 52 weeks post-randomisation. 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 to utility scores using the tariff recommended by NICE [1] at the time of analysis. At the time writing the health economic analysis plan, this is a model developed by Hernández Alava et al [7]. The area under the curve method will be used to calculate QALYs. The health outcome of interest for the CEA will be the number of fully qualifying exacerbations experienced by patients over 52 weeks (as defined in the Protocol Section 20.2 Appendix 1: Definition of Exacerbation).

Analysis of costs and outcomes

Descriptive statistics (means, standard errors, 95% confidence intervals) will be used to summarise (by each treatment arm) the health care and social care resource use, the associated costs, EQ-5D-5L scores, QALYs and number of exacerbations.

Missing data

Missing data has the potential to introduce bias into trial results as participants with incomplete health economic data may be systematically different from those with complete data [8]. Therefore 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 as recommended [9].

Cost-utility and cost-effectiveness analyses

In keeping with current guidance [5] 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 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, exacerbations and net monetary benefit (NMB)[1] over the 52 week time horizon for each of the four treatment options. Incremental Costs, QALYs, exacerbations, NMBs and the incremental cost-effectiveness ratios (ICERs)[2] of each option relative to the next best option will also be calculated. NICE's [1] 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 [10]. The resulting 1000 replicates will be plotted on the cost-effectiveness plane [11].and used to construct cost-effectiveness acceptability curves [12], showing the probability of each option having the highest NMB at different levels of WTP per QALY. Since there is no commonly-agreed threshold value for cost per exacerbation avoided, a range of plausible thresholds will be explored.

[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.

Sensitivity analyses

Sensitivity analyses will be performed to explore the impact on cost-effectiveness of variations in key parameters. Examples may include;

- Considering the impact of only including hospital service use that was related to bronchiectasis in the calculation of total healthcare costs.
- Considering the impact of using different nebuliser systems with different unit costs.
- Considering the impact of changes in inclusion criteria number three over the study period relating to the number of exacerbations experienced within a specified timeframe.
- Regression analysis without an interaction term.
- Plausible departures from the missing at random assumption of multiple imputation (performed using pattern-mixture models [13])

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Appendix

Draft tables

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

Resource item	Unit Cost (£)	Source and details
Hypertonic Saline: Sodium Chloride inhalation solution 60 mg per 1 mL		NHS Drug Tariff
Carbosisteine 375mg capsules		NHS Drug Tariff
eFlow®Rapid Nebuliser system		PARI
eFlow®Rapid Nebuliser handset		PARI
eFlow®Rapid aerosol head		PARI
Home Oxygen therapy		Health and Social Care Board personal communication
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
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
Hospital bed day		NHS Reference Costs
Other medications		NHS Drug tariff

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

	Standard Care & Hypertonic saline (n=)		**Standard Care & Carbocisteine (n=)**		**Standard Care & Hypertonic saline & Carbocisteine (n=)**		**Standard Care (n=)**	
Data type	Complete (%)	Incomplete (%)	Complete (%)	Incomplete (%)	Complete (%)	Incomplete (%)	Complete (%)	Incomplete (%)
Health service								
Discharge to 26 weeks								
26 weeks to 52 weeks								
EQ-5D-5L								
baseline								
2 weeks								
8 weeks								
26 weeks								
52 weeks								
QALYs at 52 weeks								

Table 4 Total costs (UK £) by treatment group over 52 weeks (observed cases, without imputation of missing data)

	Standard Care & Hypertonic saline (n=)		**Standard Care & Carbocisteine (n=)**		**Standard Care & Hypertonic saline & Carbocisteine (n=)**		**Standard Care (n=)**	
Service Costs	Obs	Mean (95% CI)	Obs	Mean (95% CI)	Obs	Mean (95% CI)	Obs	Mean (95% CI)
Total health care costs over 52 weeks months								

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

Table 5 EQ-5D-5L scores and total QALYs (UK £) by treatment group over 52 weeks (observed cases, without imputation of missing data)

	Standard Care & Hypertonic saline (n=)		**Standard Care & Carbocisteine (n=)**		**Standard Care & Hypertonic saline & Carbocisteine (n=)**		**Standard Care (n=)**	
EQ-5D-5L	Obs	Mean (95% CI)	Obs	Mean (95% CI)	Obs	Mean (95% CI)	Obs	Mean (95% CI)
baseline								
2 weeks								
8 weeks								
26 weeks								
52 weeks								
QALYs at 52 weeks								

Table 6 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 Standard Care	**Versus Hypertonic Saline**	**Versus Carbocisteine**
Main effect Hypertonic Saline (SE)						
Main effect Carbocisteine (SE)						
Interaction Carbocisteine X Hypertonic saline (SE)						
Constant term (SE)						
Predicted mean outcome						
Hypertonic Saline (SE)						
Carbocisteine (SE)						
Standard Care & Hypertonic saline & Carbocisteine (SE)						
Standard Care (SE)						