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J Cross, F Elender, G Barton, A Clark, L Shepstone, A Blyth, M Bachmann and I Harvey, on behalf of the MATREX Research Group

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 03/13/06. The contractual start date was in March 2005. The draft report began editorial review in May 2009 and was accepted for publication in December 2009. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

A randomised controlled equivalence trial to determine the effectiveness and cost–utility of manual chest physiotherapy techniques in the management of exacerbations of chronic obstructive pulmonary disease (MATREX)

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Objectives: To estimate the effect, if any, of manual chest physiotherapy (MCP) administered to patients hospitalised with chronic obstructive pulmonary disease (COPD) exacerbation on both disease-specific and generic health-related quality of life. To compare the health service costs for those receiving and not receiving MCP.
Design: A pragmatic, randomised controlled trial powered for equivalence. It was not possible to blind participants, clinicians or research staff to study arm allocation during the intervention.
Setting: Four UK hospitals in Norwich, Great Yarmouth, King's Lynn and Liverpool.
Participants: 526 participants aged 34–91 years were recruited between November 2005 and April 2008; of these, 372 provided evaluable data for the primary outcome. All persons hospitalised with COPD exacerbation and evidence of sputum production on examination were eligible for the trial providing there were no contraindications to performing MCP.
Interventions: Participants were allocated to either MCP or no MCP on an intention-to-treat (ITT) basis. However, active cycle of breathing techniques (ACBT) was used in both arms. Participants allocated to the intervention were guided to perform ACBT while the physiotherapist delivered MCP. Participants allocated to the control arm received instruction on ACBT only.
Main outcome measures: The primary outcome was COPD-specific quality of life, measured using the St George's Respiratory Questionnaire (SGRQ) at 6 months post randomisation. The European Quality of Life-5 Dimensions (EQ-5D) questionnaire was used to calculate the quality-adjusted life-year (QALY) gain associated with MCP compared with no MCP. Secondary physiological outcome measures were also used.
Results: Of the 526 participants, 261 were allocated to MCP and 264 to control, with 186 participants evaluable in each arm. ITT analyses indicated no significant difference at 6 months post randomisation in total SGRQ score [adjusted effect size (no MCP–MCP) 0.03 (95% confidence interval, CI –0.14 to 0.19)], SGRQ symptom score [adjusted effect size 0.04 (95% CI –0.15 to 0.23)], SGRQ activity score [adjusted effect size –0.02 (95% CI –0.20 to 0.16)] or SGRQ impact score [adjusted effect size 0.02 (95% CI –0.15 to 0.18)]. The imputed ITT and per-protocol results were similar. No significant differences were observed in any of the outcome measures or subgroup analyses. Compared with no MCP, employing MCP was associated with a slight loss in quality of life (0.001 QALY loss) but lower health service costs (cost saving of £410.79). Based on these estimates, at a cost-effectiveness threshold of λ = £20,000 per QALY, MCP would constitute a cost-effective use of resources (net benefit = £376.14). There was, however, a high level of uncertainty associated with these results and it is possible that the lower health service costs could have been due to other factors.
Conclusions: In terms of longer-term quality of life the use of MCP did not appear to affect outcome. However, this does not mean that MCP is of no therapeutic value to patients with COPD in specific circumstances. Although the cost-effectiveness analysis suggested that its use was cost-effective, much uncertainty was associated with this finding and it would be difficult to justify providing MCP therapy on the basis of cost-effectiveness alone. Future research

should include evaluation of MCP for patients with COPD producing high volumes of sputum, and an evaluation of the effectiveness of ACBT in COPD exacerbation.
Trial registration: Current Controlled Trials ISRCTN13825248.

Contents

List of abbreviations

λ	cost-effectiveness threshold
6MWT	six-minute walk test
ABG	arterial blood gas
ACBTw	active cycle of breathing techniques
ACCP	American College of Chest Physicians
AE	adverse event
BCSS	Breathlessness Cough and Sputum Scale
CAO	chronic airflow obstruction
CEAC	cost-effectiveness acceptability curve
CF	cystic fibrosis
CI	confidence interval
COAD	chronic obstructive airway disease
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CRF	case report form
DMEC	Data Monitoring and Ethics Committee
EQ-5D	European Quality of Life-5 Dimensions questionnaire
EQ-VAS	EQ-5D visual analogue scale
FET	forced expiratory technique
FEV_1	forced expiratory volume in 1 second
FRC	functional residual capacity
FVC	forced vital capacity
GCP	good clinical practice
GP	general practitioner
HRG	Healthcare Resource Group
ICER	incremental cost-effectiveness ratio
INR	international normalised ratio
ITT	intention to treat
JPH	James Paget Hospital
MCID	minimal clinically important difference
MCP	manual chest physiotherapy
MRC-D	Medical Research Council-Dyspnoea (scale)
NETSCC	NIHR Evaluation, Trials and Studies Coordinating Centre
NICE	National Institute for Health and Clinical Excellence
NMB	net monetary benefit
NNUH	Norfolk and Norwich University Hospital
NSF	National Service Framework
PD	postural drainage
PP	per protocol
PSS	personal social services
QALY	quality-adjusted life-year
QEH	Queen Elizabeth Hospital
QoL	quality of life
RCT	randomised controlled trial
REC	Research Ethics Committee
RA	research associate
SaO_2	arterial oxygen saturation
SGRQ	St George's Respiratory Questionnaire
SD	standard deviation
SF-36	Short Form–36 items

continued

TMG	Trial Management Group	UHA	University Hospital Aintree
TSC	Trial Steering Committee	V/Q	ventilation/perfusion ratio
UEA	University of East Anglia		

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Manual chest physiotherapy (MCP) techniques, involving chest percussion, vibration and assisted coughing, have long been used in the treatment of respiratory conditions. However, strong evidence for the benefit of this intervention is lacking. Specifically with respect to chronic obstructive pulmonary disease (COPD), a review of the research literature indicates a clear state of clinical equipoise. Traditionally, patients hospitalised with an exacerbation of COPD have been given MCP to assist with sputum clearance. However, uncertainty as to whether it confers either short- or long-term benefits has led to wide variation in practice, with individual clinical preference tending to dictate whether or not a patient receives treatment.

Current clinical guidelines on the management of COPD are unable to provide evidence statements on physiotherapy interventions on account of inherent methodological limitations in existing research. The aim of this study was to address this situation by providing robust evidence on the effectiveness of MCP for this clinical population.

Objectives

To estimate the effect, if any, of MCP administered to patients hospitalised with COPD exacerbation on both disease-specific and generic health-related quality of life. To compare the health service costs for those who either receive or do not receive MCP while in hospital.

Design, setting and interventions

Using a pragmatic, randomised controlled trial design powered for equivalence we compared patients who either received or did not receive MCP while in hospital, in terms of disease-specific quality of life and health-care resource use, in the medium term (6 months), on an intention-to-treat (ITT) basis. The study employed active cycle of breathing techniques (ACBT) in both trial arms. Patients allocated to the intervention arm were guided to perform ACBT while the physiotherapist delivered MCP. For patients allocated to the control arm, the physiotherapist provided instruction on the elements of ACBT and advice on suitable positions to assist with sputum clearance.

Participants

Five hundred and twenty-six participants aged 34–91 years, recruited from four secondary care hospitals between November 2005 and April 2008, were randomised; of these, 372 participants provided evaluable data for the primary study outcome. All persons hospitalised with COPD exacerbation and evidence of sputum production on examination were eligible for the trial providing there were no contraindications to performing MCP.

Main outcome measure

The primary study outcome was COPD-specific quality of life, measured using the St George's Respiratory Questionnaire (SGRQ). An effect size of 0.3 standard deviations in the SGRQ was specified in advance as the threshold for superiority.

The European Quality of Life-5 Dimensions (EQ-5D) questionnaire was employed as an additional generic health-related quality of life measure and used to calculate the quality-adjusted life-year (QALY) gain associated with MCP, compared with no MCP (incremental effect). Physiological outcome measures included the Breathlessness Cough and Sputum Scale (BCSS), the Medical Research Council-Dyspnoea (MRC-D) scale, sputum volume produced during hospitalisation, oxygen saturation at baseline and change in oxygen saturation associated with MCP. In addition, the Six-minute Walk Test (6MWT) was performed on a subsample of participants at one hospital site.

To estimate the incremental cost of MCP to the health service, physiotherapy input (including MCP), hospital admissions, outpatient visits and

rehabilitation levels over the 6-month trial period were monitored for each patient. Appropriate unit costs were assigned to each of these resources. The incremental cost and incremental effect of MCP was subsequently used to estimate the cost-effectiveness of MCP. Per-protocol (PP) analyses were performed for primary and secondary effectiveness end points and for QALYs.

Results

Health-related outcomes

Equivalence was demonstrated with respect to the primary outcome at the primary end point. The ITT analyses indicated no significant difference at 6 months in total SGRQ score [adjusted effect size (no MCP–MCP) 0.03 (95% confidence interval, CI –0.14 to 0.19)], SGRQ symptom score [adjusted effect size 0.04 (95% CI –0.15 to 0.23)], SGRQ activity score [adjusted effect size –0.02 (95% CI –0.20 to 0.16)] or SGRQ impact score [adjusted effect size 0.02 (95% CI –0.15 to 0.18)]. The imputed ITT and PP results were similar. No significant differences were observed in any of the outcome measures or subgroup analyses.

Cost-effectiveness

Compared with no MCP, employing MCP was associated with a slight loss in quality of life (0.001 QALY loss) but lower health service costs (cost saving of £410.79). Based on these estimates, at a cost-effectiveness threshold of λ = £20,000 per QALY, MCP would be estimated to constitute a cost-effective use of resources (net benefit = £376.14), on the assumption that resources could be spent elsewhere in a more efficient manner. There was, however, a high level of uncertainty associated with these results (47.6% chance of making the wrong decision by choosing MCP when λ = £20,000 per QALY) and one could not rule out the possibility that lower health service costs had been due to other factors. Moreover, though the results of the complete case analysis were in line with the base case, it should be noted that less than 50% of respondents provided complete EQ-5D data.

Conclusions

In terms of longer-term quality of life, the use of MCP does not appear to affect outcome in patients hospitalised for COPD exacerbation. Although the cost-effectiveness analysis suggested that MCP was cost-effective, much uncertainty was associated with this finding.

Implications for health care

1. This study addressed the limitations of previous research by standardising the delivery of MCP and obtaining a sample of sufficient size to derive statistically robust results for a patient-orientated, clinically meaningful outcome.
2. This study found no gain in longer-term quality of life when MCP was included in the physiotherapeutic management of acute exacerbation of COPD. However, the findings of this study do not mean that MCP is of no therapeutic value to patients with COPD in specific circumstances.
3. In terms of cost-effectiveness, MCP was associated with lower overall health service costs, with the cost of providing therapy offset by savings associated with fewer hospital admissions among patients assigned to receive MCP. However, interpretation of this apparent saving should be examined in the light of the primary outcome, which demonstrated no evidence of efficacy above normal care. As MCP was not found to be effective, it is difficult to justify providing this therapy on the basis of the results of the cost-effectiveness analysis alone. Furthermore, there is no guarantee that that any cost savings identified would be realised by employing MCP in routine care.
4. This study developed an MCP treatment that reflects professional consensus on best practice. With respect to the essential elements of MCP, it clarifies potential areas of ambiguity and provides a set of clear parameters within which treatment can be given. The high level of adherence to the MCP treatment protocol used in this trial suggests that it would be acceptable among the profession as a generic tool for delivering therapy.

Recommendations for research

With respect to the primary aim of the MATREX trial, further research is not required to demonstrate equivalence between receiving and not receiving MCP. Further research on the level of cost-effectiveness is unlikely to yield gains, as the benefits of both MCP and no MCP were similar and thus the consequences of making the wrong decision are small. As such, the cost of further research is likely to outweigh the value of information that would be gained. However, the

findings of this study do not mean that MCP is of no therapeutic value to patients with COPD in specific circumstances.

The research questions arising from this study are listed below in order of priority:

- Is MCP effective for patients with COPD producing high volumes of sputum?
- Can the risk of oxygen desaturation during MCP be predicted?
- Is ACBT effective in treating COPD exacerbation?
- What are the trends over time in admission and survival rates for COPD?
- How can health-related resource use be more accurately identified?

Trial registration

This trial is registered as ISRCTN13825248.

Chapter 1
Introduction

Chronic obstructive pulmonary disease (COPD) is a slowly progressive, not fully reversible constriction of the airways causing breathlessness, cough and respiratory distress. The primary cause is repeated exposure to cigarette smoke, which inflames the lungs and reduces lung tissue elasticity. The prevalence of COPD is estimated at between 2% and 4%, representing approximately 1–2 million people in England.[1]

COPD is a condition for which economic evaluation of therapeutic interventions is particularly relevant. The high prevalence, chronic nature of the disease, and range of therapeutic interventions make the management of COPD a considerable financial burden to health-care services. The National Institute for Health and Clinical Excellence (NICE) estimates that the direct cost of COPD to the UK NHS exceeds £491M per year (expenditure based on 2001–2 activity).[2] More than half of this cost relates to the provision of care in hospital, with more than 1 million inpatient 'bed days' per year attributable to the disease.[3] One in eight unplanned hospital stays concern COPD, making it the second largest cause of emergency admissions in the UK.[4]

Scientific background

Key features of COPD are chronic cough and excessive sputum production. These symptoms occur as a result of mucus hypersecretion and ciliary dysfunction. Manual chest physiotherapy (MCP) involves external manipulation of the thorax using the techniques of percussion and vibration. The purpose of percussion (also referred to as cupping, clapping and tapotement) is to intermittently apply kinetic energy to the chest wall and lung. This is accomplished by using a cupped hand with rhythmical flexion and extension action of the wrist. Vibration involves the application of a tremorous action over the area being drained. This is performed by manually pressing with both hands in the direction of the normal movement of the ribs during expiration. Percussion and vibration are designed to dislodge bronchial secretions which the patient then clears through involuntary or assisted coughing. The assumption underlying the use of MCP is that removing sputum from the airway improves ventilation perfusion ratios (V/Qs), prevents further mucosal injury and thereby improves lung function.

In 2001, this study's Chief Investigator (J Cross) led a comprehensive review of the literature regarding manual physiotherapy techniques.[5] The project was commissioned by the Association of Chartered Physiotherapists in Respiratory Care and its remit was to identify and critically review the literature on MCP in relation to mobilisation and clearance of secretions. The review focused on patients with compromised respiratory function and impaired mucociliary clearance who were not being mechanically ventilated. The intention of the review was to identify studies of acceptable quality designed to evaluate the use and mode of manual techniques with a view to compiling clear and concise clinical practice guidelines. This proved impossible to achieve owing to the lack of suitable evidence. However, certain key points emerged from this literature review and these are reported below.

Eight papers reported designs that evaluate a specific manual technique, using secretion clearance as the main outcome.[6–13] In these studies, comparisons were made against either a 'control' or 'standard' treatment, augmented by the addition of the manual technique in the experimental group. Four studies found no evidence that manual techniques conferred greater efficacy.[7,9,12,13] The remaining found that manual percussion was associated with sputum mobilisation,[7] vibrations and percussion were associated with an increased wet weight of sputum,[9] there was a significant increase in sputum clearance at 60 minutes post treatment with mechanical vibration but no difference over 24 hours,[12] and fast manual percussion produced the greatest sputum volume 60 minutes after treatment.[13] Chest physiotherapy appeared to be inappropriate in acutely ill patients with little or no sputum.[14] On occasion it was associated with oxygen desaturation, V/Q mismatch, a decrease in forced expiratory volume in 1 second (FEV_1) and bronchospasm.[5]

De Boeck and Zinman[15] performed a crossover trial of stable COPD patients receiving twice daily physiotherapy at home with randomisation of treatment order. Chest physiotherapy, including manual techniques, was compared with vigorous coughing. The results of this study showed no clear benefit of chest physiotherapy over cough alone. However, the small sample size means that, even with paired data analysis, only very large effect sizes are likely to be identified. In many studies, the effect of manual techniques independent of encouragement to cough was not separately determined. Rossman et al.[11] reported that cough alone appeared as effective as manual techniques

Lung volume measures

Manual techniques have sometimes been reported as producing falls in lung volumes. Campbell et al.[16] compared two groups of patients with chronic bronchitis and applied chest percussion in a postural drainage position. They reported an immediate reduction in FEV_1 associated with the procedure, this effect being lessened by the administration of a bronchodilator. The reduction in FEV_1 was negated within 20 minutes. It was concluded that this fall was due to bronchoconstriction brought about by the physiotherapy techniques of percussion and vibration. However, neither sputum volume at baseline was reported nor whether participants had been tested for airway reversibility prior to the study.

Newton and Stephenson[17] considered the effect of chest physiotherapy (breathing exercises, chest vibration and percussion in different positions or postural drainage) on pulmonary function and, in a small number of subjects, arterial blood gases (ABGs). They found no change in FEV_1, vital capacity, specific conductance or ABGs. However, functional residual capacity (FRC) and airway conductance and resistance were all seen to increase after these manoeuvres. While this study does support the view that MCP may not be appropriate in small sputum producers, the precise physiotherapy techniques used are inadequately described. May and Munt[18] suggest that forced vital capacity (FVC) increases with both chest physiotherapy and cough alone, though neither technique shows an advantage over the other.

Feldman et al.[19] used a mixed group of patients with either chronic bronchitis or cystic fibrosis (CF) characterised by chronic copious sputum production. They found that chest physiotherapy produced a significant improvement in lung function, predominately at low lung volumes, and that the effect could persist for 45 minutes after treatment. However, the heterogeneous nature of their study group raised the possibility that these benefits might be confined to higher sputum-producing patients with CF.

Rivington-Law et al.[20] conducted a crossover study of 12 patients, all with chronic bronchitis. Deep breathing exercises were compared with deep breathing exercises and chest vibrations and with no intervention. They report statistically significant increases in expiratory reserve volume in association with deep breathing exercises alone.

Sputum clearance

In patients with copious secretions, movement of sputum appears more likely to relieve airway obstruction. However, the long-term benefit of increased sputum clearance is unclear as increase in volume does not appear to be maintained 24 hours post treatment.[12] Bateman et al.[21] produced a simple and clearly reported study measuring radioisotope clearance of sputum from the lungs of 10 patients with chronic airways obstruction (not in exacerbation). These patients were regular sputum producers with a mean volume of 100 ml per day. Clearance rates were measured twice: once after physiotherapy (comprising drainage, percussion and vibration for 20 minutes) and on the other occasion without physiotherapy. Clearance, both centrally and peripherally, increased by up to five times after physiotherapy as did sputum weight produced (up to 15 times).

Bateman et al.[22] also studied six patients with chronic obstructive airway disease (COAD) in a repeated measures design. Researchers compared control (no cough), with cough alone and with MCP and cough. They report significantly greater clearance of radioactive aerosol for both intervention modalities compared with control. However, only MCP produced a statistically significant difference in clearance from the peripheral areas of the lungs ($p < 0.05$) and increased sputum weight ($p < 0.05$).

Wollmer et al.[6] undertook a study in which inhalation of radiolabelled particles (aerosol scintigraphs) was employed to measure particle deposition and clearance during chest physiotherapy. Although there was no overall effect on the deposition and clearance of radiolabelled

particles, two patients with the highest sputum production (100 ml and 130 ml) had a substantially higher clearance with chest percussion. This observation supports the suggestion that there may be differential effects of manual techniques in patients with differing levels of sputum production.

There is some evidence that contradicts this hypothesis. Van Der Schans et al.[10] investigated the effect of manual percussion as a single procedure, as well as in combination with postural drainage (PD), coughing and breathing exercises, on tracheobronchial clearance in patients with chronic airflow obstruction (CAO) and excessive tracheobronchial secretions. Again the study was small (only nine subjects) but PD and coughing, with or without manual percussion, did appear to improve mucociliary clearance more than manual percussion alone. In contrast, manual percussion did not appear to add to the efficiency of the combination of PD, coughing and breathing exercises.

Oxygenation levels

The study by Connors et al.[14] is often quoted to substantiate the claim that chest physiotherapy produces hypoxaemia. However, that study had significant methodological and analytical weaknesses. May and Munt[18] reported no significant effect (clinical or statistical) of manual techniques on either oxygen or carbon dioxide levels. Buscaglia and St Marie[23] presented a well-designed study of a homogenous group of patients, supporting the evidence that patients' response to MCP in terms of oxygenation depends on the amount of sputum produced. Wollmer et al.[6] found no significant difference in arterial oxygen saturation (SaO_2) between pre- and post-treatment values, either with or without percussion.

Update of 2001 review

The numbers of patients investigated in the studies described above are small and the focus was either on groups of patients that were very specific or heterogeneous in nature. An update of the studies presented above reveals that little has changed since 2001.[24] A systematic review conducted in 2004 to produce the American College of Chest Physicians (ACCP) guidelines found that, although some airway clearance techniques improve sputum expectoration, no high-quality evidence exists for long-term outcomes.[25] Moreover, while MCP was recommended for CF, there was some evidence that manually assisted cough might be detrimental in COPD. Thus, it was advised that this technique should not be used to treat acute exacerbations. In 2007, Garrod and Lasserson[26] conducted an overview of systematic reviews of the role of physiotherapy in the management of chronic lung diseases. With respect to MCP they considered that randomised controlled trials (RCTs) were still required to evaluate effects on health-related quality of life, exacerbation frequency and hospital admission.

Thus, a clear state of clinical equipoise remains as to whether MCP confers any benefit to patients with COPD. As a consequence, current UK guidelines for the management of COPD do not propose a clear place for MCP techniques. A National Clinical Strategy for COPD is being developed by the Department of Health (previously known as a National Service Framework [NSF]). National Strategies are 10-year plans for the NHS which aim to raise the quality of care for all people living with specified conditions. Currently a draft strategy is out for consultation with the key stakeholders and one of its remits is to ensure that if someone is admitted to hospital, the time is used effectively to avoid recurrent hospitalisation.[27] Thus, this study is ideally placed to inform evidence-based recommendations concerning MCP.

Study rationale

Crossover designs permit only short-term outcomes to be studied and require either a high degree of stability in the underlying condition or repeated and similar episodes to manifest in the same patient. Acute exacerbations of COPD do not meet this criterion and there is a need for long-term as well as short-term outcomes to be studied. Therefore, this study adopts a pragmatic RCT design, powered for equivalence.

Choice of study outcome measures

The choice of outcome measure appropriate for a trial of this type is somewhat contentious owing to the changing nature of health-care evaluation. Traditionally the focus of effectiveness trials has been on the physiological outcomes of interventions. More recently there has been recognition that quality of life is an important indicator of efficacy that is often not addressed. The choice of outcome measures in this study was therefore predicated on the assumption that long-term effectiveness must be based largely on

quality of life considerations. However, because physiological measures may provide useful short-term indicators of effectiveness, these were also included as secondary outcomes in this study.

Quality of life

Chronic obstructive pulmonary disease is a life-limiting condition with considerable effect on quality of life. A study of 141 patients with COPD admitted to hospital for exacerbations reported a considerable loss of health utility compared with individuals in a non-exacerbated state. The majority of hospitalised patients reported a state considered 'worse than death' (mean health utility –0.21).[28] Furthermore, the adverse impact on health utility appeared to be greater with increasing severity of COPD.

St George's Respiratory Questionnaire

The St. George's Respiratory Questionnaire (SGRQ) is a quality of life measure specifically designed for patients with COPD. It provides valid and reliable measures of respiratory symptoms and is sensitive to change in objective measures of respiratory function. It comprises a self-completed questionnaire containing 76 items divided into three domains. These are:

- symptoms: frequency of cough, sputum production, wheeze, breathlessness and duration and frequency of attacks
- activity: physical activities that either cause or are limited by breathlessness.
- impact: employment, being in control of health, panic, stigma, need for medication and side effects, health expectations, disturbances in daily life.

The SGRQ is rated as easy to use by 90% of respondents[29] and has been used extensively in RCTs of rehabilitation and early discharge of COPD patients.[30] It provides an effective measure of health-related quality of life during acute exacerbations[31] and reliably predicts mortality for COPD.[32–34] For these reasons, the SGRQ was selected as the primary outcome measure for this study and used as the basis for the statistical power calculation to determine sample size.

Breathlessness Cough and Sputum Scale

The Breathlessness Cough and Sputum Scale (BCSS) is a self-completed symptom-severity scale. One of the advantages of the BCSS is the simultaneous inclusion of breathlessness, cough and sputum assessments. This relatively new scale has demonstrated strong correlation with cough-specific items from the SGRQ.[35] Validation studies of the BCSS indicate that it is able to demonstrate sensitivity to within-group change and between-group differences.[36]

European Quality of Life-5 Dimensions questionnaire

The European Quality of Life-5 Dimensions (EQ-5D) questionnaire is a standardised instrument for measuring health outcomes. It provides a simple descriptive profile and a well-validated single-index value of health status. Designed for self-completion by the respondent, the EQ-5D takes only a few minutes to complete. It comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and is supplemented by a visual analogue scale (hereafter referred to as EQ-VAS) recording the respondent's self-rated health status on a vertical graduated 'thermometer', which ranges between 0 (worst imaginable health state) and 100 (best imaginable health state). Responses to the five dimension questions are then converted into a single utility index (where 0 is equivalent to death and 1 is equivalent to full health) using equations relevant to the UK population.[37]

While the SGRQ correlates well with the Short Form-36 items (SF-36) quality of life measure, the EQ-5D has been shown to be less responsive to change in the SGRQ.[38] That said, it has been shown that the EQ-5D can discriminate between COPD patients with different levels of known severity.[39] As a result, the EQ-5D was included within this study in order to complement other quality of life measures and provide a fuller description of changes in health-related quality of life.

Physiological impact of MCP

Oxygen saturation and sputum volume

With regard to the physiological impact of MCP, useful indicators suggested by the literature are its short-term impact on sputum volumes[40,41] and oxygen saturation.[20]

Medical Research Council-Dyspnoea scale

The Medical Research Council-Dyspnoea (MRC-D) scale is a five-item questionnaire in which patients categorise their own level of disability.[42] As some research suggests that lung function measures are useful predictors of morbidity but of little value in predicting quality of life,[43,44] this outcome was included solely as a baseline indicator of severity of disease.

Six-minute Walk Test

With respect to evaluating longer term physiological impacts, the Six-minute Walk Test (6MWT)[45] is easy to administer, well tolerated by patients and regarded as the most useful functional walk test for research purposes.[46] Therefore, in order to provide comparative functional outcome data, the 6MWT was selected for completion by a subsample of participants at 6 months post randomisation.

Health economics issues

As health-care resources are scarce, and the amount of funding available to the NHS is relatively fixed, there is a need to evaluate the cost-effectiveness of different health-care interventions.[47,48] Here we seek to evaluate whether the provision of MCP represents an efficient use of resources. Alternatively, it may be that a greater health benefit would be afforded by spending the same limited resources elsewhere.

Chapter 2
Methods

In this chapter, the development of the MCP treatment protocol and the methods used to conduct the intervention are described in detail. Prior to start-up, the study protocol and associated documents were reviewed and approved by the Norfolk Research Ethics Committee (REC – ref.06/Q0101/140) and relevant NHS research consortia. The study was conducted in accordance with good clinical practice (GCP) research guidelines.

Development of MCP treatment protocol

Manual chest physiotherapy is a time-consuming, labour intensive treatment requiring significant skill and strength on the part of the therapist and the mental and physical co-operation of the patient. While many physiotherapists perform MCP, the precise method, sequence and duration of its component parts can vary considerably. In order to provide a precise description of the study intervention and standardise delivery as far as possible, a treatment protocol for MCP was developed with physiotherapists involved in the trial. This comprised a series of meetings to reach consensus on the essential elements of MCP, identify potential areas of ambiguity and provide a set of clear parameters within which treatment would be based. The fundamental premise of these meetings was to arrive at a treatment protocol that clearly defined the MCP to be delivered, but allowed sufficient flexibility to preserve the profession's ethos of providing treatment according to individual need. Thus, the content, number and duration of treatments could remain at the discretion of the physiotherapist as long as variation remained within the bounds set by the protocol.

This iterative approach resulted in a treatment protocol that combined current practice with the best research evidence available to date (see Appendix 1). To prevent ambiguity, definitions for the various elements of MCP were provided, along with pictures of ideal hand positions to adopt when performing percussion and vibration techniques (see Appendix 2). With respect to the positioning of patients during MCP, a photographic list of the six most common treatment positions was provided from which the two most appropriate could be selected according to clinical need (see Appendix 3). If deemed necessary, the physiotherapist could select additional positions, provided these were recorded at the time.

The experience of the research team at the University of East Anglia (UEA) in conducting large, complex, hospital-based RCTs has highlighted the importance of employing active recruiters at each trial site. The study protocol stipulates that research associates (RAs) would identify, recruit and randomise patients and collect all trial-associated data. However, an important issue to emerge from meetings with physiotherapists was their concern that involvement in the trial would impact on already heavy case loads. In order to reassure clinicians that their time commitment would be kept to a minimum, the treatment protocol made clear the division of responsibilities between RAs and physiotherapists delivering the intervention.

Study objectives

Primary objectives

- To estimate the effect, if any, of MCP administered to patients hospitalised with COPD exacerbation on disease-specific quality of life at 6 months post randomisation.
- To compare the costs to the NHS and personal social services (PSS) for those who either receive or do not receive MCP while in hospital.

Secondary objectives

- To compare clinically relevant outcomes between treatment and control groups at 6 weeks and 6 months post randomisation. These included frequency of exacerbation, hospital readmission and sputum volume produced per 24 hours while in hospital.
- To undertake a prespecified subgroup analysis comprising subjects producing ≥ 15 ml and

< 15 ml of sputum per 24 hour period during hospitalisation.
- To undertake a prespecified subsample analysis of participants undertaking 6MWTs.
- To describe and quantify the component parts of the MCP given to patients hospitalised with a COPD exacerbation. These included position selection, duration and frequency of treatment and associated change in oxygen saturation.

As this study's design was pragmatic in nature, the major objective for data collection was to obtain information on the primary outcome measure (SGRQ) at the primary end point (6 months post randomisation).

Screening and recruitment

MATREX was designed as a multisite trial with a phased start-up for each hospital depending on recruitment rates achieved. The clinical population from which study participants were drawn comprised all patients admitted to participating hospitals with an exacerbation of COPD.

Inclusion criteria

1. Diagnosis of COPD as defined by the British Thoracic Society,[49] namely:
   i. progressive, predominantly irreversible airflow obstruction in which
   ii. FEV_1 is < 80% of the predicted value and FEV_1/FVC is less than 0.7
   iii. symptoms may include worsening breathlessness, cough, increased sputum production and change in sputum colour.
2. A COPD exacerbation as set out by the British Thoracic Society,[46] namely:
   i. a sustained worsening of the patient's symptoms from his or her usual stable state that is beyond normal day-to-day variations
   ii. the exacerbation is acute in onset.

Exclusion criteria

1. Contraindications to the use of MCP techniques,[50] namely:
   i. osteoporosis
   ii. frank haemoptysis
   iii. bronchial hyper-reactivity
   iv. known respiratory system malignancy
   v. raised intracranial pressure
   vi. uncontrolled hypertension (diastolic > 110 mmHg)
   vii. pulmonary embolism
   viii. coagulopathy [platelets < 50,000mm^3 and/or INR (international normalised ratio) ≥ 3]
   ix. bronchopleural fistula
   x. subcutaneous emphysema
   xi. left ventricular failure as primary diagnosis.
2. No evidence of excess sputum production after examination (i.e. the patient does not report excess secretions and there are no signs of excess secretions on auscultation).
3. Cognitive impairment, rendering the patient unable to give fully informed consent.

Screening and recruitment procedure

Each day, RAs screened admission lists at participating hospitals to identify potential study participants. A checklist based on study inclusion and exclusion criteria was compiled for this purpose (see Appendix 4). When a potential participant was identified, the RA liaised with the physiotherapist who then made a clinical assessment of the patient's suitability for MCP. A checklist comprising known contraindications for MCP and clinical risk factors associated with potential adverse events (AEs) was provided for this purpose (Appendix 5). Once eligibility had been confirmed, the RA went through the patient information sheet (see Appendix 6) with the potential participant and answered any queries they might have. Because rapid change in clinical condition is likely in this patient group, the RA needed to strike a balance between enabling the study intervention to occur during the most acute phase of the exacerbation and not rushing the patient in their decision. After due process, if the patient was willing to participate, the RA obtained informed consent (see Appendix 7).

Baseline data collection

On receipt of written consent, the RA assisted the participant to complete the following baseline questionnaires:

- SGRQ (Appendix 8)
- BCSS (Appendix 9)
- MRC-D scale (Appendix 10)
- EQ-5D (Appendix 11)
- COPD cost questionnaire (see Health economics measures)

Additional baseline data collected by the RA included the date of the participant's admission

to hospital, the ward/area to which they had been admitted and the attending physician responsible for their care. Additional personal and demographic information obtained at this point included the participant's name, sex, date of birth, address, post code and general practitioner (GP) details. A case report form (CRF) was compiled for this purpose (see Appendix 12).

Randomisation

Randomisation was conducted via a voice-activated, automatic telephone response system. This provided each participant with a unique study number, recorded the date of their randomisation and assigned them to receive, or not receive, MCP. The automated system also stratified randomisation by hospital, using a block size of six. The participant was provided with an information card detailing which study arm they had been allocated to (see Appendices 13 and 14). Hospital notes were marked with a removable label to inform RAs and physiotherapists in the event of readmission during the study's follow-up period.

Blinding

Baseline questionnaire data was collected prior to randomisation. Given the nature of the study intervention, it was not possible to blind participants, clinicians or research staff to study arm allocation during the intervention. However, blinding to arm allocation was achievable for certain individuals at specific points in the study, namely RAs when collecting retrospective data on health service use (see Health economics measure) and the trial statistician and trial health economist during initial data analysis.

Intervention

MCP arm

For participants randomised to receive MCP, the physiotherapist administered treatment within the bounds set by the treatment protocol (Appendix 1). After auscultation, the physiotherapist selected the most appropriate positions to achieve optimal clearance of secretions. The patient's chest was percussed while they performed thoracic expansion exercises and vibration was applied on expiration. Treatment was interspersed with periods of relaxed abdominal breathing, and the forced expiration technique (FET) in accordance with active cycle breathing techniques (ACBT) to enable chest clearance.

The precise nature of each intervention was recorded by the attending RA on a CRF compiled for this purpose (see Appendix 15). Oxygen saturation was monitored during treatment with a finger pulse oximeter (Konica Minolta Pulsox-300, Tokyo, Japan). Any sputum produced during treatment was collected in a pot which was dated and labelled accordingly.

Following MCP, the physiotherapist provided the patient with advice on positioning, with ACBT. This information was reinforced by providing the patient with an information sheet that summarised the advice (see Appendix 16). The content, number and duration of further MCP treatments during hospitalisation were at the discretion of the physiotherapist and varied according to clinical need. The patient was asked to continue to collect all further expectorant produced during the remainder of their hospital stay. Additional pots were provided for this purpose and collected by the RA as often as practical. The volume of sputum in each pot was recorded.

Control arm

The physiotherapist provided the patient with advice on positioning, cough and sputum mobilisation in accordance with ACBT. This information was reinforced by providing the patient with an information sheet that summarised this advice (Appendix 16). Oxygen saturation was obtained at this visit by means of a finger pulse oximeter. The patient was asked to collect any expectorant produced during their hospital stay. Sputum pots, dated and labelled accordingly, were provided for this purpose. These were collected by the RA as often as practical and the volume of sputum recorded. All information pertaining to participants in the control arm was recorded on a CRF compiled for this purpose (see Appendix 17).

Procedure for handling adverse events

According to the literature, possible AEs associated with MCP include: increased intracranial pressure; acute hypotension; pulmonary haemorrhage; dysrhythmia; vomiting; hypoxia; and bronchospasm.[47] Pain and/or injury to muscles, ribs, and spine can also occur as an immediate consequence of the percussion and vibration elements of this therapy. A list of potential AEs and

associated symptoms was included in the treatment protocol along with recommended actions should any occur (see Appendix 1, Section 5).

In addition to individual NHS trust's policies on AE/incident reporting, a procedure for trial-specific reporting was set in place. To this aim, an AE report form was compiled to record AEs and evidence their management (see Appendix 18). This reiterated the list of possible events and defined the reporting procedure for each one. The physiotherapist was required to provide a brief description of each AE and what action was taken, including details of any investigations and treatments. They were also asked to state whether, in their opinion, the event was related to the MCP being administered.

Movement between arms

The MCP treatment protocol (Appendix 1, Section 4) defines the circumstances under which participants would switch from the control arm to receive MCP. Essentially, these circumstances constitute a working definition for respiratory failure. If the physiotherapist or attending physician became concerned that a patient's condition had deteriorated to the extent that MCP was warranted, all of the following criteria were required to switch arm:

1. clinical evidence of sputum retention (e.g. auscultation, chest radiograph)
2. ABGs: pH less than 7.26
3. ABGs: rising carbon dioxide
4. already receiving controlled oxygen therapy
5. already receiving other supportive treatment(s).

Outcome measures

MCP treatment measures

In order to describe and quantify the component parts of the MCP administered, the following measures were obtained for each treatment session:

1. treatment position(s) selected
2. oxygen saturation immediately before treatment
3. lowest oxygen saturation during treatment
4. time taken by physiotherapist to deliver treatment
5. deviation(s) from MCP treatment protocol
6. AE(s) experienced.

MCP treatment efficacy measures

In order to estimate the effect of MCP administered to patients hospitalised with COPD exacerbation on disease-specific quality of life, the following questionnaires were administered at baseline, 6 weeks and 6 months post randomisation:

- SGRQ
- BCSS
- EQ-5D.

Follow-up questionnaires were posted to participants with a cover letter requesting that they complete and return them to the study office in the pre-paid, addressed envelope provided.

In order to compare clinically relevant outcomes between treatment and control groups, the following measures were obtained for each study participant:

- sputum volume (ml per 24 hours) during hospitalisation (see Intervention)
- number of hospital readmissions during study period
- number of hospital 'bed days' during study period.

The last two were obtained retrospectively by scrutinising hospital databases at the end of follow-up.

In addition to the measures listed above, the 6MWT was completed by a subsample of participants at 6 months post randomisation. All participants at one site (see Six-minute Walk Test) were invited by letter to undertake a walk test at the hospital. In order to minimise the inconvenience to participants, tests were arranged as far as practicable to coincide with routine outpatient appointments. Participants were recompensed for any travel costs they incurred for this visit. Each test was supervised by the physiotherapist according to specified standards[51] and undertaken in an area suitably marked with known distances. The distance (metres) achieved in 6 minutes was recorded.

Health economics measures

In order to examine the cost-effectiveness of MCP, the following data were collected:

- SGRQ
- EQ-5D
- COPD cost questionnaire – baseline (Appendix 19)
- COPD cost questionnaire – follow-up (Appendix 20)
- secondary care health service use (see Measuring costs).

The baseline COPD cost questionnaire was a study-specific, non-validated instrument designed to capture the participant's use of health services during the previous 3 months (e.g. visits to hospital, home visits from health professionals), their personal circumstances (e.g. how they travel to hospital, do they have dependents) and health-related financial costs incurred (e.g. purchase of specialised equipment, private health care). The follow-up COPD cost questionnaire was designed to complement the equivalent baseline instrument by capturing change in health service use and cost measures during follow-up.

Questionnaire response rate

Regular audits during the pilot and early part of the main trial alerted the research team to the importance of maximising returns, particularly with respect to the primary outcome at the primary end point. Therefore, an action plan was established to improve questionnaire return rates (see Appendix 24).

Data management and data quality

All paper records pertaining to study participants were collated and stored in the trial office at UEA. Study data were entered on to secure computer systems with limited access measures enforced via user names and passwords. For data files where personal information was not required (e.g. name, address, etc.), individual participants were identifiable only by the study-specific number generated at randomisation. Prior to analysis, the final data set was audited for completeness and accuracy.

Sample size

Sample size was based on the primary outcome measure, SGRQ. Treating this study as non-superiority, where an effect size of 0.3 (typically considered small) is taken as the threshold for superiority then, assuming a true zero difference in the population (90% power, 5% significance) a total of 233 subjects in each arm were required. To allow for a 15% dropout rate, we aimed to recruit 275 participants to each study arm, resulting in a total target sample size of 550 participants.

To conduct the analysis of participants undertaking 6MWTs, a randomly selected subsample of 114 participants per arm was required. This would confer 90% power (5% significance) to detect a clinically significant difference in mean distance of 54 metres assuming a standard deviation (SD) of 125 metres.[52]

Statistical methods

All statistical analyses were undertaken using the STATA (Version 9.1 SE) statistical software package (StataCorp LP, College Station, TX, USA). This section outlines the statistical analysis procedures that were performed.

Baseline analysis

Baseline comparability between the treatment arms was evaluated by summarising and comparing the following parameters. Continuous outcomes were summarised using the mean and SDs in each group separately, and for categorical outcome the number and percentage were reported:

- demographic measures: age, gender, smoking status and site
- measures of disease severity: SGRQ total score, SGRQ symptom score, SGRQ activity score, SGRQ impact score, BCSS score, oxygen saturation (%), sputum (ml), MRC-D score, EQ-5D health thermometer and EQ-5D score.

Efficacy analysis

Primary outcome measure

The primary efficacy analyses were based on the intention-to-treat (ITT) principle, including all randomised patients according to the treatment arm allocation using a full analysis set (i.e. those patients with valid outcome measurements). Additionally, we imputed data, using the method described below, and completed an imputed ITT analysis. An analysis of covariance was used, with treatment as a fixed effect and baseline scores and site as covariates. A 95% confidence interval (CI) was constructed for the mean difference in

outcome between the treatment arms. Equality was regarded as a difference in effect size of 0.3 or less in absolute value, i.e. if the upper limit of the 95% CI was less than 0.3 and the lower limit was greater than –0.3. The effect size was defined as the mean difference divided by the pooled, over treatment arm, SD of the outcome. No adjustment for multiple testing was made.

Secondary outcome measures

Analyses of the secondary outcome measures, BCSS, EQ-5D score and EQ-VAS, were also based on the analysis of covariance with treatment as a fixed effect and baseline scores and site as covariates. The analysis of the secondary outcome measure 6MWT was based on the two-sample t-test since no baseline measurements were available and it was only recorded at one site (see Six-minute Walk Test). Analysis of the number of days in hospital was based on a negative binomial regression model with treatment as a fixed effect and site as a covariate.

Secondary analyses

In order to assess the sensitivity of the results to missing or incomplete data, both missing outcome and baseline data were imputed by means of iterative chain equations using all outcome measures (bar the 6MWT), and the number of hospital days, demographic details and treatment allocation. In total, 10 data sets were imputed using the 'ICE' command in STATA.[53] Estimates were then combined using Rubin's multiple imputation approach.[54] This is considered preferable to alternative approaches such as last value carried forward as it allows for uncertainty in the missing values themselves.[55]Multiple imputations were carried out using the STATA software. This method assumes that the data are missing at random.

Previously published papers have reported that, in equivalence trials, per-protocol (PP) analyses can be preferable to ITT.[56] Hence PP analyses were also conducted using the same models as described in the section Secondary outcome measure.

Planned subgroup analyses of the primary end points by sputum levels (15 ml or less versus more than 15 ml) were undertaken by testing for an interaction between the subgroup and the treatment arm in an analysis of covariance model, with treatment as a fixed effect and baseline scores, site and subgroup as covariates.

Health economics analysis

Measuring health-specific quality of life

The economic evaluation component of this study used both the EQ-5D and the SGRQ quality of life scores to assess the cost-effectiveness of the intervention, in line with guidance from NICE.[57] Justification for using the SGRQ is provided above. Although there is some evidence that the EQ-5D may not be responsive in patients with COPD,[37] given its wide usage in health service research and the fact that it is recommended for use in cost-effectiveness analyses,[53] it was considered important to include this measure in the study. The SGRQ has the capacity to detect both physiological and functional changes which are essential for detecting any direct improvement resulting from the intervention. Thus, a number of effectiveness end points were compiled and analysed using both total and disaggregated scores.

Measuring costs

Overview

In line with guidance from NICE, published 2008,[57] in the base-case analysis we adopted an NHS and PSS perspective and sought to estimate those costs that were considered to potentially relate to the intervention in question. A patient self-report baseline cost questionnaire, the COPD cost questionnaire (Appendix 19), was developed in order to assess whether there were any differences between the two groups at randomisation. Also, for each participant over the 6-month trial period, we sought to monitor the levels of resource associated with physiotherapy input (including MCP), inpatient admissions, outpatient visits, rehabilitation and early discharge, and any other NHS and PSS costs. This enabled the total NHS and PSS cost for those resources considered to potentially relate to the intervention in question (hereafter referred to as the overall health service cost) to be estimated.

Unit costs

All costs were estimated in UK sterling (£) at 2007/8 financial year levels. Unit costs associated with the time spent with various health-care professionals were taken from Curtis,[58] where these costs were adjusted to reflect the appropriate pay scale for those who provided the care (see below for further details). NHS reference costs[55] were used to estimate unit costs for hospital admissions.

Specific cost components

Baseline health service use

A patient self-report baseline cost questionnaire (Appendix 19) was developed, where information was requested for the last 3 months (prior to randomisation) and included the number of hospital attendances and the number of consultations with other community health and social services. All participants were asked to complete this questionnaire, except those who took part in the pilot phase of the study. The mean number of visits to hospital and consultations with various health-care professionals were reported in order to assess whether there were any differences between the two groups at baseline.

Physiotherapy input

Throughout the trial period the number of MCP sessions and associated 'hands-on' time was recorded for all participants (see Appendix 15). In order to estimate the actual level of physiotherapy input each participant received, the following assumptions were made. At baseline all participants received general respiratory physiotherapy advice from a hospital physiotherapist, which was estimated to last 10 minutes. This was added to any MCP hands-on time reported to have occurred at this session in order to estimate the patient contact time at baseline. In order to estimate the actual patient contact with a hospital physiotherapist in subsequent sessions, it was assumed that each follow-up session would last a further 5 minutes in addition to any MCP hands-on time reported. Hospital physiotherapy unit costs were extracted from Curtis[58] and adjusted to reflect the different pay scales for those who provided the care (within this study MCP sessions were generally performed by a Band 6 hospital physiotherapist). This enabled the total cost of providing general respiratory physiotherapy advice and any subsequent MCP to be estimated for each participant. The mean cost was thereby calculated for both the MCP arm and the no MCP arm, with the mean incremental cost of MCP estimated by subtracting the latter from the former.

Hospital admissions

Throughout the 6-month trial period, details of all hospital admissions were recorded for each participant. For each admission the following data was extracted from medical records and hospital computer systems: time spent in hospital (days); whether the admission was respiratory or non-respiratory related; ward type (general, coronary care unit, intensive therapy unit/high-dependency unit); day care; and accident and emergency department (A&E). All admissions were assumed to be non-elective. This enabled the total number of days post randomisation (categorised by ward type) to be calculated for each participant. Unit costs in terms of average cost per bed day (for each ward type and respiratory/non-respiratory related) were estimated using NHS reference costs 2006/7.[59] As these costs were estimated at 2006/7 levels, all unit costs were inflated by 3.35% (the hospital and community health services pay and price inflation rate for 2007/8[58]) in order to equate to 2007/8 levels. This enabled the 6-month hospital admission cost to be estimated for each participant and, in turn, the mean 6-month hospital admission cost was estimated for each trial group. By subtracting the mean hospital admission cost in the no MCP arm from that in the MCP arm, it was also possible to calculate the mean incremental hospital admission cost for MCP.

Outpatient visits

Throughout the 6-month trial period, details of all outpatient visits were recorded for each participant. For each outpatient visit the following data were extracted from hospital computer systems: type of visit (first or follow-up); and speciality (respiratory or non-respiratory related). Neither the NHS reference costs 2006/7[59] nor the Personal Social Services Research Unit[58] provides cost per outpatient visit data for respiratory-related conditions. Consequently, both respiratory- and non-respiratory-related visits were assigned the appropriate weighted average cost per visit for either all first attendances or all follow-up attendances, as reported by Curtis.[58] This enabled the 6-month outpatient visit cost to be estimated for each participant and, in turn, the mean 6-month outpatient visit cost was estimated for both the MCP arm and the no MCP arm. Subsequently, the mean incremental cost of MCP was estimated by subtracting the latter from the former.

Pulmonary rehabilitation and early discharge service

At one of the hospitals (University Hospital Aintree, UHA) more intensive rehabilitation support was also available to patients with COPD (hereafter referred to as rehabilitation). For all participants at this site, throughout the 6-month trial period, details of all such contacts were thereby extracted from medical records. Each type of contact is now described. Pulmonary rehabilitation assessments were provided at

hospital by a hospital physiotherapist (Band 6), where each assessment lasted an average of 1 hour. Pulmonary rehabilitation group sessions were provided in hospital by a physiotherapist (Band 6) and a physiotherapist assistant (Band 3). Each group session lasted an average of 1.25 hours and was attended by eight patients. The early discharge from hospital scheme, which ran at the same hospital, selected patients on the basis of their clinical severity and suitability to be monitored and treated by a home team. Assessments were made by one-to-one hospital visits with a hospital physiotherapist (Band 6) and lasted an average of 2 hours. Subsequent home visits were provided by a nurse (Band 6) or a hospital physiotherapist (Band 6) and lasted an average of 0.75 hours. Finally, telephone calls were undertaken by a nurse (Band 6) and lasted an average of 5 minutes. In line with aforementioned methods, unit costs for the staff time associated with each of these contacts was estimated from Curtis[58] after making adjustments to reflect the different pay scale for those who provided the care. This enabled the 6-month rehabilitation cost to be estimated for each participant. Subsequently, the mean 6-month rehabilitation cost was estimated for each trial group, where this was calculated across all participants in each trial group, not just those at UHA. Finally, the mean incremental cost for the MCP arm was estimated by subtracting the mean rehabilitation cost in the no MCP arm from that in the MCP arm.

Other NHS and PSS costs

These were monitored by a patient self-report measure at 6 weeks and 6 months post randomisation, the COPD cost questionnaire (see Appendix 20), where respondents were asked to report the level of health service use since randomisation and being sent the previous 6-week cost questionnaire respectively. Variables which were monitored included visits to A&E, GP services, consultations with other health professionals and contact with social services.

After considering the response rates to each of the aforementioned component costs, we estimated the overall health service cost for each participant. Subsequently, the mean overall health service cost was estimated for both the MCP arm and the no MCP arm. By subtracting the latter from the former the mean incremental overall health service cost of MCP was also estimated.

Measuring effects

In order to enable the effectiveness of many interventions to be compared on a common scale, within cost-effectiveness analyses benefits are commonly assessed in terms of utility (where 0 is equivalent to death and 1 is equivalent to full health).[44] In this study, in line with recommendations by NICE,[57] we used the EQ-5D to estimate utility values and compare the benefits of MCP with no MCP. The EQ-5D asks about the level of problems (none, some/moderate or severe/extreme) with regard to mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[60] Responses to the EQ-5D were sought at baseline, 6 weeks and 6 months post randomisation. However, in the pilot phase of this study we did not collect baseline data on the EQ-5D. Utility scores were subsequently assigned to each of the elicited health-state descriptions using the York A1 tariff[37] on which utility scores range between –0.594 and 1.00. Additionally, in line with a previous analysis,[61] those participants who died within the study period were assigned a score of zero. Multiple imputation[62] was used to estimate missing EQ-5D scores, as described below.

Multiple imputations were performed using the method of chained equations and 10 sets of imputations as implemented in the STATA 'ICE' command add-on.[53] This routine uses iterative chain equations based on regression models to impute plausible values for the missing data based upon the relationships observed in the non-missing data. The variables included in the regression models are listed in Table 1.

Ten imputed values were estimated for each missing EQ-5D score, where the mean value was used within the subsequent analysis. The exception to this was when the imputed EQ-5D score was outside the range of utility scores estimated by the EQ-5D York A1 tariff (range –0.594 to 1.00),[37] where imputed scores were truncated at these values.

Mean EQ-5D scores are reported for both the MCP and no MCP arm at baseline, 6 weeks and 6 months post randomisation, along with the 6-month change scores. The EQ-5D data were also used to calculate the quality-adjusted life-year (QALY) gain/loss accrued over the 6-month trial period for each participant, where this was calculated using the area under the curve method (with adjustment for baseline differences).[63] The mean 6-month QALY gain/loss was subsequently

TABLE 1 *Variables included in multiple regression models to impute missing data*

	Time point		
Variable	**Baseline**	**6 weeks**	**6 months**
Hospital site	×		
Original trial arm allocation	×		
Number of days in hospital			×
BCSS score	×	×	×
SGRQ total score	×	×	×
SGRQ symptom score	×	×	×
SGRQ activity score	×	×	×
SGRQ impact score	×	×	×
MRC-D score	×		
Age	×		
Gender	×		
Sputum (ml)	×		
Oxygen saturation (%)	×		
EQ-5D	×	×	×
Smoking status (current vs non-current)	×	×	×
Academic attainment – degree level (yes/no)	×		
Schooling past minimum leaving age (yes/no)	×		

calculated for both the MCP arm and the no MCP arm, along with the mean incremental QALY gain for the MCP arm.

In addition to the mean incremental QALY gain for the MCP arm we also estimated the incremental effect on the SGRQ (both for the total score and for each of the three domains). This was calculated by first using the aforementioned imputation methods to estimate the missing SGRQ scores. Second, the mean change on the SGRQ (both for the total score and for each of the three domains) was estimated for both the no MCP and the MCP group. Finally, the incremental change on the SGRQ for MCP was calculated (both for the total score and for each of the three domains) by subtracting the mean score for the no MCP group from that for the MCP group.

Cost-effectiveness analysis

In the base-case analysis, the level of cost-effectiveness was estimated from the viewpoint of the NHS using the aforementioned incremental overall health service cost of MCP and mean incremental QALY gain of MCP. When two options are compared one is said to 'dominate' the other, and thereby be considered to be the more cost-effective option if it is associated with a mean cost saving (a negative incremental cost) and positive mean incremental effect. Where one intervention does not dominate the other it is common to calculate the incremental cost-effectiveness ratio (ICER) associated with each intervention group, relative to the next best alternative.[47] The ICER is calculated by dividing the mean incremental cost (ΔC) by the mean incremental effect (ΔE) ($ICER = \Delta C/\Delta E$, where E is the QALY gain and C is the cost). Subsequently, in line with guidance by NICE,[57] one might then deem options that have an ICER of less than the threshold (λ) of £20,000 per QALY to be cost-effective. However, certain ICER values are open to misinterpretation[64] as, for example, the same ICER value can be reached from both (1) a costing saving and positive incremental effect and (2) an increase in cost and negative incremental effect, where both of these situations have quite different interpretations (in contrast to the latter, the former would be deemed favourable). As a result it is recommended that the net monetary benefit (NMB) is calculated (where $NMB = \lambda \times E - C$), with a positive NMB denoting that the option was estimated to be cost-effective at the threshold in question.[65] Within this study,

where dominance did not occur, we calculated the range of λ values over which the incremental net benefit (i.e. NMB for no MCP – NMB for MCP) was positive, where the point estimate of the ICER for MCP is given by the value of λ when the incremental net benefit is zero (assuming that neither a cost saving nor a negative effect occurs). Additionally, as NICE guidance suggests that options that have a positive incremental net benefit at λ values of £20,000 to £30,000 per QALY will be deemed cost-effective,[57] we also calculated the incremental net benefit when λ was equivalent to £20,000 per QALY.

Additional cost-effectiveness analyses were undertaken using the aforementioned incremental overall health service cost of MCP and the incremental effect of MCP according to the SGRQ (both for the total score and each of the three domains).

Decision uncertainty

In order to estimate the level of uncertainty associated with the decision as to which option was most cost-effective, probabilistic methods were used to estimate the cost-effectiveness acceptability curve (CEAC) for each option, where the CEAC depicts the probability that an intervention is cost-effective at different levels of the cost-effectiveness threshold (λ).[65,66] The CEAC was constructed using the technique of non-parametric bootstrapping,[67] whereby 10,000 simulations of the (per participant) cost and effect were drawn for each option (with replacement) from the original cost and effect data. The probability of being cost-effective was then equivalent to the proportion of the 10,000 simulations for which each option had the highest net benefit at different values of λ.

With regard to these calculations, it should be noted, as has been pointed out previously,[65,66] that as the ICER and CEAC are calculated in different ways it is possible for the most cost-effective option (as determined by the ICER) to have the lowest probability of being cost-effective (according to the CEAC).

Subgroup analysis

Due to the potential for the costs and benefits of MCP compared with no MCP to vary according to the level of sputum, we undertook a prespecified subgroup analysis in which we estimated the costs and benefits for both participants who produced ≥15 ml of sputum and participants who produced < 15 ml of sputum (where sputum was the average level of production over a 24-hour period during initial hospitalisation). Our a priori hypothesis was that, if MCP were to be more cost-effective for a particular group, it would be for those who had produced ≥15 ml.[21,6,22] Thus, for high and low sputum production, in addition to estimating the incremental cost and incremental QALY gain for MCP, the incremental net benefit of MCP was calculated when λ was equivalent to £20,000 per QALY.

Sensitivity analysis

Sensitivity analysis is often undertaken in order to assess how robust conclusions are to methodological assumptions that were made as part of the analysis.[47] Our aforementioned methods were considered to be those of the 'base-case' analysis. Therefore, we conducted the following sensitivity analyses in order to assess what impact different assumptions had on our results. First, due to the fact that missing EQ-5D scores were imputed, we conducted a complete case analysis,[68] whereby results were analysed only for those participants who had complete cost and EQ-5D data. Second, we changed the assumptions about the unit costs to be applied to respiratory-related admissions. This was undertaken as it was unclear that all 'respiratory-related' conditions within the NHS reference costs 2006/7[59] would be representative for our population group. First, we assumed that the unit cost for respiratory-related conditions was equivalent to those denoted as COPD-related in the NHS reference costs [analysis (a)]. Second, we assumed that the unit cost for respiratory-related conditions was equivalent to the weighted average for all admissions as denoted in NHS reference costs 2006/7 [analysis (b)]. Third, we changed our assumption about what services might potentially relate to the intervention in question. In analysis (a) we assumed that only respiratory-related admissions could potentially relate to MCP, and in analysis (b) we assumed that only physiotherapy time at baseline and subsequent follow-up MCP sessions could potentially relate to MCP. Finally, we conducted a PP analysis. For each of the above analyses the following factors are reported, both in terms of the overall mean levels for both the MCP and no MCP groups and the incremental level for MCP: (1) hospital admission costs (this is the largest cost-driver); (2) overall health service costs; (3) 6-month QALY gain; and (4) net benefit at λ = £20,000 per QALY. Finally, the range of λ values for which MCP was estimated to be cost-effective was also reported.

Changes to study protocol

With respect to the primary outcome measure for the MATREX trial, length of stay in hospital was proposed in our original bid. However, the funder considered that this was not an appropriate outcome measure as it can be influenced by other, non-intervention factors and that alternative, patient-orientated outcomes should be used in power calculations. The primary outcome measure was therefore changed to a COPD-specific quality of life measure (SGRQ) and the power of the study recalculated accordingly.

In order to assess the adequacy of the MCP treatment protocol (see Development of MCP treatment protocol) and proposed outcome measures, the study commenced with a pilot phase for the first 6 months of recruitment. Close monitoring and review of preliminary data by the study's management groups [Trial Management Group (TMG), see Appendix 21; Trial Steering Committee (TSC), see Appendix 22; Data Monitoring and Ethics Committee (DMEC), see Appendix 23] indicated the need for certain changes to the study protocol and the rationale for these are detailed below. Changes were approved by the lead REC, relevant NHS research consortia and the research commissioning body (NIHR HTA programme).

Testing and refining the MCP treatment protocol

The original treatment protocol stipulated that patients in the MCP arm should be encouraged to cough (Appendix 1, Section 2.5.1). However, this was not listed as an explicit instruction in the control arm. Thus, when assessing the effect of MCP, 'deliberate' coughing could act as a confounding variable. In order to ensure parity between trial arms, the treatment protocol was amended to include this instruction for control arm patients (Appendix 1, Section 3.1.1). In addition, an AE report form was compiled to make reporting procedures more explicit (Appendix 18). A number of CRFs were also compiled to ensure consistency in data collection (Appendices 12, 15 and 17).

Changes to inclusion and exclusion criteria

The original commissioning brief included the term 'infective exacerbation' in its call for research proposals. While COPD patients tend to be admitted under the rubric of an 'infective exacerbation', infectivity status is not routinely established. In clinical practice it is increased sputum volume (regardless of infectivity) that triggers the administration of MCP. Therefore, infective status was removed as a prerequisite for trial eligibility on the grounds that this most closely reflects clinical practice and clinical decision-making.

Six patients who appeared to meet the trial's inclusion criteria were excluded by the physiotherapy team at one particular site because they were receiving anticoagulant therapy. These exclusions were in line with the physiotherapists' clinical practice guidelines. As clotting risk factors were implicit in two of the study protocol's exclusion criteria (haemoptysis and low platelet count), MCP was considered to pose an additional risk of internal bleeding for patients taking anticoagulant medication. After advice from the TSC it was agreed that conducting an additional screen for raised INR was sufficient to ensure that MCP would not be administered inappropriately. As INR is routinely checked on admission, this information would be readily available to trial recruiters. Therefore, the exclusion criterion (INR > 3) was adopted with immediate effect at all sites for the remainder of the recruitment period.

Finally, the definition of COPD given in the study protocol was updated to reflect current NICE guidelines.[49]

Changes to recruitment and follow-up periods

The original study protocol stated that follow-up would take place at 6 weeks, 3 months, 6 months and 1 year post randomisation. However, issues that arose during the early stages of recruitment led to the following changes:

- The pilot phase indicated relatively poor questionnaire response rates for the first two follow-ups. Therefore, in order to minimise the demands made on participants and maximise future questionnaire return rates, the 3-month follow-up was withdrawn.
- As a result of slower than anticipated recruitment and in order to achieve an adequate sample size, the recruitment period was extended by 12 months. To compensate for slow recruitment during the first year and complete the study within a reasonable length of time, the 1-year follow-up was withdrawn. Thus, the 6-month follow-up became the study's primary end point.

Health economics protocol changes

In order to calculate the QALY gain associated with the intervention, in the original protocol it was stated that the EQ-5D would be administered at 3 months and 1 year post randomisation. However, in 2005 it was recommended that baseline differences be adjusted for when estimating the QALY gain associated with an intervention.[63] Thus, from the start of the main trial (participant 100 onwards) the EQ-5D was also administered at baseline to provide a more complete picture of change in quality of life. Additionally, following the removal of 3-month and 1-year follow-up, the time points for administering subsequent EQ-5Ds were switched to 6 weeks and 6 months post randomisation.

In the original protocol it was stated that a societal perspective would be taken with regard to the health economic analysis. Guidance from NICE, which was issued after this trial started,[47] does however recommend that an NHS and PSS perspective be taken within cost-effectiveness analyses. In accordance with this guidance we thereby changed the perspective of the cost-effectiveness analysis to be from an NHS and PSS viewpoint, in order to enable our results to be compared with those for other studies adopting a similar perspective.

In the original protocol it was stated that health service use declared by patients would be cross-checked with the relevant hospital/primary care records. This was not undertaken for the reasons stated in Chapter 3 in the section Measuring costs.

Six-minute Walk Test

The study pilot revealed logistic problems in setting up and conducting 6MWTs. In order to satisfy concerns regarding patient safety, NHS trusts require walk tests to be conducted by individuals with appropriate medical training and at a venue where cardiopulmonary resuscitation equipment and additional medical support are readily to hand. None of the RAs working at three of the hospital sites was suitably qualified and physiotherapists delivering the study intervention did not have time to conduct additional procedures. However, at the fourth site to join the study, a qualified physiotherapist was seconded full time to deliver the MCP and undertake all RA functions. This provided the opportunity to satisfy concerns regarding patient safety during 6MWTs. In order to capture this important measure of physical function, it was decided that all participants at the fourth site would be approached to undertake walk tests as opposed to the 50% sample across all sites as stipulated in the protocol. Shortening the follow-up period meant that walk tests, originally planned for completion at 1 year, were conducted at 6 months post randomisation.

Amendments to study title

Given that infective status was no longer a prerequisite for participation the word ‘infective’ was removed from the study title (see Changes to inclusion and exclusion criteria). Following review of the first draft of this report by the TMG two further changes have been made. First, the Consolidated Standards of Reporting Trials (CONSORT) statement for RCTs recommends that when trials are powered to test for equivalence, this should be stated in the study title.[56] Therefore, the word ‘equivalence’ has been inserted into the title of this report. Second, while blinding to arm allocation was conducted where possible (see Blinding) use of the term ‘single blind’ is considered to be misleading.[69] Therefore, the phrase ‘single blind’ has been removed from the title of this report. These last two changes to the study title do not appear in the latest approved version of the study protocol (version 7.1, 1 July 2007).

Chapter 3
Results

Recruitment

The study commenced recruitment on 21 November 2005 and closed to recruitment on 30 April 2008 (total recruitment period was 29 months, 9 days).

Recruitment sites

The original study timetable allowed for a 3-month pilot at one site to test the adequacy of the MCP treatment protocol, the suitability of the proposed questionnaires and the feasibility of the original recruitment target (three participants per week per site). Consequently, the trial opened to recruitment at the Norfolk and Norwich University Hospital (NNUH: Norfolk and Norwich University Hospital Trust, Norwich, UK) on 21 November 2005. At the end of 3 months only 24 participants had been recruited, yielding insufficient data to adequately assess the pilot's aims. Therefore, the pilot was extended to the James Paget Hospital (JPH: James Paget Hospital NHS Trust, Great Yarmouth, UK) which opened to recruitment on 27 February 2006.

After obtaining REC approval for study amendments arising from the pilot (see Chapter 2, Changes to study protocol) the main trial commenced with the Queen Elizabeth Hospital (QEH: Queen Elizabeth Hospital NHS Trust, King's Lynn, UK) opening to recruitment on 11 October 2006. Participants recruited during the pilot at NNUH (n = 65) and JPH (n = 36) were retained and incorporated into the main trial. Recruitment continued at all three sites for a further 6 months. During this time it became clear that a fourth site would be required to achieve an adequate sample size within a reasonable time frame. Therefore, University Hospital Aintree (UHA: University Hospital Aintree NHS Trust, Liverpool, UK) joined the trial on 30 April 2007 and recruitment continued at all four sites for a further 12 months. All sites closed to recruitment on 30 April 2008. Figure 1 shows cumulative monthly recruitment for the entire recruitment period. In total, 526 participants were consented and randomised. This figure was 96% of the original recruitment target (550).

CONSORT statement

A summary of participant flow through each phase of the trial is provided in Figure 2. This CONSORT diagram provides a summary of recruitment and retention at all four sites combined. Non-responses reported for the two follow-up periods refer to the

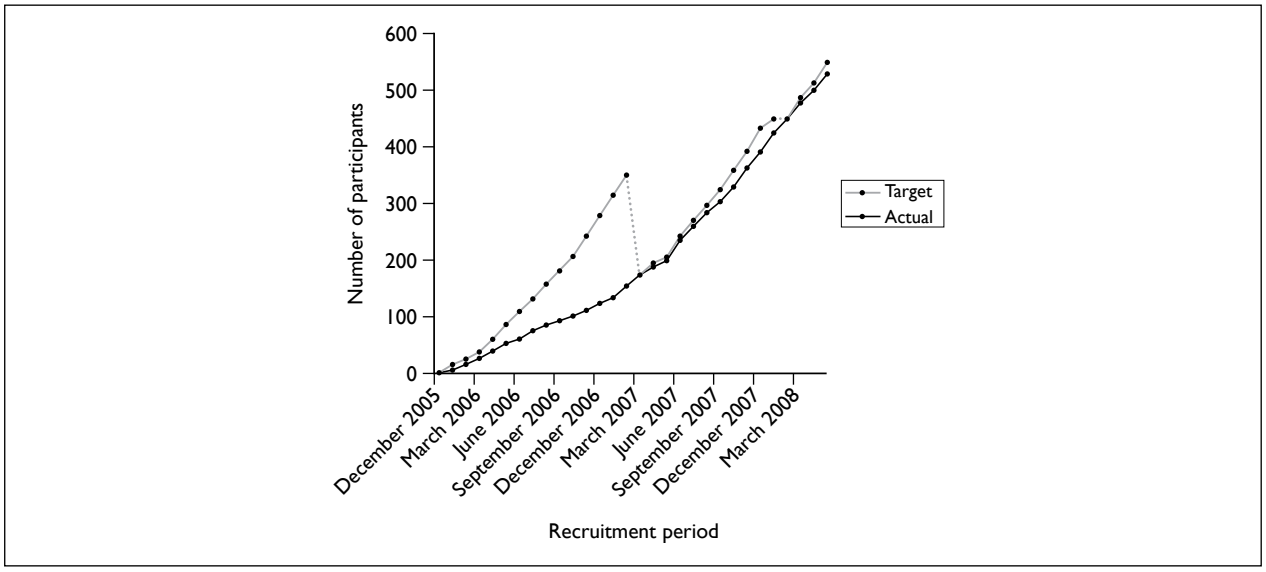

FIGURE 1 *Cumulative monthly recruitment against target, 1 December 2005 to 30 April 2008.*

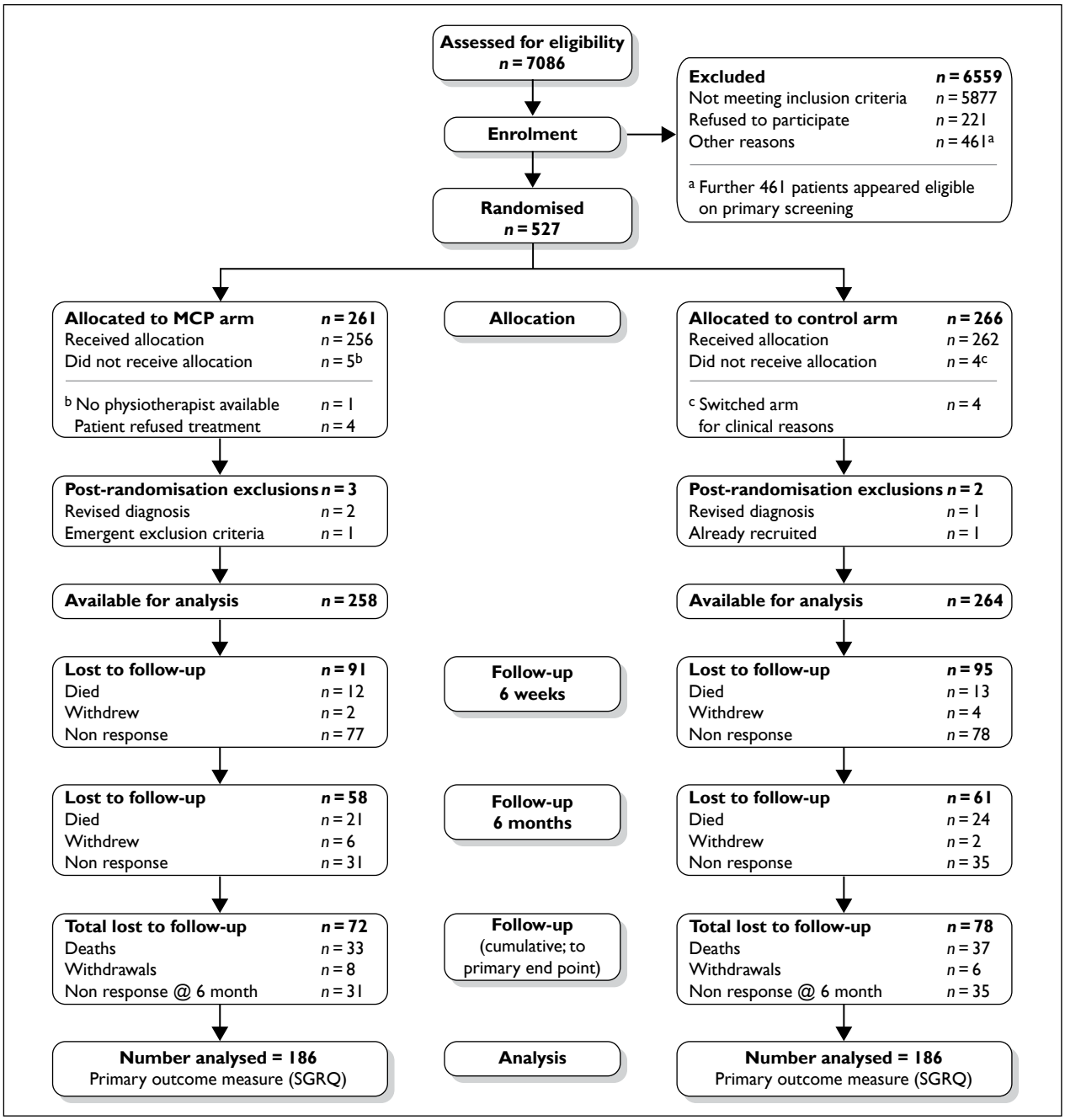

FIGURE 2 *CONSORT flow diagram.*

primary outcome measure only (SGRQ). Details of each phase are described below.

Screening for eligibility

During the 29-month recruitment period, 7086 patients admitted with respiratory symptoms were screened, of which 5877 (83%) did not meet the trial's inclusion/exclusion criteria. Of the remaining 1209 patients, a further 461 patients appeared eligible on preliminary screening, but were not approached for logistical reasons. These comprised:

- being discharged (n = 241)
- no physiotherapist available (n = 73)
- not under care of respiratory consultant (n = 55)
- lives out of area (n = 51)
- already seen by a physiotherapist (41).

Inclusion and exclusion criteria

Full details of trial inclusion and exclusion screenings are provided in Figure 3. It indicates that the bulk of respiratory admissions (83%) did not meet the trial's eligibility criteria. Of these, the majority concerned patients who did not have COPD or the reason for their admission was not an exacerbation of their condition (85%). The remaining exclusions were either owing to clinical contraindications for MCP (8%) or where ability to give informed consent was compromised in some way (7%).

Repeat screenings

More than 2000 screenings involved trial recruiters scrutinising records of people already excluded on a previous admission. Of these repeat screenings, 141 eventually yielded an additional 117 trial participants, which constituted 22% of the final sample size. Table 2 provides a breakdown of repeat screenings that led to recruitment and the reasons for initial exclusion.

Consent

In total, 748 patients were approached to participate in the study, 526 of whom gave their consent. This equates to an overall consent rate of 71% for the trial. The consent rate during the first 3 months of recruitment was considerably lower (38%) leading to an audit of reasons for refusal and strategies to ameliorate them (Table 3).

Randomisation

In total 527 participants were randomised to receive either MCP plus advice on chest clearing or advice on chest clearing alone. Unfortunately, this included one person who was consented and randomised twice. This error was realised shortly after the participant's second 'recruitment' and the corresponding randomisation number was

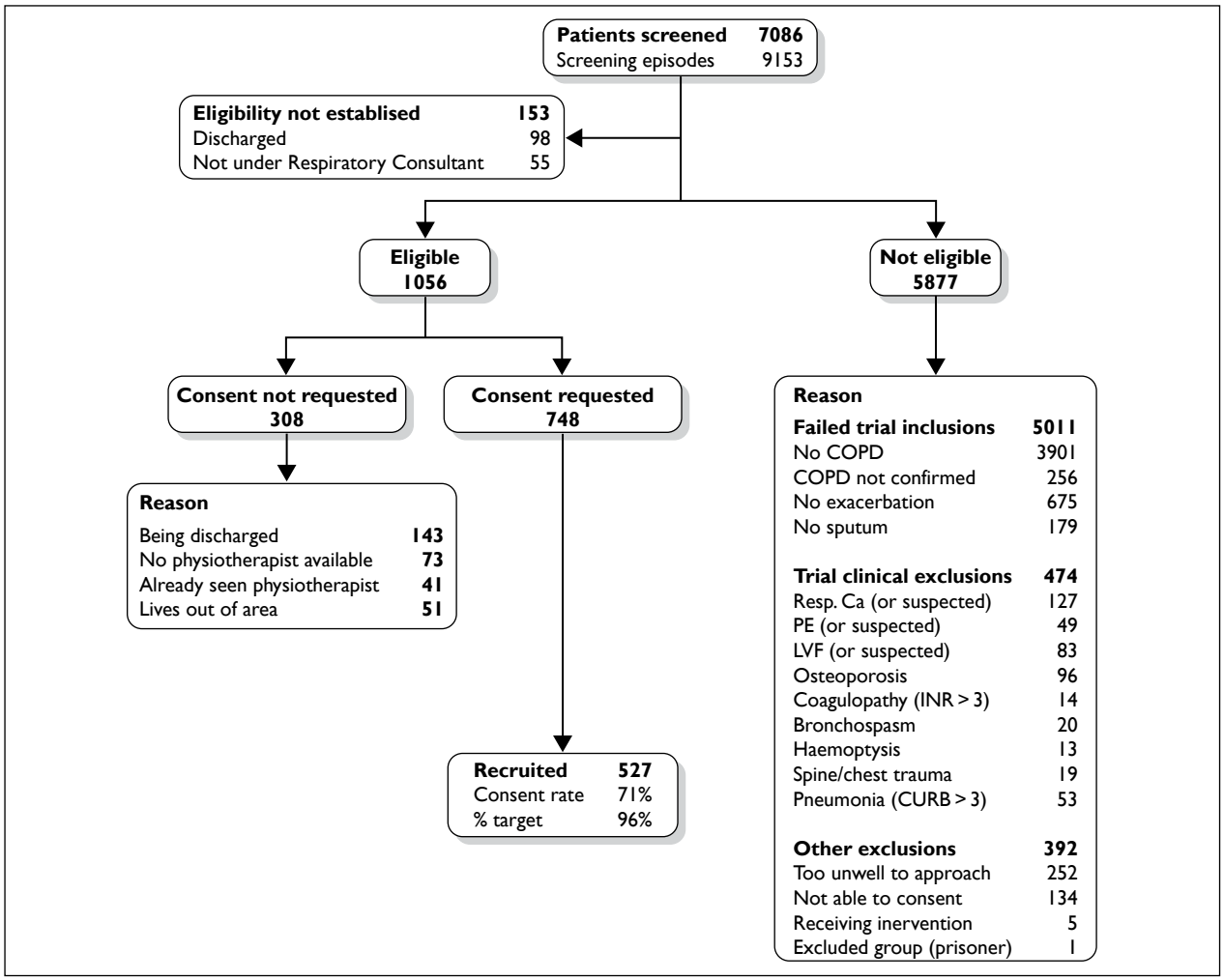

FIGURE 3 *Screening pathway from admission to consent, 21 November 2005 to 30 April 2008. CURB score, a composite score comprising 1 point for each of the following:* ***c****onfusion (defined as an AMT of 8 or less),* ***u****rea > 7 mmol/l (blood urea nitrogen > 19),* ***r****espiratory rate of 30 breaths per minute or greater and* ***b****lood pressure < 90 mmHg systolic or diastolic blood pressure 60 mmHg or less; LVF, left ventricular failure; PE, pulmonary embolism; Resp. Ca., respiratory cancer.*

TABLE 2 *Repeat screenings leading to successful recruitment, 21 November 2005 to 30 April 2008*

Rationale for initial exclusion	Number of screenings
Clinical reasons	
COPD diagnosis not established	27
Not admitted for COPD exacerbation	22
No sputum	11
Clinical exclusion suspected	16
Too unwell to consent	14
Other reasons	
Discharged	23
Consent declined	15
No physiotherapist available	8
Already seen physiotherapist	5
Total	**141**

abandoned for all follow-ups. Fortunately the participant was randomised to the same arm (control) on both occasions. The CONSORT diagram (Figure 2) describes this double allocation as a post-randomisation exclusion. Thus, the actual sample size achieved was 526 with 261 randomised to the MCP arm and 265 to the control arm. Results quoted in the remainder of this report are based on these figures using the format: total n–MCP n = control n (i.e. 526–261 = 265).

Post-randomisation exclusions

In total, there were 5–3 = 2 post-randomisation exclusions during the course of the trial. Retrospective changes in diagnosis (whereby inclusion criteria were no longer satisfied) led to 3–2 = 1 participants being withdrawn shortly after recruitment. These comprised two individuals who were rediagnosed with asthma and one who was rediagnosed with Kennedy syndrome. Additionally, one participant was withdrawn from the MCP arm owing to an emergent contraindication to treatment (i.e. pulmonary embolism). This patient had not received MCP prior to their exclusion from the trial. Finally, as mentioned previously, one person in the control arm was recruited twice. Follow-up data were not requested from these post-randomisation exclusions; consequently all subsequent analyses are based on the data provided by 522–258 = 264 participants (see Figure 2).

Movement between study arms

In total, 9–5 = 4 participants did not receive the intervention to which they had been allocated. Four patients randomised to receive advice on chest clearing alone were considered by the physiotherapist to be sufficiently ill to make MCP essential for clinical reasons. Conversely, four patients allocated to receive MCP declined the treatment offered by the physiotherapist. One patient allocated to receive MCP was discharged before the physiotherapist could give the treatment. This participant's study allocation number was held open and they were readmitted with another COPD exacerbation within the 6-month follow-up period. However, on that occasion treatment with MCP was declined.

Follow-up

6-week follow-up

In total, 186 = 91 + 95 participants did not complete questionnaires at the 6-week time point. This equates to a 35% loss to follow-up, significantly higher than the 15% target set in the study protocol. Deaths (25 = 12 + 13) accounted for 5% of the total number recruited and withdrawals (6 = 2 + 4) for 1%, leaving the majority (29%) attributable to non-return of postal questionnaires (155 = 77 + 78).

6-month follow-up

In total, 119 = 58 + 61 losses occurred between 6 weeks and 6 months post randomisation. These comprised: 45 = 21 + 24 deaths, 8 = 6 + 2 withdrawals and 66 = 31 + 35 non-return of questionnaires. Thus, the total loss to follow-up from randomisation to the study end point comprised: 5 = 3 + 2 post-randomisation exclusions, 70 = 33 + 37 deaths, 14 = 8 + 6 withdrawals and 66 = 31 + 35 non-responses at 6 months post randomisation. These losses equate to 1%, 13%, 3% and 12% respectively of the starting sample size (n = 526). This equates to a final retention figure of 71% for the primary outcome measure at the study's primary end point.

Site-specific recruitment, retention and follow-up

In line with recent recommendations for reporting complex RCTs of non-pharmacological treatment interventions[70] an additional CONSORT diagram is provided in Figure 4.

Extra boxes relating to care-providers have been added to show recruitment achieved and MCP

TABLE 3 *Audit of non-consenting patients: pilot phase (n = 38)*

Patient profile	**Number/detail**	
Gender	20 male, 18 female	
Age	Mean 69 (range 59–86)	
Number of hospitalisations during last year	Mean 2.2 (range 1–9)	
Number of days in hospital during last year	Mean 15 (range 2–104)	
Mortality	Two deaths during 12-week time frame	
Reasons given for non-consent	**Number**	**Strategy to ameliorate**
Feeling too unwell to think about study	15	Additional phrase added to introduction script[a]
Unwilling to receive MCP	7	Stress that the physiotherapist tailors the treatment to each individual
Unwilling to be randomised to control arm	4	Reiterate importance of RCT principle
Need time to think about it	4	Repeat visits (next day and/or next admission)
Need to ask family member (leading to subsequent non-consent)	4	Delay specific consent request for patients who appear unwilling
		Facilitate conversation with treating physician
Unwilling to collect sputum	2	Empathy and encouragement
Reason not given and/or unclear	2	Gentle enquiry

a 'We know that this is a difficult time for you but this study is trying to find out the best way of treating people with your condition when they ARE feeling very poorly.'

treatment delivered at each hospital site. Follow-up phases have also been expanded to give information on non-response rates for secondary outcome measures. Details of particular note are summarised below.

Site-specific recruitment rates

Both the length of time open to recruitment and the consequent accrual achieved shows variation between sites. The site yielding the largest number of participants (166) in the shortest time period (12 months) was UHA, achieving an average monthly recruitment rate of 13.8 participants. Recruitment rates at NNUH (158 over 29 months) and JPH (130 over 26 months) were broadly similar, with an average recruitment per month of 5.4 and 5.0 respectively. Recruitment at QEH accrued 73 participants over an 18-month period, equating to an average of 4.1 participants per month.

Post-randomisation exclusions and study arm switching

Of the three post-randomisation exclusions owing to revised diagnoses, two occurred at JPH and one at NNUH. The exclusion concerning an emergent contraindication to MCP occurred at JPH and the participant randomised twice was recruited at NNUH. Of the four control arm participants switched to the MCP arm for clinical reasons, three occurred at NNUH and one at QEH. Of the five participants in the MCP arm who refused treatment, four occurred at QEH and one at JPH.

Follow-up response rates for secondary outcome measures

At 6 weeks post randomisation, the non-response rates for all questionnaire-based outcome measures were broadly similar (range 30–34%). With the exception of the COPD cost questionnaire, all 6-month non-response rates were lower (range 4–19%). Following amendments to the study protocol (see Chapter 2, Six-minute Walk Test) the 6MWT was conducted at one site only (UHA). This physiological outcome measure showed the highest non-response rate. More than half of those contacted to conduct walk tests either refused to participate or subsequently failed to attend the appointment that had been arranged with the physiotherapist.

MCP treatment

Information on the number, frequency and duration of MCP delivered during the study period is provided in Table 4. In total, 257 participants received 658 sessions of MCP

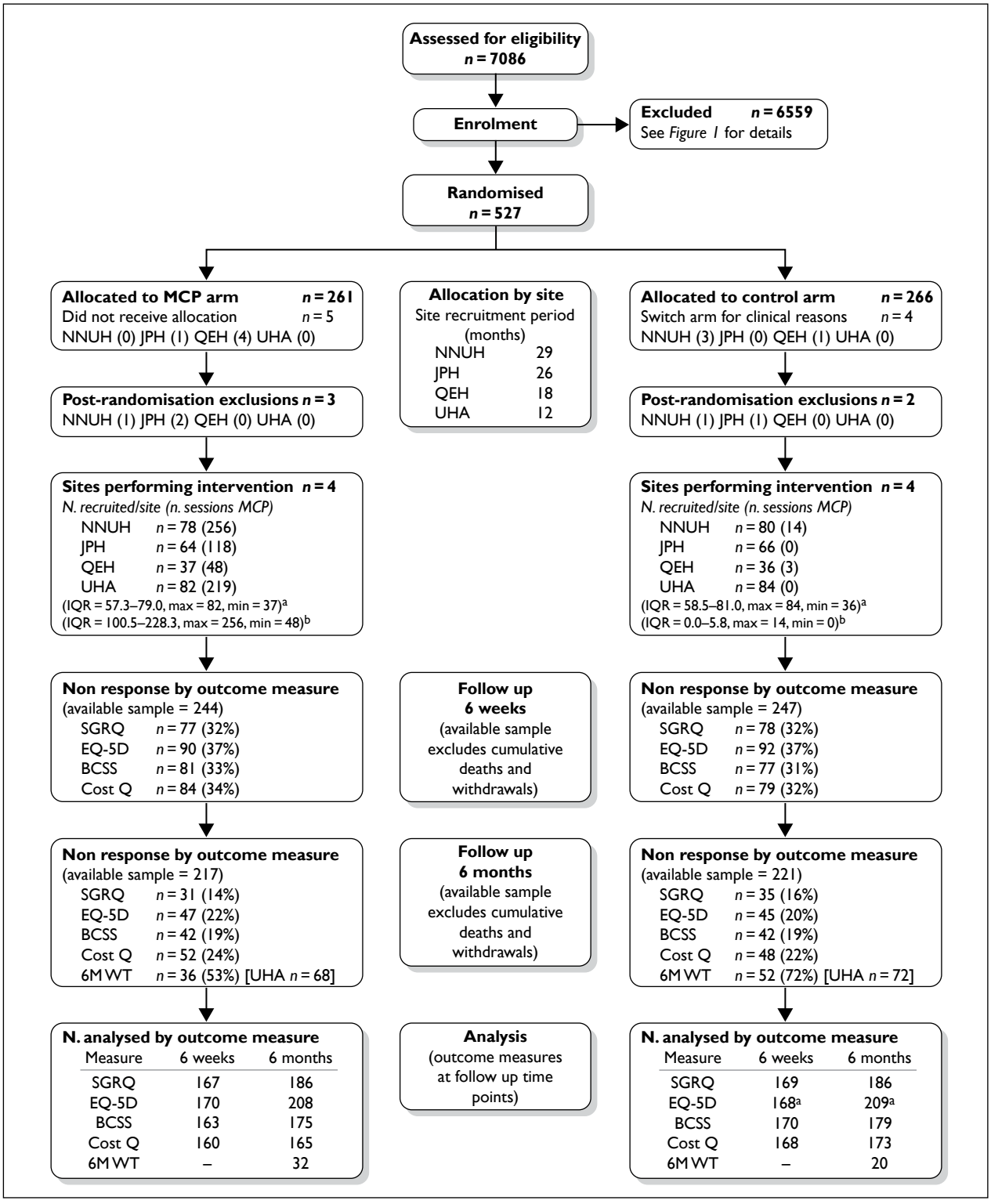

FIGURE 4 *Site-specific CONSORT flow diagram (including follow-up details for secondary outcome measures). a, inter quartile range for number of participants. b, inter quartile range for number of treatments.*

TABLE 4 *Summary of MCP treatment parameters (n = 658 sessions)*

MCP treatment parameter	Min.	Max.	Mean/ median	Breakdown of parameter: *n* (% total sessions)			
Number of MCP sessions/patient	1	21	2.53/2	***n* sessions per patient**	***n* patients (total = 257)**	***n* sessions[a] (total = 658)**	**% Total sessions**
				1	97	97	14
				2	70	140	21
				3	47	141	22
				4	20	80	12
				5	6	30	5
				6	3	18	3
				7	5	35	5
				8 or more	9	117	18
Number of positions/ session	1	3	1.91/2	1 position: 248 sessions (38%)			
				2 positions: 404 sessions (61%)			
				3 positions: 6 sessions 1%)			
Time taken per session	1	41	11.9/11	< 5 minutes: 14 sessions (2%)			
				5–10 minutes: 266 sessions (40%)			
				11–19 minutes: 323 sessions (49%)			
				20–25 minutes: 44 sessions (7%)			
				≥ 26 minutes: 11 sessions (2%)			
O_2 saturation (%) – immediately prior to MCP	74	100	92.0/93	Less than 85%: 30 (4%)			
				85% to 89%: 111 (17%)			
				90% to 94%: 413 (63%)			
				95% to 100%: 98 (15%)			
O_2 saturation (%) – lowest during MCP	69	99	91.3/92	< 85%: 44 (7%)			
				85–89%: 130 (20%)			
				90–94%: 385 (58%)			
				95–100%: 93 (14%)			
O_2 saturation (%) – change during MCP	–18	+13	–0.7/0	Drop in O_2 saturation: 268 (41%)			
				No change in O_2 saturation: 258 (39%)			
				Increase in O_2 saturation: 126 (19%)			
Deviations from MCP treatment protocol	*n* = 258			One position only: 248 (38%)			
				O_2 saturation not recorded: 6 (< 1%)			
				Patient declined treatment: 4 (< 1%)			
Alternative positions selected	*n* = 44			Upright: 31 (5%)			
				Leaning forward: 10 (2%)			
				Flat on back: 3 (<1%)			

a Numbers quoted comprise the total number of sessions received by trial participants between 1 December 2005 and 30 October 2008. This includes MCP given during readmissions and also includes participants who were followed up for more than 6 months (see Chapter 2, Changes to recruitment and follow-up periods).

over the 3-year recruitment/follow-up period. The number of MCP sessions administered to patients varied considerably (range 1–25) with the majority receiving two or three sessions between randomisation and the end of their follow-up period. In the majority of sessions (61%) the physiotherapist selected two different positions in which to place the patient when performing percussion and vibration techniques. However, in approximately one-third of sessions, only one treatment position was adopted.

While the length of time spent performing MCP varied considerably (range 1–41 minutes), half of all sessions lasted between 11 and 19 minutes (average session length 11.9 minutes).

On four occasions patients requested that the physiotherapist stopped treatment and on six occasions an AE truncated treatment. These scenarios made up the majority of sessions lasting less than 5 minutes (n = 14).

Immediately prior to each MCP session, the patient's oxygen saturation was recorded with a finger pulse oximeter. While this reveals an average pretreatment reading of 92.0%, again wide variation is apparent across the total number of sessions (range 69–99%). Similarly, while the average lowest oxygen saturation during MCP appears little changed from baseline (91.3%) this figure was compiled from readings ranging from 69% to 99%. With respect to change in oxygen levels, nearly half of all MCP sessions were associated with a drop in oxygen saturation (41%). However, for a similar proportion (39%) no change was evident. The largest drop in oxygen saturation was from 92% prior to treatment to 74% during MCP (see Adverse events). Averaging all change values reveals a slight drop in oxygen saturation overall (–0.7%) but, again, this figure conceals wide variation across all treatment sessions (range –18% to + 15%).

Adverse events

Of the 658 MCP treatments performed by physiotherapists during the study, a total of 15 AEs were reported (Table 5). These comprised: increased shortness of breath (n = 5); pain (n = 5);

TABLE 5 *Adverse events, December 2005 to April 2008 (n = 658 MCP sessions)*

Site	Adverse event	Response	Outcome	Attributed to MCP (clinical review)
NNUH	Tachycardia (130 b.p.m.)	This treatment stopped	Symptoms resolved	Yes
NNUH	Atrial fibrillation	This treatment stopped	Symptoms resolved	No – exacerbation of pre-existing condition
NNUH	Thoracic haematoma 1 day post treatment	Treatment discontinued, no further MCT given	Further three admissions owing to cardiac events – patient died	No
NNUH	Patient reported chest wall pain	Treatment position changed	Pain alleviated	No – exacerbation of pre-existing condition
NNUH	Tachycardia (125 b.p.m.) Starting 0_2 saturation: 79% Lowest 0_2 saturation: 71%	This treatment stopped	Symptoms resolved	Yes
JPH	Patient reported very SOB Starting 0_2 saturation: 88% Lowest 0_2 saturation: 80% Patient asked to stop MCP	This treatment stopped	Symptoms resolved	Yes
NNUH	Patient reported worsening pleuritic pain	This treatment stopped	Symptoms resolved	Yes

TABLE 5 *Adverse events, December 2005 to April 2008 (n = 658 MCP sessions) (continued)*

Site	Adverse event	Response	Outcome	Attributed to MCP (clinical review)
JPH	Patient reported very SOB in second position Starting 0_2 saturation: 95% Lowest 0_2 saturation: 94%	This treatment stopped Patient auscultated Breathing exercises and coughing implemented	Symptoms resolved	Yes
QEH	Patient reported cramp	Treatment position changed.	Pain alleviated	No – exacerbation of pre-existing condition
JPH	Patient reported SOB and asked to stop MCP Starting 0_2 saturation: 95% Lowest 0_2 saturation: 84%	Treatment suspended Nurse alerted Nebuliser given	Symptoms stabilised	Yes
JPH	Patient reported SOB and asked to stop MCP Starting 0_2 saturation: 88% Lowest 0_2 saturation: 85%	This treatment stopped	Symptoms resolved	Yes
JPH	Patient exhibited increased wheeze 0_2 saturation constant: 98%	Treatment suspended Broncospasm confirmed on auscultation	Symptoms stabilised	Yes
UHA	Patient reported back pain	Symptoms reported 1 day after treatment	No further treatment given	No
JPH	0_2 saturation drop on turning (patient on 35% oxygen) Starting 0_2 saturation: 92% Lowest 0_2 saturation: 74%	Treatment suspended Patient returned to sitting position. 0_2 saturation quickly recovered to 92%	Symptoms stabilised MCP restarted	Yes[a]
NNUH	Patient reported sharp pain in lower abdomen and asked to stop MCP	This treatment stopped	Symptoms resolved	No – exacerbation of pre-existing condition

b.p.m., beats per minute; SOB, short of breath.
a MCP given on two further occasions with 0_2 saturation remaining stable at 92%.

arrhythmia (n = 3); bronchospasm (n = 1); and thoracic haematoma (n = 1). The shortness of breath reported by patients was accompanied by varying degrees of reduced oxygen saturation (–18% to 0%). Four patients requested that MCP treatment be stopped. AEs were subject to periodic review by the study's management groups. Given their nature (i.e. consistent with the literature) and frequency (i.e. 2% of total treatments), these AEs were not considered to present any significant issues with respect to patient safety and continuation of the trial.

Data quality

Prior to analysis, the final data set was audited for completeness and accuracy. This comprised a cross-check of electronic database entries against original paper records for a randomly selected

sample of participants (n = 26, 5% of full data set). In addition, a double data entry check of questionnaire returns entered on electronic databases was performed for participants recruited before 1 January 2007 (n = 125, 23% of total recruited). The results of this audit revealed no significant issues in terms of data quality (see Appendix 25).

Baseline data

Characteristics of randomised participants are shown in Table 6. No differences were identified between the treatment arms.

Numbers analysed

A total sample size of 522 was used for all analyses. The proportion of participants for which information was not available on the primary outcome measures at 6 weeks did not differ significantly between treatment arms (p = 0.96, chi-squared test) or at 6 months (p = 0.786, chi-squared test).

Primary analyses

The results for the primary ITT analyses are given in Table 7a and 7b.

TABLE 6 *Baseline characteristic of randomised subjects*

	MCP arm (*n* = 258)			**No MCP arm (*n* = 264)**		
	N	**Mean**	**SD**	***N***	**Mean**	**SD**
Age (years)	258	69.08	9.85	264	69.58	9.51
SGRQ symptom score	249	79.23	14.42	255	79.61	14.18
SGRQ activity score	249	84.97	15.46	258	84.10	15.87
SGRQ impact score	249	56.58	19.13	258	57.57	18.85
SGRQ total score	249	68.94	14.66	255	69.13	14.76
BCSS score	249	6.23	2.11	256	6.44	2.18
O_2 saturation (%)	254	92.33	3.67	252	92.77	5.03
Sputum volume (ml)	240	8.17	11.09	255	7.89	9.63
EQ-VAS score	196	44.95	21.03	202	46.64	21.42
EQ-5D score	199	0.45	0.32	202	0.43	0.36
		n/N	**%**		***n/N***	**%**
Female		115/258	44.57		109/264	41.29
Smoking status						
Current		43/221	19.46		49/224	21.88
Ex-smoker		175/221	79.19		172/224	76.79
Never		3/221	1.36		3/224	1.34
Sputum > 15 ml		38/240	15.83		42/255	16.47
Site						
JPH		62/258	24.03		65/264	24.62
NNUH		77/258	29.84		79/264	29.92
QEH		37/258	14.34		36/264	13.64
UHA		82/258	31.78		84/264	31.82
MRC-D score						
1		0/250	0.00		1/255	0.39
2		11/250	4.40		14/255	5.49
3		27/250	10.80		27/255	10.59
4		68/250	27.20		75/255	29.41
5		144/250	57.60		138/255	54.12

Total SGRQ score

No statistically significant difference in mean total SGRQ score was found at the 6-week time point in either unadjusted or adjusted for baseline values and hospital site analyses. At 6 weeks, the mean difference (95% CI) in the unadjusted analysis was 0.84 (–3.22 to 4.91) and for the adjusted analysis was 1.61 (–1.33 to 4.55), with the advice for chest therapy arm having a, non-significantly, higher score. Converting these CIs to effect size CIs, the result of the unadjusted analysis was 0.04 (–0.17 to 0.26) and for the adjusted analysis was 0.09 (–0.07 to 0.24). Both unadjusted and adjusted CIs are within the predefined limits of equivalence, indicating equivalence.

No statistically significant difference in total SGRQ score was found at the 6-month time point in either unadjusted or adjusted for baseline values and hospital site analyses. At 6 months, the mean difference (95% CI) in the unadjusted analysis was –0.36 (–4.31 to 3.59) and for the adjusted analysis was 0.51 (–2.67 to 3.69), with the advice for chest therapy arm having a lower unadjusted score but a higher adjusted score. Converting these to effect sizes, the result of the unadjusted analysis was –0.02 (–0.22 to 0.19) and the result of the adjusted analysis 0.03 (–0.14 to 0.19). Both unadjusted and adjusted CIs are within the predefined limits of equivalence, indicating equivalence.

SGRQ symptom score

No statistically significant difference in mean SGRQ symptom score was found at the 6-week time point in either unadjusted or adjusted for baseline values and hospital site analyses. At 6 weeks, the mean difference (95% CI) in the unadjusted analysis was 2.73 (–2.02 to 7.48) and for the adjusted analysis was 3.12 (–1.00 to 7.25). Converting these to effect sizes, the result of the unadjusted analysis was 0.12 (–0.09 to 0.34) and for the adjusted analysis 0.14 (–0.04 to 0.33). Both unadjusted and adjusted CIs are outwith the predefined limits of equivalence with the advice for chest therapy arm having a possibly higher symptom score than the MCP.

No statistically significant difference in mean SGRQ symptom score was found at the 6-month time point in either unadjusted or adjusted for baseline values and hospital site analyses. At 6 months, the mean difference (95% CI) in the unadjusted analysis was 0.02 (–4.68 to 4.73) and for the adjusted analysis was 0.87 (–3.50 to 5.25), with the advice for chest therapy arm having a, non-significant, higher score. Converting these to effect sizes, the results of the unadjusted analysis was 0.00 (–0.20 to 0.21) and for the adjusted analysis was 0.04 (–0.15 to 0.23; these are within the predefined limits of equivalence, indicating equivalence.

SGRQ activity score

No statistically significant difference in mean SGRQ activity score was found at the 6-week time point in either unadjusted or adjusted for baseline values and hospital site analyses. At 6 weeks, the mean difference (95% CI) in the unadjusted analysis was –1.93 (–6.18 to 2.32) and for the adjusted analysis was –0.16 (–3.55 to 3.23). Converting these to effect sizes, the result for the unadjusted analysis was –0.10 (–0.31 to 0.12) and for the adjusted analysis was –0.01 (–0.18 to 0.16). The unadjusted interval includes the possibility that the MCP arm is slightly superior to the advice for chest therapy arm; however, the adjusted analysis interval is within the predefined limits of equivalence.

No statistically significant difference in mean SGRQ activity score were found at the 6-month time point in either unadjusted or adjusted for baseline values and hospital site analyses. At 6 months, the mean difference (95% CI) in the unadjusted analysis was –1.58 (–5.50 to 2.34) and for the adjusted analysis was –0.36 (–3.76 to 3.04). Converting these to effect sizes, the result for the unadjusted analysis was –0.08 (–0.29 to 0.12) and for the adjusted analysis was –0.02 (–0.20 to 0.16); both of these intervals are within the predefined limits of equivalence.

SGRQ impact score

No statistically significant difference in mean SGRQ impact score was found at the 6-week time point in either unadjusted or adjusted for baseline values and hospital site analyses. At 6 weeks, the mean difference (95% CI) in the unadjusted analysis was 1.72 (–2.89 to 6.33) and for the adjusted analysis was 2.12 (–1.30 to 5.53). Converting these to effect sizes, the result for the unadjusted analysis was 0.08 (–0.13 to 0.29) and for the adjusted analysis 0.10 (–0.06 to 0.25), both intervals within the predefined limits of equivalence.

No statistically significant difference in mean SGRQ impact score was found at the 6-month time point in either unadjusted or adjusted for baseline values and hospital site analyses. At

TABLE 7a *Primary outcome measure results: ITT analysis*

	MCP arm			No MCP arm			Unadjusted analysis no MCP–MCP			Adjusted analysis[a] no MCP–MCP		
	n	**Mean**	**SD**	***n***	**Mean**	**SD**	**Mean difference**	**95% CI**	***p*-value**	**Mean difference**	**95% CI**	***p*-value**
6 weeks												
SGRQ total score	167	62.96	18.50	169	63.81	19.37	0.84	−3.22 to 4.91	0.6833	1.61	−1.33 to 4.55	0.282
Effect size							0.04	−0.17 to 0.26		0.09	−0.07 to 0.24	
SGRQ symptom score	168	67.29	22.08	169	70.02	22.29	2.73	−2.02 to 7.48	0.2594	3.12	−1.00 to 7.25	0.137
Effect size							0.12	−0.09 to 0.34		0.14	−0.04 to 0.33	
SGRQ activity score	170	81.30	19.01	173	79.37	20.93	−1.93	−6.18 to 2.32	0.3714	−0.16	−3.55 to 3.23	0.926
Effect size							−0.10	−0.31 to 0.12		−0.01	−0.18 to 0.16	
SGRQ impact score	170	50.32	21.55	173	52.04	21.85	1.72	−2.89 to 6.33	0.4639	2.12	−1.30 to 5.53	0.223
Effect size							0.08	−0.13 to 0.29		0.10	−0.06 to 0.25	
6 months												
SGRQ total score	186	63.88	19.05	186	63.52	19.68	−0.36	−4.31 to 3.59	0.8573	0.51	−2.67 to 3.69	0.753
Effect size							−0.02	−0.22 to 0.19		0.03	−0.14 to 0.19	
SGRQ symptom score	186	68.38	23.13	186	68.40	23.01	0.02	−4.68 to 4.73	0.9925	0.87	−3.50 to 5.25	0.695
Effect size							0.00	−0.20 to 0.21		0.04	−0.15 to 0.23	
SGRQ activity score	188	82.49	18.81	187	80.91	19.74	−1.58	−5.50 to 2.34	0.4279	−0.36	−3.76 to 3.04	0.836
Effect size							−0.08	−0.29 to 0.12		−0.02	−0.20 to 0.16	
SGRQ impact score	188	51.53	22.58	187	51.60	22.50	0.07	−4.51 to 4.65	0.9752	0.43	−3.29 to 4.14	0.822
Effect size							0.00	−0.20 to 0.2		0.02	−0.15 to 0.18	

a The difference has been adjusted to take into account baseline value and hospital site.

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TABLE 7b *Primary outcome measures results: imputed ITT analysis*

	MCP arm			No MCP arm			Unadjusted analysis no MCP–MCP			Adjusted analysis[a] no MCP–MCP		
	n	Mean	SD	*n*	Mean	SD	Mean difference	95% CI	*p*-value	Mean difference	95% CI	*p*-value
6 weeks												
SGRQ total score	258	62.89	26.45	264	63.56	23.71	0.67	−3.79 to 5.13	0.764	0.60	−3.65 to 4.84	0.776
Effect size							0.04	−0.20 to 0.27		0.03	−0.19 to 0.26	
SGRQ symptom score	258	66.71	31.64	264	68.66	34.13	1.95	−3.76 to 7.65	0.496	1.97	−3.57 to 7.52	0.479
Effect size							0.08	−0.15 to 0.30		0.08	−0.14 to 0.29	
SGRQ activity score	258	80.59	28.44	264	78.92	24.64	−1.67	−6.07 to 2.72	0.449	−1.27	−5.51 to 2.98	0.550
Effect size							−0.08	−0.31 to 0.14		−0.06	−0.28 to 0.15	
SGRQ impact score	258	50.44	31.36	264	52.03	27.75	1.59	−3.76 to 6.95	0.551	1.05	−4.01 to 6.11	0.674
Effect size							0.07	−0.17 to 0.31		0.05	−0.18 to 0.28	
6 months												
SGRQ total score	258	63.496	23.47	264	63.30	21.64	−0.15	−3.77 to 3.46	0.935	−0.23	−3.56 to 3.10	0.891
Effect size							−0.01	−0.19 to 0.18		−0.01	−0.18 to 0.16	
SGRQ symptom score	258	67.79	39.50	264	67.72	40.75	−0.07	−4.72 to 4.58	0.976	−0.01	−4.51 to 4.49	0.996
Effect size							0.00	−0.20 to 0.20		0.00	−0.19 to 0.19	
SGRQ activity score	258	79.19	32.40	264	77.92	34.65	−1.27	−6.12 to 3.57	0.605	−0.95	−5.66 to 3.77	0.692
Effect size							−0.05	−0.24 to 0.14		−0.04	−0.22 to 0.15	
SGRQ impact score	258	51.44	24.41	264	51.55	23.56	0.11	−4.22 to 4.44	0.961	−0.43	−4.47 to 3.61	0.832
Effect size							0.00	−0.20 to 0.21		−0.02	−0.21 to 0.17	

a The difference has been adjusted to take into account baseline value and hospital site.

6 months, the mean difference (95% CI) in the unadjusted analysis was 0.07 (–4.51 to 4.65) and for the adjusted analysis was 0.43 (–3.29 to 4.14). Converting these to effect sizes, the result for the unadjusted analysis was 0.00 (–0.20 to 0.21) and for the adjusted analysis was 0.02 (–0.15 to 0.18); both of these intervals are within the predefined limits of equivalence.

Secondary analyses

Secondary outcome measures

Results of the secondary outcome measures are given in Table 8a and 8b.

EQ-VAS score

No statistically significant differences in mean EQ-VAS score were found at the 6-week time point in either the unadjusted (p = 0.963) or adjusted analyses (p = 0.798). At 6 weeks the mean difference (95% CI) in the unadjusted analysis was –0.11 (–4.88 to 4.66) and for the adjusted analysis was –0.68 (–5.90 to 4.55). Similarly, no statistically significant differences were found at the 6-month time point in either the unadjusted (p = 0.663) or adjusted analyses (p = 0.297). At 6 months the mean difference (95% CI) in the unadjusted analysis was 0.96 (–3.37 to 5.29) and for the adjusted analysis was 2.65 (–2.37 to 7.65).

EQ-5D score

No statistically significant difference in mean EQ-5D score was found at the 6-week time point in either the unadjusted (p = 0.689) or adjusted analyses (p = 0.442). At 6 weeks the mean difference (95% CI) in the unadjusted analysis was 0.01 (–0.05 to 0.08) and for the adjusted analysis was 0.03 (–0.04 to 0.10). Similarly, no statistically significant differences were found at the 6-month time point in either the unadjusted (p = 0.372) or adjusted analyses (p = 0.886). At 6 months the mean difference (95% CI) in the unadjusted analysis was –0.03 (–0.10 to 0.04) and for the adjusted analysis was –0.01 (–0.07 to 0.06).

BCSS score

No statistically significant difference in mean BCSS score was found at the 6-week time point in either the unadjusted (p = 0.120) or adjusted analyses (p = 0.208). At 6 weeks the mean difference (95% CI) for the unadjusted analysis was 0.45 (–0.12 to 1.03) and for the adjusted analysis was 0.33 (–0.18 to 0.84). Similarly, no statistically significant differences were found at the 6-month time point in either the unadjusted (p = 0.858) or adjusted analyses (p = 0.978). At 6 months the mean difference (95% CI) for the unadjusted analysis was 0.06 (–0.55 to 0.66) and for the adjusted analysis was 0.01 (–0.54 to 0.56).

Six-minute Walk Test

A statistically significant difference in mean total distance walked in 6 minutes was found between the treatment arms at the 6 months time point (p = 0.0210). The mean difference (95% CI) was 83.23 (13.09 to 153.37) with the no MCP arm walking further on average than the MCP arm.

Number of days in hospital

No significant difference was found in the total number of days spent in hospital (p = 0.4209). The 95% CI for the incidence rate ratio or the ratio of the means was 0.91 to 1.24), indicating that the advice only arm could result in a 24% higher mean number of days in hospital or that the MCP arm could result in a 9% lower mean number of days in hospital.

Subgroup analysis of SGRQ score by sputum volume

Subgroup analyses of the primary outcome measures by baseline sputum volume, split into 15 ml or less versus more than 15 ml, are given in Table 9 and Figures 5 and 6. Neither subgroup analysis was significant.

Per-protocol analyses

The results of the PP analyses are given in Tables 10 and 11.

Primary outcomes

The results of the PP analyses of primary outcomes were similar to those of the ITT analyses with equivalence being demonstrated for total SGRQ score, SGRQ activity score and SGRQ impact score at 6 weeks and 6 months. Equivalence was also demonstrated for SGRQ symptom score at 6 weeks for both unadjusted and adjusted for baseline and site analyses. However, equivalence was not demonstrated for SGRQ symptom score at 6 weeks in adjusted for baseline and site analysis as the 95% CI for the effect size (–0.07 to 0.32) extended beyond 0.30 SDs.

Secondary outcomes

The results of the PP analyses of secondary outcomes were similar to those of the ITT analyses with no significant differences in scores on EQ-VAS, EQ-5D or BCSS. The results of the 6MWT were identical as the PP and ITT groups did not differ for this outcome.

TABLE 8a *Secondary outcome measures results: ITT analysis*

	MCP arm			No MCP arm			Unadjusted analysis no MCP–MCP			Adjusted analysis[a] no MCP–MCP		
	n	Mean	SD	*n*	Mean	SD	Mean difference	95% CI	*p*-value	Mean difference	95% CI	*p*-value
6 weeks												
BCSS score	163	5.41	2.70	170	5.87	2.62	0.45	−0.12 to 1.03	0.1204	0.33	−0.18 to 0.84	0.208
EQ-VAS score	148	52.07	20.04	152	51.95	21.87	−0.11	−4.88 to 4.66	0.9626	−0.68	−5.90 to 4.55	0.798
EQ-5D score	168	0.48	0.32	166	0.50	0.32	0.01	−0.05 to 0.08	0.6891	0.03	−0.04 to 0.10	0.442
6 months												
BCSS score	175	5.60	2.96	179	5.66	2.84	0.06	−0.55 to 0.66	0.8577	0.01	−0.54 to 0.56	0.978
6MWT (metres)	32	174.72	109.53	20	257.95	141.15	83.23	13.09 to 153.37	0.0210			
Number of days in hospital[b]	258	15.95	16.49	264	16.98	18.04				1.07[c]	0.91 to 1.24	0.4209
EQ-VAS score	167	51.29	20.97	173	52.25	19.65	0.96	−3.37 to 5.29	0.6630	2.65	−2.35 to 7.65	0.297
EQ-5D score	209	0.48	0.33	207	0.45	0.35	−0.03	−0.10 to 0.04	0.3720	−0.01	−0.07 to 0.06	0.886

a The difference has been adjusted to take into account baseline value and hospital site.
b Analysed with a negative binomial regression model.
c Incidence rate ratio – IRR (95% CI).

TABLE 8b *Secondary outcome measure: imputed ITT analysis*

	MCP arm			No MCP arm			Unadjusted analysis no MCP – MCP			Adjusted analysis[a] no MCP – MCP		
	n	Mean	SD	*n*	Mean	SD	Mean difference	95% CI	*p*-value	Mean difference	95% CI	*p*-value
6 weeks												
BCSS score	258	5.56	4.21	264	6.01	3.24	0.45	−0.10 to 0.99	0.107	0.35	−0.17 to 0.86	0.188
EQ-VAS score	258	50.42	40.10	264	50.13	47.26	−0.29	−5.45 to 4.88	0.912	−0.53	−5.74 to 4.67	0.837
EQ-5D score	258	0.46	1.64	264	0.46	1.45	0.01	−0.08 to 0.09	0.897	0.01	−0.08 to 0.10	0.768
6 months												
BCSS score	258	5.65	5.81	264	5.65	4.74	0.00	−0.68 to 0.69	0.994	−0.10	−0.75 to 0.55	0.759
EQ-VAS score	258	49.76	26.39	264	51.74	27.15	1.97	−2.16 to 6.11	0.347	1.78	−2.34 to 5.91	0.395
EQ-5D score	258	0.46	0.74	264	0.42	0.92	−0.04	−0.11 to 0.03	0.246	−0.03	−0.10 to 0.04	0.344

a The difference has been adjusted to take into account baseline value and hospital site.

TABLE 9 *Subgroup analysis of SGRQ by sputum levels*

Outcome	Sputum < 15 ml		Sputum ≥ 15 ml		Interaction *p*-value
	Effect	95% CI	Effect	95% CI	
6 weeks					
SGRQ total score	2.41	−0.89 to 5.72	−2.00	−9.72 to 5.72	0.348
SGRQ symptom score	5.57	0.85 to 10.29	−6.51	−15.01 to 1.99	0.209
SGRQ activity score	−0.12	−4.13 to 3.89	−3.16	−11.24 to 4.93	0.870
SGRQ impact score	3.13	−0.57 to 6.83	0.03	−9.33 to 9.38	0.283
6 months					
SGRQ total score	1.11	−2.38 to 4.59	2.62	−6.47 to 11.70	0.932
SGRQ symptom score	1.57	−3.03 to 6.17	2.97	−8.28 to 14.23	0.951
SGRQ activity score	−0.69	−4.45 to 3.07	2.51	−7.18 to 12.19	0.495
SGRQ impact score	1.93	−2.17 to 6.02	2.45	−7.80 to 12.70	0.741

Health economics analysis

Measuring costs

Baseline health service use

In total, 367 participants completed one or more sections of the baseline cost questionnaire. In Table 12 the number of participants who responded to particular questions are detailed for both the no MCP group (overall n = 264) and the MCP group (overall n = 258), along with either the percentage who reported they had a hospital attendance or the corresponding mean number of visits for those who responded. In retrospect, particular questions within the baseline questionnaire were poorly designed. For example, with regard to question 14 (Appendix 19), if a box was not ticked it was not clear whether a patient did not have a contact or did not answer that particular question. That said, very few participants reported that they had seen any of the listed health professionals (two reported seeing a health visitor and 15 said they had seen a chiropodist or podiatrist). Overall, it can be seen that the use of particular health services in the 3 months prior to randomisation was comparable in both study arms. However, the percentage reporting hospital attendance for COPD or using oxygen at home and the mean number of GP surgery visits that were COPD related was higher in the no MCP group than in the MCP group.

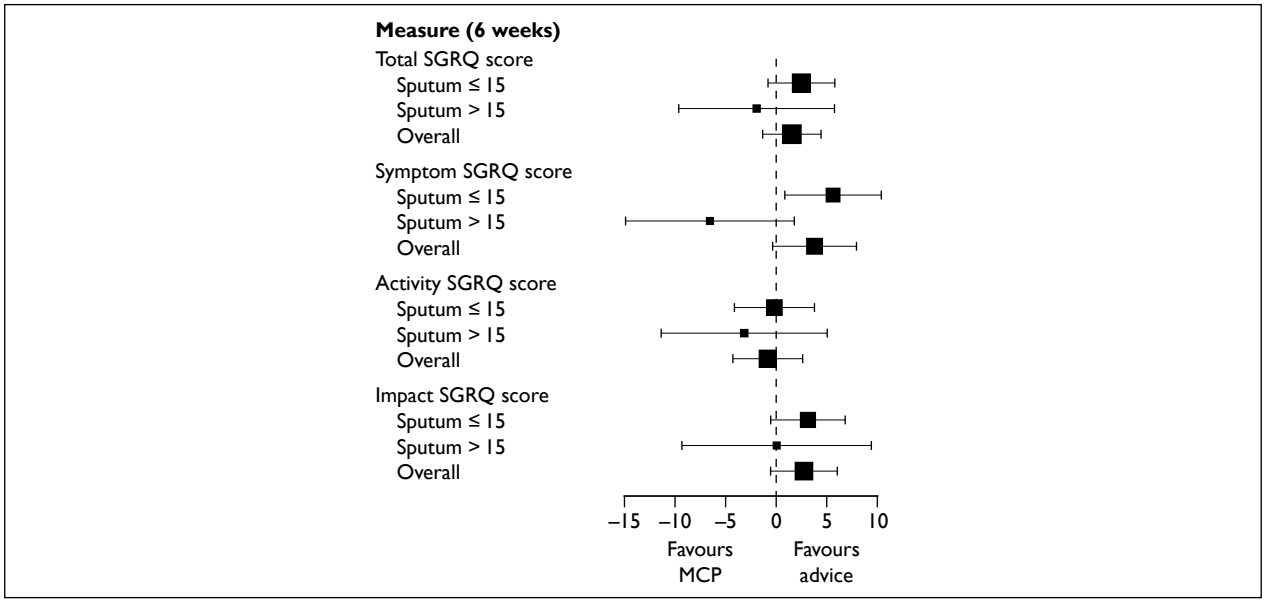

FIGURE 5 *6-week subgroup analysis of SGRQ by sputum.*

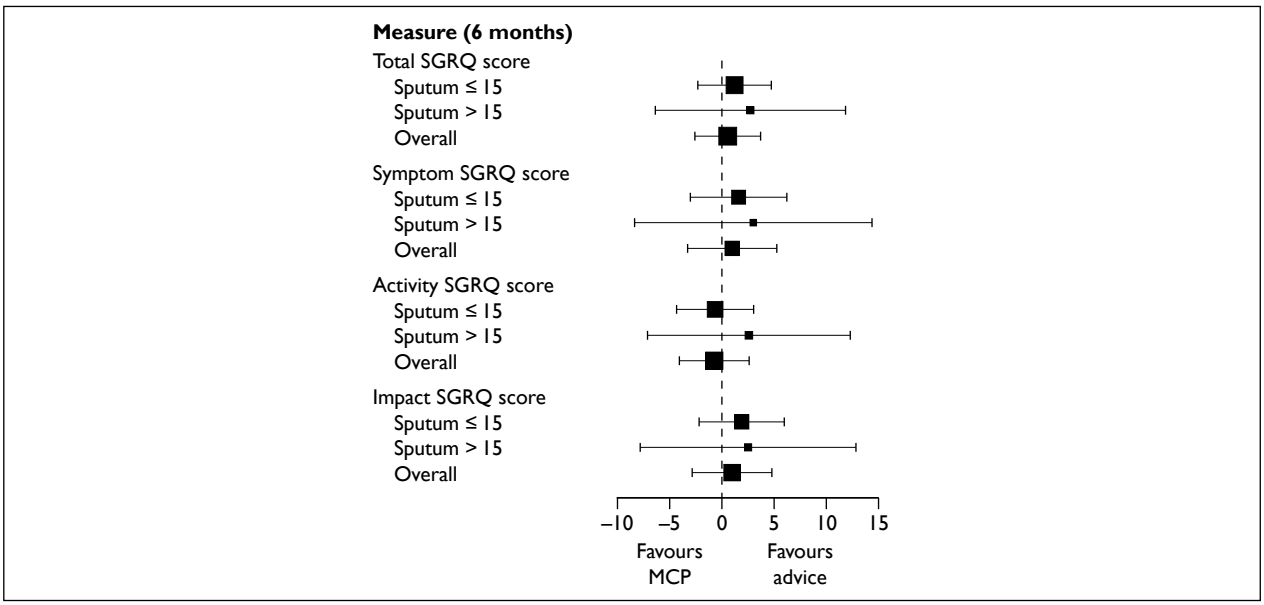

FIGURE 6 *6-month subgroup analysis of SGRQ by sputum.*

Physiotherapy input

Complete data was obtained for all 522 participants who were followed up. At baseline 4 of the 264 in the control arm received MCP, compared with 251/258 in the intervention arm, where the mean hands-on time for those receiving such treatment was 12.25 minutes (range 7–16 minutes) and 12.37 minutes (range 1–41 minutes) respectively. Further MCP follow-up sessions were provided to the same four participants in the control arm (range 1–9 sessions), and to 155 participants in the intervention arm (range 1–16 sessions), where the average total MCP hands-on time associated with all follow-up treatments was equal to 32.75 minutes (range 3–88 minutes) and 28.37 minutes (range 2–260 minutes) respectively. Thus, the per-participant average total MCP hands-on time was equal to 0.68 minutes (range 0–99 minutes) in the control arm, compared with 29.08 minutes (range 0–272) in the intervention arm. After adding a further 10 minutes to each baseline contact and a further 5 minutes to each follow-up session, the mean physiotherapy contact time was estimated to be 10.93 minutes in the control arm, compared with 46.27 minutes in the intervention arm.

Physiotherapy advice and MCP was generally provided by a Band 6 hospital physiotherapist, the average salary for which was £27,120 in 2007/8.[58] Curtis[58] estimated that the unit cost per hour of client contact was £40 for a Band 5 hospital physiotherapist. When this unit cost was adjusted to reflect band 6 costs, the unit cost per hour of client contact was estimated to be £44.91. When combined with the aforementioned average physiotherapy contact time the mean cost of the physiotherapy input was estimated to be £8.18 in the control arm, compared with £34.63 in the intervention arm. The mean incremental cost, for those allocated to receive MCP, was thereby estimated to be £26.45 per patient.

Hospital admissions

Complete data was obtained for all 522 participants who were followed up. The mean length of stay (post randomisation) at the initial inpatient admission was 5.31 days in the no MCP arm (range 1–27 days), compared with 5.84 in the MCP arm (range 1–51 days). The mean number of admissions (including the initial visit) in the 6-month trial period was 3.89 for participants in the control arm (range 1–23 admissions), compared with 3.47 in the intervention arm (range 1–28 admissions), where the mean length of stay in each of those admissions was estimated to be 5.04 in the no MCP arm, compared with 5.50 days in the MCP arm. The associated mean total number of days was estimated to be 16.98 in the control arm (range 0–118 days), compared with 15.95 in the intervention arm (range 0–102 days). The Healthcare Resource Group (HRG) codes from the NHS references costs 2006/07[59] which were deemed to relate to general respiratory admissions are listed in Table 13 (respiratory neoplasms were considered not to be applicable to this population group).[57]

The estimated weighted average cost per bed-day for both these respiratory-related general

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TABLE 10 *Primary outcome measure results: PP analysis*

	MCP arm			No MCP arm			Unadjusted analysis no MCP–MCP			Adjusted analysis[a] No MCP–MCP		
	n	Mean	SD	*n*	Mean	SD	Mean difference	95% CI	*p*-value	Mean difference	95% CI	*p*-value
6 weeks												
SGRQ total score	163	62.77	18.62	168	63.73	9.41	0.96	–3.15 to 5.08	0.6448	1.60	–1.37 to 4.58	0.290
Effect size							0.05	–0.17 to 0.27		0.08	–0.07 to 0.24	
SGRQ symptom score	163	67.48	22.06	168	69.86	22.26	2.38	–2.42 to 7.17	0.3302	2.90	–1.27 to 7.06	0.173
Effect size							0.11	–0.11 to 0.32		0.13	–0.06 to 0.32	
SGRQ activity score	166	80.90	19.05	172	79.25	20.94	–1.65	–5.94 to 2.64	0.4501	0.07	–3.37 to 3.50	0.970
Effect size							–0.08	–0.30 to 0.13		0.00	–0.17 to 0.17	
SGRQ impact score	166	50.16	21.69	172	52.02	21.91	1.86	–2.80 to 6.53	0.4324	2.07	–1.38 to 5.53	0.239
Effect size							0.09	–0.13 to 0.30		0.10	–0.06 to 0.25	
6 months												
SGRQ total score	182	63.88	18.88	184	63.40	19.73	–0.48	–4.45 to 3.49	0.8121	0.34	–2.84 to 3.53	0.832
Effect size							0.02	–0.23 to 0.18		0.02	–0.15 to 0.18	
SGRQ symptom score	182	68.45	23.07	184	68.36	23.10	–0.09	–4.83 to 4.66	0.9710	0.87	–3.56 to 5.30	0.699
Effect size							0.00	–0.21 to 0.20		0.04	–0.15 to 0.23	
SGRQ activity score	184	4.28	0.98	185	4.19	1.03	–1.68	–5.64 to 2.28	0.4040	–0.46	–3.90 to 2.99	0.795
Effect size							–0.09	–0.29 to 0.12		–0.02	–0.20 to 0.15	
SGRQ impact score	184	51.52	22.31	185	51.47	22.55	–0.05	–4.64 to 4.54	0.9829	0.18	–3.53 to 3.89	0.924
Effect size							0.00	–0.21 to 0.20		0.01	–0.16 to 0.17	

a The difference has been adjusted to take into account baseline value and hospital site.

TABLE 11 *Secondary outcome measures results: PP analysis*

	MCP arm			No MCP arm			Unadjusted analysis no MCP–MCP			Adjusted analysis[a] No MCP–MCP		
	n	Mean	SD	*n*	Mean	SD	Mean difference	95% CI	*p*-value	Mean difference	95% CI	*p*-value
BCSS score	158	5.43	2.70	169	5.87	2.63	0.44	–0.14 to 1.02	0.1345	0.31	–0.20 to 0.83	0.232
EQ-VAS score	145	52.17	20.09	151	51.83	21.89	–0.33	–5.15 to 4.47	0.8902	–0.56	–5.85 to 4.72	0.834
EQ-5D score	165	0.48	0.32	164	0.50	0.32	0.02	–0.05 to 0.09	0.6116	0.03	–0.04 to 0.11	0.403
BCSS score	171	5.64	2.95	178	5.63	2.83	–0.01	–0.62 to 0.60	0.9716	–0.05	–0.60 to 0.49	0.848
6MWT (metres)	32	174.72	109.53	20	257.95	141.15	83.23	13.09 to 153.37	0.0210			
Number of days in hospital[b]	253	16.02	16.57	260	16.85	18.11				1.05	0.90 to 1.23	0.5208
EQ-VAS	163	51.53	20.90	171	51.93	19.54	0.40	–3.95 to 4.75	0.8559	2.35	–2.66 to 7.36	0.356
EQ-5D score	206	0.48	0.34	203	0.45	0.35	–0.02	–0.09 to 0.04	0.4869	–0.00	–0.07 to 0.07	0.933

a The difference has been adjusted to take into account baseline value and hospital site.
b Analysed with a negative binomial regression model.

TABLE 12 *Baseline levels of health service use in the past 3 months*

	MCP arm		No MCP arm	
	n	**% Yes**	***n***	**% Yes**
Hospital attendance (COPD related)	181	38.7%	186	44.1%
Hospital attendance (other reasons)	168	15.5%	178	15.2%
Use of oxygen at home	185	22.2%	185	23.8%
		Mean		**Mean**
GP surgery visit (COPD related)	174	2.23	178	2.35
GP surgery visit (other reasons)	158	0.43	158	0.37
GP home visit (COPD related)	170	0.64	174	0.76
GP home visit (other reasons)	157	0.06	157	0.00
GP telephone consultation (COPD related)	168	0.42	169	0.83
GP telephone consultation (other reasons)	157	0.08	157	0.01
Nurse surgery visit (COPD related)	168	0.65	164	0.51
Nurse surgery visit (other reasons)	157	0.27	162	0.20
Nurse home visit (COPD related)	167	0.26	161	0.61
Nurse home visit (other reasons)	155	0.27	162	0.10
Nurse telephone consultation (COPD related)	164	0.04	159	0.20
Nurse telephone consultation (other reasons)	152	0.06	160	0.01

n, number who completed the respective question.

admissions and non-respiratory-related admissions are reported in Table 14. Assessment costs were not reported in the NHS reference costs 2006/07[59] and we consequently assumed that these were equivalent to the aforementioned average cost per bed-day on a general ward, where assessments were again categorised as either respiratory- or non-respiratory-related. NHS reference costs do not categorise coronary care unit, intensive therapy unit/high-dependency unit, day care, or A&E admissions as either respiratory or non-respiratory related; consequently the same unit cost was applied to both these types of admissions.

When these unit costs were assigned with the corresponding length of stay data, it was possible to estimate per-participant hospital admission costs. In the control arm the mean 6-month hospital admission cost was £6075.95 (range £332.47–£40,055.06), compared with £5650.26 (range £332.47–£37,728.11) in the intervention arm, giving an incremental cost of –£425.68 for the MCP arm.

Outpatient visits

Complete data were obtained for all 522 participants who were followed up. Throughout the 6-month trial period 200 of the 264 participants in the control arm had one or more outpatient visits, compared with 201/258 in the intervention arm. Overall the mean number of visits was 2.11 for those in the control group (range 0–13 visits), compared with 2.10 visits in the intervention arm (range 0–17 visits). Curtis[58] estimated that the weighted average cost per visit for a first attendance was £55, compared with £71 for a follow-up attendance. It was thereby estimated that the mean 6-month outpatient visit cost was £140.43 in the control arm, compared with £140.69 in the intervention arm, which is equivalent to an incremental cost of £0.25.

Rehabilitation and early discharge service

In total 166 participants were recruited at the hospital providing this service (UHA) and complete data were recorded for each of these participants. Five of the 84 participants in the control group received at least one pulmonary rehabilitation assessment, compared with 4/82 in the intervention group. The mean number of attendances was 0.07 per participant (range 0–2 assessments) in the no MCP arm compared with 0.07 per participant (range 0–2 assessments) in the MCP arm. Pulmonary rehabilitation group sessions were attended by 3/84 in the no MCP arm, compared

TABLE 13 *Procedures from* NHS reference costs 2006/07[59] *deemed respiratory related*

HRG code	HRG label
DZ19A	Other Respiratory Diagnoses with Major CC
DZ19B	Other Respiratory Diagnoses with CC
DZ19C	Other Respiratory Diagnoses without CC
DZ22A	Unspecified Acute Lower Respiratory Infection with Major CC
DZ22B	Unspecified Acute Lower Respiratory Infection with CC
DZ22C	Unspecified Acute Lower Respiratory Infection without CC
DZ21A	COPD or Bronchitis with length of stay 1 day or less, discharged home
DZ21B	COPD or Bronchitis with Intubation with Major CC
DZ21C	COPD or Bronchitis with Intubation with CC
DZ21D	COPD or Bronchitis with Intubation without CC
DZ21E	COPD or Bronchitis with NIV without Intubation with Major CC
DZ21F	COPD or Bronchitis with NIV without Intubation with CC
DZ21G	COPD or Bronchitis with NIV without Intubation without CC
DZ21H	COPD or Bronchitis without NIV without Intubation with Major CC
DZ21J	COPD or Bronchitis without NIV without Intubation with CC
DZ21K	COPD or Bronchitis without NIV without Intubation without CC
DZ22A	Unspecified Acute Lower Respiratory Infection with Major CC
DZ22B	Unspecified Acute Lower Respiratory Infection with CC
DZ22C	Unspecified Acute Lower Respiratory Infection without CC
DZ27A	Respiratory Failure with Intubation with Major CC
DZ27B	Respiratory Failure with Intubation with CC
DZ27D	Respiratory Failure without Intubation with Major CC
DZ27E	Respiratory Failure without Intubation with CC
DZ27F	Respiratory Failure without Intubation without CC
DZ49Z	Respiratory Nurse education/support
PA09A	Major Upper Respiratory Tract Disorders with CC
PA09B	Major Upper Respiratory Tract Disorders without CC
PA10A	Minor Upper Respiratory Tract Disorders with CC
PA10B	Minor Upper Respiratory Tract Disorders without CC
PA11Z	Acute Upper Respiratory Tract Infection and Common Cold
PA14A	Lower Respiratory Tract Disorders without Acute Bronchiolitis with CC
PA14B	Lower Respiratory Tract Disorders without Acute Bronchiolitis without CC
PA33A	Intermediate Upper Respiratory Tract Disorders with CC
PA33B	Intermediate Upper Respiratory Tract Disorders without CC

CC, complications; NIV non-invasive ventilation.

with 3/82 in the MCP arm. The mean number of sessions was 0.25 per participant (range 0–16 sessions) in the no MCP arm compared with 0.40 per participant (range 0–16 sessions) in the MCP arm. Hospital visits to a hospital physiotherapist were made by 25 of the 84 participants in the no MCP arm compared with 19/82 in the MCP arm, in order to assess their suitability for the early discharge service. The corresponding mean number of hospital visits was 0.54 (range 0–7 visits), and 0.32 (range 0–3 visits) respectively. Each of these 25/84 participants in the no MCP arm and 19/82 in the MCP arm received a subsequent home visit from a Band 6 nurse. The corresponding figures for a hospital physiotherapist were 17/84 and 11/82 respectively. The mean number of home

TABLE 14 *Hospital admissions: estimated unit costs*

Ward type	Specialty	Cost per bed day (£)
General	Respiratory	332.47
	Non-respiratory	422.21
Assessment	Respiratory	332.47
	Non-respiratory	422.21
Day case	Respiratory	151.07
	Non-respiratory	151.07
Intensive therapy unit	Respiratory	1121.11
	Non-respiratory	1121.11
Coronary care unit	Respiratory	465.41
	Non-respiratory	465.41
A&E	Respiratory	160.95
	Non-respiratory	160.95

visits was 2.25 for a specialist nurse (range 0–32 visits) in the no MCP arm [hospital physiotherapist = 0.25 (range 0–2 visits)], compared with 1.87 (range 0–29 visits) in the MCP arm [hospital physiotherapist = 0.24 (range 0–5 visits)]. Of those in the no MCP arm 24/84 received at least one telephone contact, compared with 18/82 in the MCP arm. The corresponding mean number of telephone calls per participant was 2.23 (range 0–40) and 1.94 (range 0–35) respectively.

The unit cost of 1 hour patient contact time was estimated to be £44.91 for a physiotherapist (Band 6), £31.16 for a physiotherapist assistant Band 3: average salary £15,678 in 2007/08[58]), and £49.03 for a Band 6 nurse, where this increased to £57.50 for a home visit by a Band 6 hospital physiotherapist. The cost of a home visit by a nurse was not estimated by Curtis,[58] consequently we assumed that the cost of a home visit by a Band 6 nurse was equivalent to that for a Band 6 hospital physiotherapist. The subsequently estimated per-participant cost for each type of contact is shown in Table 15, where this includes a travel cost of £2.60 for each home visit, as estimated by Curtis.[58]

In Table 16 the mean cost of each of the above types of rehabilitation are reported for each trial group. The costs are similar in both arms, though the mean cost was slightly higher in the control group in relation to home visits (from a Band 6 nurse) and hospital physiotherapy visits. Thus, the overall rehabilitation cost was £56.54 in the no MCP arm, compared with £44.72 in the MCP arm, giving an incremental cost of –£11.82.

Other NHS and PSS costs

In order to estimate the total number of visits over the 6-month trial period, with regard to the other resource use variables listed in the follow-up questionnaire (see Appendix 20), it was necessary for a participant to complete the particular follow-up questions at both the 6-week and 6-month follow-up time point. With regard to the questions concerning A&E visits, GP visits and nurse consultations at the GP practice, the number of participants who fulfilled this task is listed in Table 17. This indicates a high level of missing data with responses available for only approximately half of the participants in each trial arm. However, the unit costs associated with these visits [A&E visit (£161, see Table 14), GP visit (£32[58]) and nurse consultation (£11[58]] are relatively small compared

TABLE 15 *Rehabilitation: estimated unit costs for each contact type*

Contact type	Cost per participant contact (£)
Pulmonary rehabilitation assessment	44.91
Pulmonary rehabilitation group sessions	11.89
Home visit – Band 6 nurse	45.72
Home visit – hospital physiotherapist	45.72
Hospital visit – hospital physiotherapist	89.83
Telephone contact	4.09

TABLE 16 *Rehabilitation: estimated mean costs for each trial group*

	Mean cost per participant (£)	
Contact type	**No MCP arm**	**MCP arm**
Pulmonary rehabilitation assessment	1.02	1.04
Pulmonary rehabilitation group sessions	0.95	1.52
Home visit – specialist nurse	32.73	27.10
Home visit – hospital physiotherapist	3.64	3.44
Hospital visit – hospital physiotherapist	15.31	9.10
Telephone contact	2.89	2.52

with those previously reported for hospital admission costs for which complete data were obtained. Given that the mean number of visits were approximately equal in both arms, we did not attempt to estimate the level of other NHS and PSS costs for each participant. Further difficulties arose with regard to analysing results from this questionnaire in that certain questions returned ambiguous data with respect to zero responses and/or missing data (i.e. when asked to report any contact with social services, if the respondent left the box unticked it was not clear whether there had been no contacts or whether they had failed to answer this particular question). In light of the decision to exclude these costs from the analysis, we did not cross-check them against the relevant hospital/primary care records as specified in the original protocol.

Given that no costs were assigned to other NHS and PSS levels of resource use, the overall health service cost for each participant was estimated by summing the aforementioned specific component costs (i.e. physiotherapy cost, hospital admission cost, outpatient visit cost, rehabilitation cost), where complete data on each of these variables was available for all 522 participants (no imputation was undertaken). The estimated mean costs derived from these four components are given in Table 18. The mean value was estimated to be £6281.10 in the no MCP arm compared with £5870.31 in the MCP arm. Thus the mean incremental overall health service cost of MCP was estimated to be equivalent to a cost saving of £410.79.

Measuring effects

Responses to the EQ-5D were as follows. At baseline 401 (76.2%) of the 522 participants completed the EQ-5D (99 pilot phase participants were not asked to complete EQ-5D at baseline). By 6 weeks post-randomisation 25 participants had died and this number rose to 70 at 6 months post-randomisation. Over the 6-month trial period, for the 37 who died in the no MCP arm the date of death was on average 74.89 days post-randomisation (median = 37 days, range 7 to 179 days). The corresponding mean value for the 33 in the MCP arm was 68.30 days post-randomisation (median = 33 days, range 4 to 172 days). Each of these participants was assigned an EQ-5D score of 0.00 from their date of death. A further 309 participants completed the EQ-5D at 6 weeks post-randomisation, compared to 346 at 6 months. Hence, EQ-5D scores were available for 58.7% and 65.8% of participants at 6 weeks and 6 months, respectively (see Table 19).

After using multiple imputation to estimate missing EQ-5D scores, the mean score at baseline was estimated to be 0.418 in the no MCP arm compared with 0.438 in the MCP arm. At 6 weeks

TABLE 17 *Levels of 'other NHS and PSS' resource use reported over the trial period*

	MCP arm			No MCP arm		
	n	**%**	**Mean**	***n***	**%**	**Mean**
A&E visit	125	48.4	1.10	137	51.9	1.36
GP visit	124	48.1	4.40	140	53.0	4.98
Nurse consultation	122	47.3	2.43	136	51.5	2.74

TABLE 18 *Estimated mean costs (£): no MCP, MCP and incremental cost (four component costs and overall health service cost)*

	No MCP arm	MCP arm	Incremental cost of MCP
Physiotherapy cost	£8.18	£34.63	26.45
Hospital admission cost	£6075.95	£5650.26	–425.68
Outpatient visit cost	£140.43	£140.69	0.25
Rehabilitation cost	£56.54	£44.72	–11.82
Overall health service cost	£6281.10	£5870.31	–410.79

A negative incremental cost denotes a cost saving for MCP compared with no MCP.

(6 months) these scores were 0.496 (0.439) and 0.507 (0.466) respectively (see Table 20). The mean 6-month QALY gain was estimated to be 0.020 for the no MCP arm compared with 0.018 in the MCP arm, giving an incremental QALY gain of –0.002 for MCP.

Response rates for the SGRQ are listed in Figure 4. The mean scores for the SGRQ (both for the total score and each of the three domains) are presented in Tables 21–24, where these are estimated for the 264 participants in the no MCP and the 258 in the MCP arm as missing values were estimated via imputation. These mean values can be seen to be comparable to those based on available data (see Tables 6 and 7). When the 6-month change scores are calculated (see Tables 21–24) it can be seen that, on average, both groups improved post intervention according to both the SGRQ total score and each of the three domains (a negative change score denotes an improvement). However, the mean change was higher for the no MCP group, compared with the MCP group, on the SGRQ activity, impacts and total score. Thus, according to each of these measures, no MCP was estimated to be more effective than MCP, where the mean incremental effect of MCP was estimated to be 0.50 (activity), 0.91 (impact) and 0.89 (total). In contrast, the mean incremental effect on the SGRQ symptoms scale was –0.09 for MCP.

Cost-effectiveness analysis

As reported above, the incremental cost of MCP was estimated to be equivalent to a mean cost saving of £410.79, and the incremental effect was estimated to be equivalent to a mean QALY loss of 0.002. The resulting incremental net benefit was estimated to be positive for λ values $\leq$ £237,100.51, which implies that if society was willing to pay $\leq$ £237,100.51 per QALY gain, then MCP would represent an efficient use of NHS resources as it would enable resources to be freed up and spent elsewhere in a more efficient manner. Indeed the incremental net benefit of MCP was estimated to be £376.14 when λ was equivalent to £20,000 per QALY, suggesting that MCP was cost-effective.

Similar methods were used to estimate the cost-effectiveness of MCP according to the SGRQ total and domain scores. As the λ for each of these measures is unknown, we simply calculated the

TABLE 19 *Mean EQ-5D scores and number and percentage of respondents based on available data*

	MCP arm				No MCP arm			
	Mean	SD	*n*	%	Mean	SD	*n*	%
Baseline	0.447	0.323	199	77.1	0.428	0.356	202	76.5
6 weeks	0.484[a]	0.318	168	65.1	0.498[d]	0.323	166	62.9
6 months	0.479[b]	0.335	209	81.0	0.449[e]	0.346	207	78.4
6-month QALY gain	0.003[c]	0.149	116	43.8	0.010[f]	0.148	121	45.7

a Includes *n* = 13 deaths.
b Includes *n* = 33 deaths.
c Includes *n* = 20 deaths
d Includes *n* = 12 deaths.
e Includes *n* = 37 deaths.
f Includes *n* = 14 deaths.

TABLE 20 *Mean EQ-5D scores (missing values imputed)*

	MCP arm	No MCP arm
Baseline	0.438	0.418
6 weeks	0.507[c]	0.496[a]
6 months	0.466[d]	0.439[b]
6-month QALY gain	0.018[d]	0.020[b]

a Includes *n* = 13 deaths.
b Includes *n* = 33 deaths.
c Includes *n* = 12 deaths.
d Includes *n* = 37 deaths.

TABLE 21 *Mean scores on the SGRQ symptoms domain*

	MCP arm	No MCP arm
Baseline	79.07	78.91
6 weeks	66.71	68.66
6 months	67.79	67.72
6-month change	–11.28	–11.19

TABLE 22 *Mean scores on the SGRQ activity domain*

	MCP arm	No MCP arm
Baseline	84.69	83.92
6 weeks	80.59	78.92
6 months	79.19	77.92
6-month change	–5.50	–6.00

TABLE 23 *Mean scores on the SGRQ impacts domain*

	MCP arm	No MCP arm
Baseline	57.61	56.59
6 weeks	52.03	50.44
6 months	51.55	51.44
6-month change	–6.06	–5.15

TABLE 24 *Mean scores on the SGRQ total score*

	MCP arm	No MCP arm
Baseline	68.97	69.10
6 weeks	62.89	63.56
6 months	63.76	62.99
6-month change	–5.22	–6.10

range of threshold values below which MCP would be deemed cost-effective. As MCP was associated with a cost saving and, compared with no MCP, an improvement in effect on the SGRQ symptoms domain, MCP was estimated to dominate no MCP on to this domain. Conversely, no MCP was more effective than MCP according to the SGRQ activity scores (Table 24), such that the cost saving associated with MCP would mean that MCP was cost-effective if the λ was below £817.62 (Table 25). The similarly calculated λ for the SGRQ impacts and total score are listed in Table 25. Again these can be interpreted such that the implementation of MCP may increase the level of resources that can be spent elsewhere, where the gain in SGRQ associated with these extra resources being spent elsewhere can more than offset any loss associated with implementing MCP.

Decision uncertainty

The CEAC for each option are plotted in Figure 7. It can be seen that the probability of each option being cost-effective is very similar, and at λ = £20,000 per QALY the probability of MCP being cost-effective was estimated to be 52.6%. Equally, at this value of λ it is estimated that there was a 47.6% chance of making the wrong decision by choosing to implement MCP. This demonstrates that there is a high degree of uncertainty over which is the more cost-effective option.

Subgroup analysis

At baseline, sputum levels were measured for 495 of the 522 participants, with rates for the no MCP and MCP arms of 255/264 and 240/258 respectively. Of these, 42 produced $\geq$15 ml of sputum per 24-hour period in the no MCP arm compared with 38 in the MCP arm. The mean overall health service cost

TABLE 25 *Estimates of cost-effectiveness for MCP according to the SGRQ*

	Incremental effect	Range of cost-effectiveness for MCP
SGRQ symptoms	–0.09	Dominates no MCP
SGRQ activity	0.50	$\lambda \leq$ £817.62
SGRQ impacts	0.91	$\lambda \leq$ £450.99
SGRQ total	0.89	$\lambda \leq$ £464.02

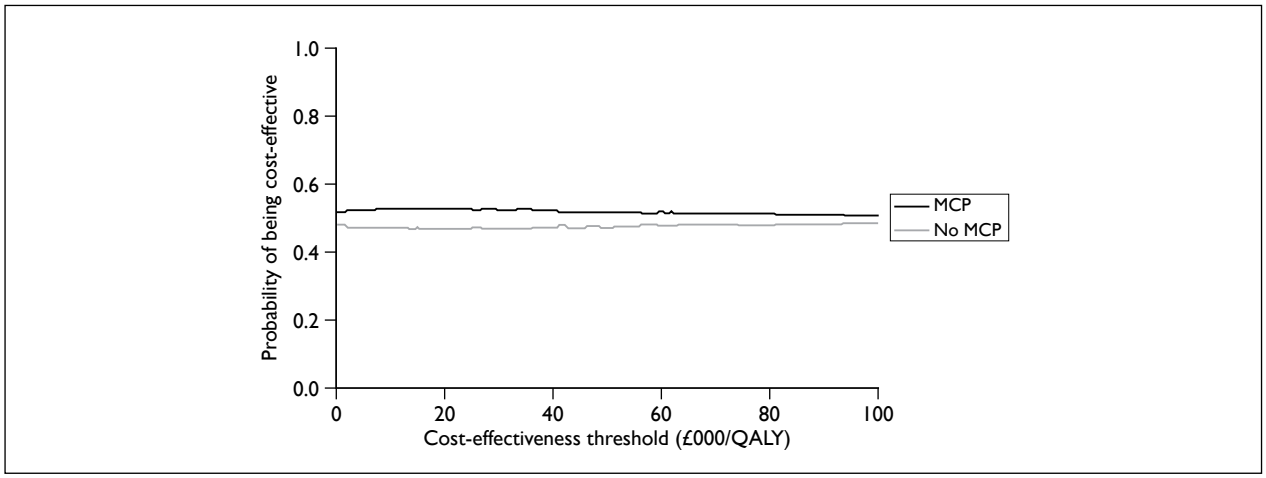

FIGURE 7 *Decision uncertainty: cost-effectiveness acceptability curves: MCP and no MCP arms.*

for these participants was £5991.80 and £7602.49, respectively, giving an incremental cost of £1610.70 for MCP. The associated QALY gains were estimated to be 0.027 for no MCP and 0.040 for MCP, giving an incremental 6-month QALY gain of 0.013. At a value of = £20,000 per QALY this gave an incremental net benefit of –£1352.73 for MCP, suggesting that MCP was not cost-effective for those who had produced ≥15 ml of sputum. This is supported by the associated ICER estimate of £124,874.60 per QALY.

For those producing < 15 ml of sputum, the mean overall health service cost was £6424.00 in the no MCP arm compared with £5730.13 in the MCP arm, giving an incremental cost of –£693.87. Associated QALY gains were estimated to be 0.021 and 0.014, giving an incremental 6-month QALY gain of –0.007 for MCP. At a value of λ = £20,000 per QALY this gave an incremental net benefit of £551.91 for MCP, suggesting that MCP was cost-effective for this subgroup. Indeed the incremental net benefit was estimated to be positive for λ values ≤ £97,754.58, implying that if society was willing to pay this amount per QALY gain, then MCP would represent an efficient use of NHS resources as it would enable them to be freed up and spent elsewhere in a more efficient manner. These results are counter to our a priori expectations.

Sensitivity analysis

Complete cost data was available for all 522 participants who were followed up for analysis purposes. The response rate for the EQ-5D is shown in Table 19, where it can be seen that only 121 in the no MCP arm and 116 in the MCP arm completed the EQ-5D at each of the three follow-up points. The results of the complete case analysis were in line with the base case as compared to no MCP, MCP was estimated to be associated with lower hospital admission costs (Table 26), lower overall health service costs (Table 27), lower quality of life (Table 28) and to be cost-effective at a threshold of λ = £20,000 per QALY (Table 29). Similar results were also achieved when different unit costs were attached to respiratory related admissions, non respiratory-related admissions were excluded from the analysis, and a PP analysis was undertaken (see Tables 25–28). The exception to this was when it was assumed that only physiotherapy time could potentially relate to MCP (analysis 3b), where MCP was shown to be associated with higher health service costs and lower quality of life than no MCP (see Tables 27 and 28 respectively). Here MCP was dominated by no MCP as it was more expensive and less effective.

TABLE 26 *Sensitivity analysis: hospital admission costs*

	MCP arm (£)	No MCP arm (£)	MCP incremental cost (£)
Base case	5650.26	6075.95	–425.68
1. Complete case analysis	5967.47	6334.09	–366.62
2a. Unit cost per bed day (COPD specific)	4890.58	5294.24	–403.66
2b. Unit cost per bed day (average for NHS)	6826.93	7286.72	–459.78
3a. Exclusion of non-respiratory admissions	4386.58	4614.91	–228.34
3b. Physiotherapy time costs (only)	–	–	–
4. Per protocol	5673.89	6048.21	–374.31

TABLE 27 *Sensitivity analysis: overall health service costs*

	MCP arm (£)	No MCP arm (£)	Incremental cost of MCP (£)
Base case	5870.31	6281.10	–410.79
1. Complete case analysis	6202.23	6586.04	–383.81
2a. Unit cost per bed day (COPD specific)	5110.62	5499.40	–388.78
2b. Unit cost per bed day (average for NHS)	7046.97	7491.87	–444.90
3a. Exclusion of non-respiratory admissions	4606.62	4820.07	–213.45
3b. Physiotherapy time costs (only)	34.63	8.18	26.45
4. Per protocol	5893.06	6235.72	–342.67

TABLE 28 *Sensitivity analysis: 6-month QALY gain*

	MCP arm	No MCP arm	Incremental effect of MCP
Base case	0.018	0.020	–0.002
1. Complete case analysis	0.003	0.010	–0.007
2a. Unit cost per bed day (COPD specific)	0.018	0.020	–0.002
2b. Unit cost per bed day (average for NHS)	0.018	0.020	–0.002
3a. Exclusion of non-respiratory admissions	0.018	0.020	–0.002
3b. Physiotherapy time costs (only)	0.018	0.020	–0.002
4. Per protocol	0.017	0.018	–0.001

TABLE 29 *Sensitivity analysis: most cost-effective intervention*

	Net benefits at λ = £20,000 per QALY	Range of cost-effectiveness for MCP
Base case	£376.14	$\lambda \leq$ £237,100.51
1. Complete case analysis	£243.12	$\lambda \leq$ £54,561.94
2a. Unit cost per bed day (COPD specific)	£354.13	$\lambda \leq$ £224,392.74
2b. Unit cost per bed day (average for NHS)	£396.95	$\lambda \leq$ £64,656.66
3a. Exclusion of non-respiratory admissions	£178.80	$\lambda \leq$ £123,197.41
3b. Physiotherapy time costs (only)	–£61.11	Dominated
4. Per protocol	£410.24	$\lambda \leq$ £256,783.35

Chapter 4
Discussion

In this chapter the interpretation, limitations and generalisability of this study will be considered.

Interpretation

Recruitment rate

From the start, recruitment to the study was slower than anticipated. The original project timetable was based on a phased start across three hospitals, each with an average recruitment target of three participants per week. This recruitment rate was derived from mean admission data for the target population at intended sites during 2001–2. However, after 10 months' screening of all respiratory admissions at two hospitals, the number of COPD cases identified by trial recruiters was lower than predicted from hospital coding data. Study screening indicated that less than 30% of admissions were the result of COPD whereas hospital episode data from previous years suggested a figure nearer 60%. To some extent, this mismatch might be explained by the introduction of early discharge and admission prevention policies implemented since 2001. Adoption of COPD Guidelines[49] published in 2004 (which place an emphasis on managing exacerbations in the community where possible) had a further impact upon the feasibility of achieving the original recruitment target.

These combined issues forced the trial management group to re-examine the recruitment strategy in order to complete the study within a reasonable time frame. This process identified UHA as a suitable additional site. Hospital episode statistics (HES) for UHA indicated between approximately 143 and 187 COPD admissions per month (based on 2006–7 figures). Assuming similar levels of exclusions and non-consents as seen at the Norfolk sites, this would yield an additional eight participants per week. However, learning the lessons from recruitment estimates based on HES data at Norfolk sites, an on-site feasibility study was also conducted. This yielded 2 months of admission/discharge data against trial eligibility and indicated that UHA did admit a sufficient number of patients with COPD to substantially boost recruitment. In the event, this site achieved an average recruitment rate of 3.5 participants per week (based on 48 weeks active recruitment during the 12-month recruitment period).

Consent rate

Consent was kept under review by the trial management group and strategies that were employed to maximise this proved successful. Overall a consent rate of 71% would appear excellent for this population group, which was overall elderly and with significant health impairment as judged by SGRQ and EQ-5D scores at baseline.

Movement between study arms

Movement between arms was minimal and was driven by clinical need; however, the strict 'switch arm' criteria developed for the protocol were not always strictly adhered to. These criteria were intentionally set at a very significant level of illness,[49] and perhaps this was too high for the clinicians to adhere to. The impact of this is minimal on the study; however, it raises important issues with regard to developing satisfactory criteria in the protocol for switching arms and methods of protocol development to ensure that clinicians adhere to these.

Follow-up – losses and response rates

The death rate within this study of 13% is consistent with others reported in the literature. Miravitlles *et al.*[71] report a death rate of 10.3% during a 2-year follow-up of patients following acute exacerbation of COPD; however, their average SGRQ (total) scores were much lower (better) than those reported the current study. Fruchter[72] reports an overall mortality of 22% at the 6-month time point in a study that considered long-term survival in elderly patients with COPD. However, that study population had a minimum age of 65 and a mean of 75.8 compared with 69.33 for this current study. The withdrawal rate from this study was low, but there was a loss to follow-up

greater than the 15% predicted at inception. This was despite implementing an effective action plan (Appendix 24).

MCP treatment protocol

The MCP protocol was designed to be as representative as possible of current practice and followed the best available research evidence. Yohannes[73] conducted a survey of physiotherapists working in UK acute admitting hospitals regarding their treatment of patients admitted with acute exacerbation of COPD. This asked which physiotherapy treatments they employed and with what frequency: 77% responded that they treated this patient group, with 88% of these reporting using ACBT. A statistically significantly smaller proportion used manual techniques in conjunction with the active cycle (26% vibration, 8% percussion, 11% shaking) always or often; however, 66% still used these techniques sometimes or rarely.

The protocol for this study included ACBT in both trial arms. This was a very useful standardisation as it reflects current practice. For participants randomised to the control arm, the physiotherapist delivered a short training session on the principles of ACBT and explained how this technique could be used to help clear their chest. Participants in the MCP arm were actively guided through at least one session of ACBT with the physiotherapist percussing their chest on expiration. Thus, it could be argued that what was being compared was ACBT plus or minus MCP. However there is a suggestion in the results that perhaps a short teaching session on ACBT is equally effective in terms of quality of life 6 month post intervention as several sessions of ACBT performed with support from the physiotherapist. Therapists could therefore be encouraged to provide ACBT training (or an equivalent airway clearance technique) sooner rather than later particularly in light of the perception that the sputum-rich phase of the disease is early in its course. Current initiatives that delay first admission as long as possible will compound this situation unless there is a change in service provision. Thus, it will be important to communicate any emergent ACBT training message to primary as well as secondary care.

Review of the literature suggests that there is little evidence of efficacy for these MCP techniques and that clinically their use is diminishing while the active cycle remains the treatment of choice.[73] This would appear to be substantiated by the acceptability of the protocol to physiotherapists, and their high level of adherence indicates that the main aim of defining and generalising the intervention was achieved. The one exception was in often selecting one treatment position when two were stipulated (248 sessions, 38%). However, it is important that treatments are tailored in response to findings on clinical assessment, and clinical expertise indicates that it is likely that treatment conducted with the patient seated is equally efficacious when using the ACBT in this group of patients. Additionally there may have been no clinical rationale for treating in more than one position, for example if there was clinical evidence of a unilateral lung problem.

Changes to protocol

Some changes to the protocol were made at the recommendation of the TSC; these included the recording of an INR value within prespecified limits as an inclusion criterion. This was to reassure clinicians that there was little chance that a pulmonary embolus was part of the presenting clinical picture. The TSC considered a similar scenario that had arisen with regard to patients on oral steroids being excluded from the study. There is no evidence that MCP is contraindicated for patients on prophylactic bone protection. Even where osteoporosis exists there is little research evidence to suggest a likelihood of percussion and vibration causing rib damage, although clinically this is considered a contraindication. Therefore, while it was considered reasonable to exclude patients with overt osteoporosis, it was not deemed necessary to extend this to those at risk of the disease.

Baseline characteristics

This study demonstrated higher than average SGRQ scores at baseline. It would appear that these were approximately 5–10 points higher than reported by other studies on similar populations.[71,74] This perhaps reflects recent improvements in treatment (i.e. bronchodilators and steroids) that keep people out of hospital for longer. Anecdotal evidence suggests that there is an increasing trend for admitted patients to be very sick with end-stage disease and multiple comorbidities. In addition, the average age for patients admitted with COPD has also increased. These factors are, however, balanced at baseline by the randomisation process, giving excellent comparability.

Oxygen saturation

Manual chest physiotherapy has been associated in the literature with clinically significant falls in oxygen saturation.[14] The results from this study indicate that almost half the sessions of MCP resulted in a fall in oxygen saturation (268; 41%). However, 258 (39%) sessions resulted in no change in oxygen saturation and a further 126 (19%) sessions resulted in an increase in oxygen saturation. This raises the possibility that de-saturation is happening more often than previously reported. This is possibly due to the heterogeneous patient groupings and/or small sample size in these studies. Interpretation of these results is difficult because MCP did not occur in isolation. Therapists were required to choose positions in which to administer the treatment, and hence these changes could result from position changes altering V/Q ratios as much as from the MCP itself. It is however interesting to note the high frequency of falling oxygen saturation and this might be an indication for the routine use of oxygen saturation monitoring during physiotherapy treatment. It should be noted that the SGRQ scores of this group indicate a significant level of impairment and these factors may be related. Hence this may be considered an important finding as people hospitalised with COPD are now increasingly likely to be in end-stage disease and there is little robust information to guide clinicians on the risk of significant de-saturation in this patient group. Importantly, clinically significant falls in oxygen saturation were recorded as AEs and the rate of these is very small. Details can be found in Table 5.

MCP treatment efficacy

The primary outcome of this study was to find equivalence in total SGRQ between the intervention and the control group 6 months after intervention. This result suggests that there is no gain in quality of life when including MCP in the physiotherapy management of acute exacerbation of COPD. The difference in total SGRQ at 6 months, after adjusting for baseline, was 0.51 (–2.67 to 3.69) which is within the prespecified limits of equivalence stated in the protocol. This also excludes the minimal clinically important difference (MCID) of 4, as suggested by Jones et al.,[75,76] although the trial was not powered to demonstrate equivalence by the MCID. The differences in SGRQ subscores at 6 months were again within the prespecified limits of equivalence stated in the protocol: the difference in symptom score was 0.87 (–3.50 to 5.25), activity score –0.36 (–3.76 to 3.04) and impact score 0.43 (–3.29 to 4.14). Thus the MCID is not excluded from the symptom score or the impact score, but is excluded from the activity score.

In the short-term time point, 6 weeks after intervention, the difference in total SGRQ score was 1.61 (–1.33 to 4.55) which was within the prespecified limits of equivalence stated in the protocol. However, it does not exclude the MCID but does exclude an effect greater than 4.55 with 95% confidence. The difference in SGRQ subscores at 6 weeks was mixed, with equivalence not being demonstrated for symptom score with a difference of 3.12 (–1.00 to 7.25), which exceeds our definition of equivalence by 3% of a SD, but being demonstrated for activity score with a difference of –0.16 (–3.55 to 3.23) and impact score with a difference of 2.12 (–1.30 to 5.53). There were no major differences from the ITT analysis with either the imputed ITT analysis or the PP analysis.

The secondary outcome measures included BCSS, EQ-VAS, EQ-5D utility score, number of days in hospital and the 6MWT. The BCSS difference at 6 months was 0.01 (–0.54 to 0.56) demonstrating no significant difference and equivalent to with 0.56, i.e. almost half a point. At 6 weeks the difference was 0.33 (–0.18 to 0.84), suggesting equivalence to within 1 point on the scale. The EQ-VAS difference at 6 months was 2.65 (–2.35 to 7.65) on a scale of 0 to 100, suggesting no large difference, and at 6 weeks the difference was –0.68 (–5.90 to 4.55). The difference in EQ-5D utility score at 6 months was –0.01 (–0.07 to 0.06) on a scale of 0 to 1, implying no large differences; similarly at 6 weeks the differences was 0.03 (–0.04 to 0.10). The difference in the number of nights in hospital during the 6 months post intervention was not significant with the ratio of means (non-MCP/MCP) being 1.07 (0.91 to 1.24), suggesting that on average the non-MCP group spent 7% longer in hospital. Not providing MCP could increase the number of days in hospital by 24% or, alternatively, providing MCP could increase the number of days in hospital by 9%. A difference in the 6MWT was found ($p = 0.0210$) with the non-MCP arm walking further on average than the MCP arm. However, this was only available for 52 individuals in one centre and therefore results were statistically underpowered with limited ensuing generalisablity. There were no major differences from the ITT analysis with either the imputed ITT analysis or the PP analysis.

Subgroup analyses showed no evidence that the effectiveness of MCP differed by baseline sputum

levels in terms of SGRQ or its subscores at either 6 months or 6 weeks. However, it should be noted that the study was not sufficiently statistically powered to detect a difference in effect by subgroup.

Cost-effectiveness

As NHS resources are relatively fixed one has to assess the impact that providing MCP or no MCP would have, both in terms of overall costs and benefits. Provision of MCP did not improve overall quality of life. However, it was associated with lower overall health service costs, compared with no MCP, as the cost of providing MCP was offset by lower hospital admissions costs. Although there is much uncertainty over which is the more cost-effective option (see Figure 7), economists would argue that decisions as to which option is most efficient have to be made on the basis of available evidence.[65,77] Moreover, in contrast to the classic statistical approach, it is generally accepted within health economics that it is the mean estimate that is of interest to policy makers[78,79] where, assuming one seeks to maximise health subject to a budget constraint, this equates to choosing the option that has the most favourable cost-effectiveness ratio.[66] Our mean estimates suggest that provision of MCP would reduce overall costs, and thereby enable resources to be spent elsewhere. Moreover, as the health benefits provided by those extra resources are likely to more than offset any loss in quality of life that may be associated with provision of MCP, rather than no MCP, this would suggest that MCP represents a cost-effective use of resources. Additionally, a number of sensitivity analyses were conducted, which generally suggested that these results were robust to the assumptions we made within our analysis.

Limitations

Subgroup analysis of > 15ml sputum

The preplanned subgroup analysis for patients producing more than 15 ml of sputum per day demonstrated equivalence. It should however be noted that this finding is limited by the number of participants who met this criteria and the sample size was statistically underpowered. This small subset is probably consistent with patients at the end stage of their disease, substantiated by their very poor SGRQ scores. This patient group is more likely to have stopped smoking with a consequential reduction in inflammatory lung response. It is suggested that overproduction of sputum is most apparent in the prediagnosis phase of COPD and that sputum production per se is not a headline diagnostic feature of the disease.[2]

Cost-effectiveness

The plausibility of the above result does depend upon whether MCP was truly associated with lower hospital admission costs, or whether this result occurred by chance. In terms of explanations, we did not find that MCP was associated with shorter hospital stays (mean = 5.50 days, compared with 5.04 with no MCP), but rather that the lower costs seemed to arise because of fewer hospital admissions (mean = 3.47 for MCP, compared with 3.89 for no MCP). Moreover, as MCP was actually associated with a (non-significant) loss in quality of life we cannot explain why hospital admission costs were lower in the MCP group. Indeed, although the baseline characteristics were similar in the two groups, we cannot rule out the possibility that hospital admission costs were lower in the MCP groups owing to the presence of fewer comorbidities (i.e. that hospital admission costs would have been lower for this group) even if MCP had not been provided. This argument is partially supported by the fact that the mean level of quality of life at baseline was estimated to be lower for those with no MCP (0.418), compared with those with MCP (0.438) (see Table 16). Moreover, at baseline, the percentage reporting a hospital attendance for COPD and the mean number of GP surgery visits that were COPD related was also higher in the no MCP group, compared with the MCP group. The uncertainty of our results is further supported by the fact that MCP was estimated to be more cost-effective for those with lower levels of sputum, which was counter to our a priori expectations. Further evidence of the difficulty in explaining variation in hospital admission costs is provided by Wong et al.[80] who suggest that, in addition to disease severity, the number of comorbidities, social factors such as marital status and the need for social work intervention are also linked to readmission rates and length of stay of patients with acute exacerbation of COPD.

With regard to the economic methods, it is acknowledged that there are no a priori guidelines about how much data is sufficient to collect within cost-effectiveness studies, and no data as to the incremental value of collecting specific cost items.[81]

As a result, the general recommendation is to focus on: (1) high-cost services that are likely to make up a high proportion of the total cost; and (2) those services that are likely to account for a large proportion of the difference in costs between the two interventions in question.[47] Within this study we implemented these recommendations by monitoring the costs associated with the intervention (MCP), hospital admissions, outpatient visits and levels of rehabilitation. However, in line with other economic studies,[82–88] we did not monitor medication costs. Thus this constitutes one potential limitation, along with the fact that oxygen use at home was not monitored for the duration of the study. Similarly, though we advanced upon certain economic studies that did not monitor baseline levels of resource use,[76,77] there were limitations with regard to the baseline questionnaire in that it did not request sufficient information for one to assign a unit cost to each hospital attendance. Moreover, there were also deficiencies in that it was difficult to differentiate as to whether no response to certain questions meant that a participant had not used the service in question, or whether they had not completed the respective question (i.e. data was missing). That said, with regard to the resources that were monitored for the duration of the study we did manage to collect complete data for each participant, something which is rarely achieved in an economic analysis.

One further aspect to note is that the costs and benefits of both MCP and no MCP were only estimated over the 6-month trial period. It should therefore be noted that had, for example, a lifetime perspective been taken, the results might have been quite different. We chose not to extrapolate beyond the 6-month trial period as, for the reasons outlined above, we consider it to be unclear as to whether MCP was truly associated with lower hospital admission costs. Similarly, threshold analysis[47] was not undertaken as we consider there to be uncertainty as to whether MCP was truly associated with a cost-saving or a loss in quality of life.

Generalisibility

Initially this study could have had a limited generalisability as the catchment characteristics could have led to a charge of its being representative of a rural, relatively affluent patient population. However the study's generalisability was greatly broadened by the inclusion of UHA and the balanced recruitment that was achieved from the variety of sites.

The study's pragmatic stance, adopted throughout the trial, means the results of the MATREX trial have a high degree of generalisibility.

Chapter 5
Conclusions

Implications for healthcare

- Owing to a clear state of clinical equipoise as to whether MCP confers any benefit to patients with COPD, current UK guidelines for its management do not propose a clear place for MCP techniques. This study addressed the limitations of previous research by standardising the delivery of MCP and obtaining a sample of sufficient size to derive statistically robust results for a patient-orientated, clinically meaningful outcome.
- This study found no gain in longer-term quality of life when MCP was included in the physiotherapy management of acute exacerbation of COPD. However, the findings do not mean that MCP is of no therapeutic value to patients with COPD in specific circumstances.
- This study found that MCP was associated with lower overall health service costs, with the cost of providing therapy offset by savings associated with fewer hospital admissions among patients assigned to receive MCP. However, interpretation of this apparent saving should be examined in the light of the primary outcome, which demonstrated no evidence of efficacy above normal care. In light of this we consider that, as MCP was not found to be effective, it is difficult to justify providing MCP on the basis of the results of the cost-effectiveness analysis alone. Furthermore, there is no guarantee that any cost savings identified would be realised by employing MCP in routine care.
- In order to standardise treatment given during the course of this study, an MCP treatment protocol was developed in collaboration with physiotherapists involved in the trial. This protocol reflects professional consensus on best practice with respect to the essential elements of MCP, clarifies potential areas of ambiguity and provides a set of clear parameters within which treatment can be given. The high level of adherence to the MCP treatment protocol used in this trial suggests that it would be acceptable among the profession as a generic tool for delivering therapy.

Recommendations for research

With respect to the primary aim of the MATREX trial, further research is not required to demonstrate equivalence between receiving and not receiving MCP. Further research on the level of cost-effectiveness is unlikely to yield gains as the benefits of both MCP and no MCP are similar, and thus the consequences of making the wrong decision are small. As such, the cost of further research is likely to outweigh the value of information that would be gained. However, the findings of this study do not mean that MCP is of no therapeutic value to COPD patients in specific circumstances. Research questions arising from this study are listed below in order of priority.

Is MCP effective for COPD patients producing high volumes of sputum? While the subgroup analysis for patients producing more than 15 ml of sputum per day demonstrated equivalence, the significance of this finding is limited by the number of participants who met this criteria and is thus statistically underpowered. Given that overproduction of sputum is most apparent among patients with COPD early in the course of their disease history, staging the intervention in the primary care setting may overcome the difficulties this study experienced with sample size.

Can the risk of oxygen desaturation during MCP be predicted? The results from this study indicate that almost half the sessions of MCP resulted in a fall in oxygen saturation from baseline. This raises the possibility that desaturation is happening more often than previously reported. Given that people hospitalised with COPD are increasingly likely to be in end-stage disease, there is little robust information to guide clinicians on the risk of significant desaturation in this patient group. Examining SGRQ BCSS and MRC-D scale as predictors of oxygen desaturation during therapy interventions may provide useful information for clinical decision-making.

Is ACBT effective in treating COPD exacerbation? The protocol for this study included ACBT in both trial arms. Thus, to some extent what was being

compared was ACBT plus or minus MCP. There is a need to formalise this emergent element of the MATREX study design and examine the effectiveness of ACBT in isolation. There is also an opportunity to examine the mode of delivery of ACBT. Results from this study suggest that a short teaching session on ACBT might be equally effective in terms of quality of life 6 months post intervention as several sessions of ACBT performed with support from the physiotherapist. Given recent trends in hospital admissions for COPD, future research regarding physiotherapy intervention with this patient population should focus on examining the effectiveness of ACBT taught in primary care settings.

What are the trends over time in admission and survival rates for COPD? This study's high attrition rate between screening and recruitment (over 7000 respiratory admissions screened to yield 526 participants) suggests caution against over-reliance on hospital coding to identify eligible patients. This is an important principle to pass on to future studies when calculating potential recruitment rates. In particular, the changing nature of COPD treatment pathways has meant that extrapolating historical admission rates is liable to overinflate the number of patients available. Extending the study of this cohort of COPD patients as a longitudinal design would produce important data regarding admission rates and survival. There is also the potential to map SGRQ and/or EQ-5D to other instruments as a predictor of outcome. In particular, the DOSE index is a simple valid tool for assessing the severity of COPD. The index is derived from the MRC-D score, airflow Obstruction, Smoking status and Exacerbations; it is related to a range of clinically important outcomes such as health-care consumption and has the capability to predict future events.[89]

How can health-related resource use be more accurately identified? There is a need to develop robust instruments to identify health-related resource use for specific patient groups. Within this study there were deficiencies in the COPD cost questionnaire relating to non-acute NHS and PSS levels of resource use. Specifically, it was difficult to conclude whether no response to certain questions meant that a participant had not used the service in question or whether they had not completed the respective question (i.e. data was missing). Future studies might overcome this by inserting a 'Not used' option for particular questions.

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The Project Management Group met throughout the project and comprised the authors contributing to this report. Jane Cross (Senior Lecturer in Respiratory Physiotherapy) was the Chief Investigator and grant holder and had overall responsibility for the integrity of the work as a whole. Frances Elender (Senior Research Associate) was responsible for trial management, compiling the treatment protocol and drafting the final report. Garry Barton (Lecturer in Health Economics) had overall responsibility for economic evaluation and its reporting. Allan Clark (Lecturer in Medical Statistics) carried out and reported on the efficacy analysis. Lee Shepstone (Professor of Medical Statistics) had overall responsibility for statistical elements of the study protocol and implementation of the efficacy analysis. Annie Blyth (Research Associate) designed and implemented recruitment strategies, drew up hospital resource use data collection instruments and drafted treatment elements of

the final report. Max Bachmann (Professor of Health Care Interfaces) and Ian Harvey (Professor of Epidemiology and Public Health) contributed substantially to the study design, interpretation of results and revising the final report for important intellectual content. All authors read and approved the final manuscript.

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Appendix 1

Manual chest physiotherapy treatment protocol

The MATREX trial
MAnual Therapy for Respiratory EXacerbations

ISRCTN13825248

MATREX TRIAL OFFICE
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MANUAL CHEST THERAPY – TREATMENT PROTOCOL

Trial Recruiter/Assessor: prime responsibilities – patient identification, data collection/management
Physiotherapist: prime responsibilities – therapeutic care, conducting intervention

The content, number and duration of treatments will be at the discretion of the physiotherapist applying the therapy and varied according to clinical need within the bounds set by this protocol.

PERSON	ACTION	REFERENCE/ SOURCE
	1.0 IDENTIFYING & RECRUITING PATIENTS	
Recruiter	1.1 Identify potential participant (checklist) 1.1.1 Liaise with Physiotherapy team	Treatment Protocol Appendix 1
Physio.	1.2 Identify possible risk factors (checklist) 1.2.1 Make clinical judgement as to patient's continued suitability 1.2.2 Confirm eligibility with Trial Recruiter	Treatment Protocol Appendix 2
Recruiter	1.3 Approach patient regarding study 1.3.1 Give Patient Information Sheet 1.3.2 Answer queries, explain RCT principle if necessary 1.3.3 Provide sufficient time for patient to decide * 1.3.4 If patient willing, obtain consent	 Study Protocol Appendix 7 Study Protocol Appendix 8
Recruiter	1.4 Randomise patient to intervention or control arm. 1.4.1 Provide patient with Trial Information Card stipulating arm 1.4.2 Ensure patient's records are marked accordingly 1.4.3 Complete baseline questionnaires 1.4.4 Liaise with Physiotherapy team, stipulate arm, negotiate 1st visit	 Study Protocol Appendix 4
Physio.	1.5 On 1st visit: 1.5.1 Remind patient that physiotherapy visit is part of trial 1.5.2 Implement universal infection control precautions 1.5.3 Observe any additional patient-specific precautions posted 1.5.4 Advise Trial Recruiter where increased risk exists	
*Rapid change in clinical condition is likely in this group. Thus, the recruiter needs to strike a balance between enabling the intervention to occur during the most acute phase of each COPD exacerbation and not **rushing the patient** in their decision		

	2.0 INTERVENTION ARM	
Recruiter	2.1 Record baseline oxygen saturation 2.1.1 If receiving, patient to continue on controlled oxygen therapy 2.1.2 If available, obtain continuous oximetry data during intervention 2.1.3 Record additional vital signs physiotherapist deems necessary 2.1.4 Record whether patient is likely to be ambulatory or not	
Physio.	2.2 Auscultate patient 2.2.1 Select 2 most appropriate positions according to clinical findings 2.2.2 Turn patient to position 1 2.2.3 Use pillows to support patient as required 2.2.4 Place light towel (one layer) on area of chest to be percussed 2.2.5 Encourage patient to breath deeply during treatment	Treatment Protocol Appendix 3
Physio.	2.3 **Percuss** thorax with cupped hand(s) directly over the lung segment(s) being drained. 2.3.1 Use both/one hand as deemed necessary 2.3.2 Adapt rate, depth and force of technique to meet individual needs	Definition: Treatment Protocol Appendix 4
Physio.	2.4 **Vibrate** chest over percussed area using two hands 2.4.1 Vibrate on each exhalation 2.4.2 Adapt rate, depth and force of technique to meet individual needs	Definition: Treatment Protocol Appendix 4
Physio.	2.5 Repeat alternate percussion and vibration in short bursts 2.5.1 Encourage **cough** (spontaneous, directed, FET, manual as deemed necessary) after each cycle of percussion/vibration 2.5.2 Collect expectorate 2.5.3 Repeat till 2 consecutive attempts at clearance produce no further expectorate	Definition: Treatment Protocol Appendix 4
Physio.	2.6 Turn patient to position 2 2.6.1 Repeat 2.3 – 2.5.3	
Physio.	2.7 Modify treatment within above parameters depending on assessment of patient's condition/tolerance 2.7.1 Select further position(s) if deemed necessary 2.7.2 After last position, return patient to original/suitable position	
Recruiter	2.8 Record main treatment parameters (i.e. positions & total time) 2.8.1 Record major deviations + brief explanation from Physiotherapist	
Physio.	2.9 Transfer total expectorant to trial-specific sputum pot 2.9.1 Monitor oxygen saturation until return to baseline	
Physio.	2.10 Provide patient with advice sheet on positioning, managing cough and mobilisation 2.10.1 Do not explicitly instigate ACBT or PEP aid 2.10.2 Ask patient to collect further sputum produced post-treatment 2.10.3 Advise patient on next visit (if appropriate)	Study Protocol Appendix 2
Recruiter	2.11 Record wet weight of sputum produced during intervention 2.11.1 Label trial-specific sputum pots with patient details 2.11.2 Ensure patient has sufficient sputum pots for daily use 2.11.3 Liaise with Physiotherapist regarding next visit (if applicable)	
Recruiter	2.12 Independent of physiotherapy visits, on daily basis - 2.12.1 Collect sputum pots and record total wet weight /24 hours 2.12.2 Record oxygen saturation (24 hour average) 2.12.3 Complete Breathlessness, Cough & Sputum Scale	
	3.0 CONTROL ARM	

Physio.	3.1 Provide patient with advice sheet on positioning, managing cough and mobilisation 3.1.1 Encourage **cough** (spontaneous, directed, FET, manual as deemed necessary) 3.1.2 Do not explicitly instigate ACBT or PEP aid 3.1.3 Request patient collects sputum produced each day 3.1.4 Advise patient on next visit (if appropriate)	Study Protocol Appendix 2
Recruiter	3.2 Record oxygen saturation 3.2.1 If available, record continuous oximetry data 3.2.2 Record whether patient is likely to be ambulatory or not 3.2.3 Label trial-specific sputum pots with patient details 3.2.4 Ensure patient has sufficient sputum pots for daily use 3.2.5 Liaise with Physiotherapist regarding next visit (if applicable)	
Recruiter	3.3 Independent of physiotherapy visits, on daily basis - 3.3.1 Collect sputum pots and record total wet weight/24 hours 3.3.2 Complete Breathlessness, Cough & Sputum Scale	
	4.0 MOVEMENT BETWEEN ARMS	
Physio.	4.1 Assess the need to move from control to intervention arm when patient's Early Warning Score gives cause for concern and ALL the following apply: 4.1.1 Clinical evidence of sputum retention (e.g. auscultation, chest x ray) 4.1.2 Arterial blood gases: pH less than 7.26 4.1.3 Arterial blood gases: rising CO_2 4.1.4 Already receiving controlled oxygen therapy 4.1.5 Already receiving other supportive treatment(s)	
Physio.	4.2 **At each visit** - use above criteria to assess whether the patient remains in their original or re-ascribed arm	
Recruiter	4.3 Record all movements between arms 4.3.1 Record Physiotherapist's reasons for each re-assignment	

	5.0 ADVERSE EVENTS	OBSERVATION
Physio.	**5.1 If the patient shows signs of increased intracranial pressure** 5.1.1 Stop therapy 5.1.2 Instigate Emergency Medical Procedure as per Trust policy	Disoriented, LOC enlarged pupils, headache, vomiting
Physio.	**5.2 If the patient shows signs of acute hypotension** 5.2.1 Stop therapy 5.2.2 Instigate Emergency Medical Procedure as per Trust policy	Pallor, sweating, ↓ consciousness.
Physio.	**5.3 If the patient suffers a pulmonary haemorrhage** 5.3.1 Stop therapy 5.3.2 Instigate Emergency Medical Procedure as per Trust policy	Visible loss of blood
Physio.	**5.4 If the patient shows signs of dysrhythmia** 5.4.1 Stop therapy 5.4.2 Instigate Emergency Medical Procedure as per Trust policy	Pallor, sweating, chest pain, ↓ consciousness.
Physio.	**5.5 If the patient vomits & aspirates** 5.5.1 Stop therapy and position patient appropriately 5.5.2 Clear airway and suction as needed 5.5.3 Administer oxygen 5.5.4 Maintain airway 5.5.5 Contact appropriate physician *	Visible vomit, harsh breathing, oropharyngeal sounds, prolonged coughing.
Physio.	**5.6 If the patient becomes hypoxic** 5.6.1 Stop therapy 5.6.2 Administer controlled oxygen therapy 5.6.3 Return patient to previous/suitable resting position 5.6.4 Contact appropriate physician * 5.6.5 Ensure adequate ventilation	Falling O_2 sats. tachpnoea, blue lips, tachycardia, confusion
Physio.	**5.7 If the patient shows signs of bronchospasm** 5.7.1 Stop therapy 5.7.2 Return patient to previous/suitable resting position 5.7.3 Consider administering/increasing oxygen delivery 5.7.4 Consider use of broncodilators 5.7.4 Consult appropriate physician *	Tight chest, audible wheeze, abdominal paradox.
Physio.	**5.8 If the patient suffers pain or injury to muscles, ribs, or spine** 5.8.1 Stop therapy associated with pain or problem 5.8.2 Exercise care in moving patient 5.8.3 Consult appropriate physician if deemed necessary	Patient response to treatment.
Recruiter	**5.9 For all adverse events** 5.9.1 Record on Case Report Form 5.9.2 Follow Trial-specific Adverse Event reporting procedure 5.9.3 Follow Trust Policy on Adverse Event/Incident Reporting	
**** apply clinical experience to select appropriately from: HO, SHO, Registrar, Senior Nurse***		

Abbreviations:	
RCT – Randomised Controlled Trial	**LOC** – Loss of Consciousness
FET – Forced Expiratory Technique	**EMP –** Emergency Medical Procedure
ABCT – Active Cycle Breathing Technique	**HO** – House Officer
PEP – Positive Expiratory Pressure	**SHO** – Senior House Officer

Appendix 2

Manual chest physiotherapy – treatment definitions

MANUAL CHEST THERAPY – TREATMENT DEFINITIONS

1. RATIONALE

Manual chest therapy is time consuming, labour intensive treatment requiring significant skill and strength on the part of the therapist and the mental and physical cooperation of the patient.

Manual Chest Therapy is designed to:

- Improve the mobilisation of bronchial secretions (1-8)
- Match ventilation and perfusion (9-13)
- Normalise functional residual capacity (14-21)

These outcomes are based on the effects of gravity and external manipulation of the thorax. This includes turning, postural drainage, percussion, vibration and cough.

2. TURNING

Turning is the rotation of the body around the longitudinal axis to promote unilateral or bilateral lung expansion (9,12) and improve arterial oxygenation (9-11,22). Regular turning can be to either side or the prone position (23) with the bed at any degree of inclination (as indicated and tolerated). Patients either turn themselves, are turned by the therapist or using a special bed or device (11,12,24-26).

3. POSTURAL DRAINAGE

Postural drainage is the drainage of secretions by the effect of gravity, from one or more lung segments to the central airways where they can be removed by cough or mechanical aspiration (1-3,7,8,14,17,20,27-29,30,31). Each position consists of placing the target lung segment(s) superior to the carina. Positions are generally held for 3-15 minutes but may be held for longer in particular situations (2,7,8,10,20,29,32-35). Standard positions are often modified by the therapist depending on the patient's condition and tolerance.

4. PERCUSSION

Percussion involves the external manipulation of the thorax. It is also referred to as cupping, clapping, and tapotement. The purpose of percussion is to intermittently apply kinetic energy to the chest wall and lung. This is accomplished by using a cupped hand (Figure 1) with rhythmical flexion and extension action of the wrist.

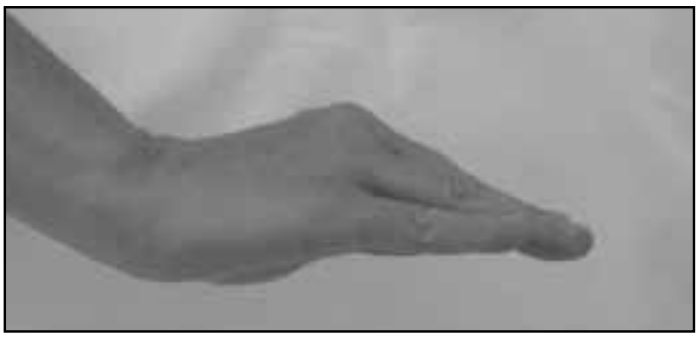

Figure 1.
Cupped hand position adopted during percussion

The force of percussion should be adapted to suit the individual. The technique is often done with two hands but, depending on the lung segment(s) being drained, it may be more appropriate to use one hand. No conclusive evidence demonstrates the superiority of one method over the other (2,8,36-39). To minimise the risk of desaturation in patients with moderate or severe lung disease, it is recommended that percussion is performed in 15-20 second 'bursts' with pauses for 5 seconds or longer between bouts (40).

4. VIBRATION

Vibration involves the application of a tremorous action over the area being drained. This is performed by manually pressing with both hands (Figure 2) in the direction of the normal movement of the ribs during expiration. The vibratory action may be coarse or fine. No conclusive evidence supports the efficacy of vibration or an optimum frequency of delivery (1,2,7,18,19,21,30,33,34,41-43).

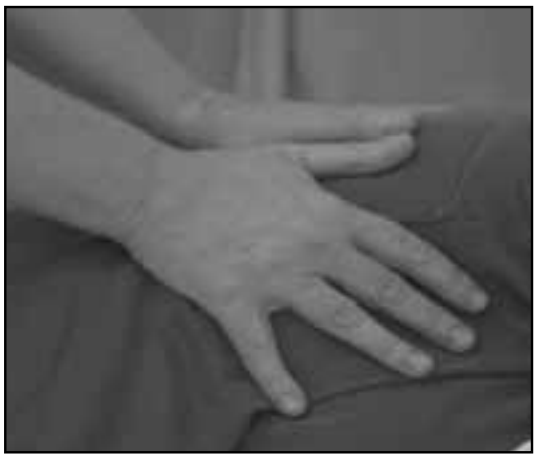

Figure 2. Hand position adopted during vibration

5. COUGH

A *spontaneous effective cough* is a reflex mechanism utilizing maximum forced exhalation to clear irritants or secretions from the airway. The forced exhalation is preceded by a maximal inspiratory effort followed by closure of the glottis. Contraction of expiratory muscles produces increased intrathoracic pressures against the closed glottis, which culminates in an explosive release of gas at high velocity as the glottis opens (44).

Directed cough seeks to mimic the attributes of an effective spontaneous cough to help to provide voluntary control over this reflex and to compensate for physical limitations. For example; by increasing glottic control, inspiratory and expiratory muscle strength, coordination, and airway stability (44).

Forced Expiratory Technique (FET), also known as "huff coughing," consists of one or two huffs (forced expirations) from mid-to-low lung volumes with the glottis open followed by a period of relaxed, controlled diaphragmatic breathing (44). The process is repeated until maximal bronchial clearance is obtained. It can be reinforced by self-compression of the chest wall using a brisk adduction movement of the upper arms.

Manually assisted cough is the external application of mechanical pressure to the epigastric region or thoracic cage coordinated with forced exhalation (44).

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Appendix 3

Manual chest physiotherapy – treatment positions

MATREX TRIAL - TREATMENT POSITIONS

According to clinical findings, select TWO most appropriate positions

1. Propped - right

2. Propped - left

3. Flat - right

4. Flat - left

5. Tipped* – right

6. Tipped* - left

*** range 15^0 - 20^0**

Note: further positions from this list can also be selected if deemed necessary

Appendix 4

Trial recruiter screening checklist

Trial Recruiter Checklist - identifying potential participants

AFFIX PATIENT ID LABEL

SOURCE OF ADMISSION……..

CRITERION	YES	NO	
The following MUST apply for patient to be INCLUDED			
1. COPD diagnosed			HISS, PAS
2. COPD considered unstable			Referral letter
The following MAY be present			
3. Increased wheeze			Admission notes
4. Increased dyspnoea			Admission notes
5. Increased sputum production			Admission notes
6. Tight chest			Admission notes
7. Fluid retention			Admission notes
8. Sputum infected			Path and/or x ray
If ANY of the following apply, the patient MUST NOT BE INCLUDED			
9. Unstable head/neck injury			Admission notes
10. Frank haemoptysis			Admission notes
11. Bronchial hyper-reactivity			Admission notes
12. Osteoporosis			Patient notes
13. Respiratory system malignancy			Patient notes
14. Recent spinal surgery/injury			Patient notes
15. Unable to give consent			Ward staff
16. No excess sputum production *			Admission notes
POTENTIAL PARTICIPANT?			

*** It may be difficult to assess from routine information whether the patient does/does not suffer from excess sputum production. If this criterion is unclear AND there are no other exclusions, retain the patient as a possible participant and refer to the physiotherapist for second level screening (Checklist 2)**

Screening Questions:

- **Do you normally produce phlegm?**
- **Are you producing more phlegm than you do when you are well**
- **Do you feel you have phlegm on your chest?**

Appendix 5

Physiotherapist screening checklist

Physiotherapist Checklist – final patient screening

AFFIX PATIENT ID LABEL

The following conditions are contra-indications for Manual Chest Therapy. They may not be routinely diagnosed and recorded in patient notes If you consider ANY apply, EXCLUDE patient from trial.

CONTRA-INDICATION	YES	NO	NOT KNOWN
Raised intracranial pressure			
Uncontrolled hypertension (diastolic > 110)			
Pulmonary Embolism			
Coagulopathy (platelets <50)			
Coagulopathy INR >3			
Bronchopleural Fistula			
Subcutaneous Emphysema			
Left Ventricular Failure = primary diagnosis			

The following risk factors impact on patient suitability for manual chest therapy
Assess their likely presence/absence and use you clinical judgement to decide whether Manual Chest Therapy remains appropriate for this patient

RISK FACTORS	NO	NOT KNOWN	YES	Include? (√ , x)	Reason (brief explanation for decision)
Pleural effusion					
Pulmonary TB					
Empyema					
Lung contusion					
Rib fracture					
Flail Chest					
Wound/healing tissue on thorax					
Recent spinal infusion/anaesthesia					
Distended abdomen					
Patient complaint of chest-wall pain					
Patient confused and/or anxious					
Other					
INCLUDE PATIENT IN TRIAL?				**YES(√)**	**NO(x)**

Adapted from AARC Clinical Practice Guideline, Postural Drainage Therapy, *Respiratory Care* 1991;**36**:1418–142.

Appendix 6

Patient information sheet

Invitation to participate in a research project

Is Manual Chest Therapy a beneficial and cost-effective treatment for people hospitalised with Chronic Obstructive Pulmonary Disease (COPD)?

You are being invited to take part in a research project. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?
Manual Chest Therapy is a technique used by physiotherapists to help people 'clear their chests' when their condition causes them to produce a lot of phlegm (sputum). The physiotherapist places the patient in various positions and 'claps' their back to loosen the build up of phlegm and help them cough it up. Although the technique is used quite often, clinicians are uncertain whether people with COPD benefit from this treatment. It may be that letting people clear their chests themselves is just as effective. We want to see if giving Manual Chest Therapy in hospital makes any difference to people's speed of recovery and whether there are any noticeable longer term benefits once they get back home.

Why have I been chosen?
You have been invited to take part in this research because you have been diagnosed with COPD and needed to come in to hospital to stabilise your symptoms. We will be running this project in several hospitals across East Anglia. In all, we are looking for 550 people to take part.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?
Because we do not know which way to treat patients is best, we need to make comparisons. Everyone taking part in this project will be put into one of two groups at random (as if "by the toss of a coin"). Half will be in **Group 1** and half in **Group 2.**

If you are selected to be in Group 1:
A physiotherapist will come and see you whilst you are in hospital. The number of times they come will depend on how troublesome your phlegm is. They will give you Manual Chest Therapy and measure the amount of phlegm you cough up. Once the treatment is finished, the physiotherapist will give you advice on the best way to continue clearing your chest.

If you are selected to be in Group 2:
A physiotherapist will come and see you whilst you are in hospital and give you advice on the best way to clear your chest. If at any time, the physiotherapist becomes concerned you are not able to clear your chest on your own, they may decide to change the group you are in and give you Manual Chest Therapy until your condition stabilises.

Whichever group you are in:
Whilst you are in hospital - before anything else happens, a researcher will talk to you about the study and then ask you some questions about your general use of health services and your quality of life. In all, this should take about 45 minutes. She will then give you 2 questionnaires. One asks questions about how you are managing generally and how COPD affects your life. The other asks questions about how breathless you feel. You can fill these out on your own, or the researcher can help you if you wish. In all, these questionnaires should take about 30 minutes to complete. You will then be asked to collect the phlegm you cough up during the day in special measuring pots. Each day, the researcher will visit you to collect the pots and ask you to fill in a short questionnaire on how you are feeling that day.

When you have gone home - 6 weeks after you have been discharged, a researcher will send you a number of questionnaires asking questions about your health and your quality of life. In all, these questionnaires should take about 40 minutes to complete and you can fill them out with the help of a friend or relative if you wish. We will send a stamped addressed envelope at the same time so you can return them easily. One questionnaire asks questions about how much you have needed to use particular health services. With your permission, a researcher will check this against information held at your GP Practice. The researcher will write to you again at 6 and 12 months, asking you to complete the same questionnaires. At one of your routine checkups at the hospital, you may also be asked to do a 'walking test' where we measure how far you can comfortably walk in 6 minutes.

What is the treatment being tested?
The treatment being tested is Manual Chest Therapy. This involves a physiotherapist placing the patient in a number of positions to help drain the phlegm from their lungs. The physiotherapist then 'claps' the patient on the chest and 'vibrates' the area with their hands to help dislodge phlegm. The physiotherapist then helps the patient cough up the dislodged phlegm. The treatment takes between 5 and 20 minutes depending on how much phlegm the patient is producing.

What are the alternatives?
When patients produce a lot of phlegm, the physiotherapist can give them advice on how best to cough it up. This includes information on the best positions to lie in and the various techniques that can be used for effective breathing and coughing.

What are the side effects and risks of the treatment being tested?
Some people find Manual Chest Therapy uncomfortable. The physiotherapist tries to minimise discomfort by adapting the positions used and the force of the 'clapping' to suit each patient individually. Sometimes the treatment can make people more breathless than usual. If this happens, the physiotherapist monitors the patient carefully until this increased breathlessness eases off.

Rarely, coughing up a large amount of phlegm can make people sick. If this happens, the physiotherapist makes sure the patient can clear their airway and helps them to feel more comfortable. Very occasionally, the physical nature of Manual Chest Therapy can provoke underlying medical conditions such as high blood pressure, heart problems and airway spasms. In the unlikely event any of these things happen, the physiotherapist follows a set course of action to help the patient.

What are the possible disadvantages of taking part?
If you are put in the group that does not receive Manual Chest Therapy, you may feel you are 'missing out' on a treatment that could help you. However, because clinicians are unsure of its benefits, Manual Chest Therapy is not routinely given to every patient hospitalised with COPD. This means that if you chose not to participate in this project, there is still no guarantee you will receive this treatment.

What are the possible benefits of taking part?
Whichever group you are in, the physiotherapist is there to help you.
The information we get from this study may help us to treat future patients hospitalised with COPD more effectively.

What if something goes wrong?
If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms will be available to you.

Will my taking part in this project be kept confidential?
All information which is collected about you during the course of the research will be kept strictly confidential. We will need to consult your medical records to collect information on your condition and the results of tests routinely carried out as part of your hospital treatment. All the information we obtain relating to you will be treated in the strictest confidence and stored in line with the Data Protection Act (1998). Only investigators from our team (who have formal legal duties of confidentiality) will have access to this information. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it. With your agreement, we will write to your GP to let them know you are participating in this trial.

What will happen to the results of the research?
We aim to publish the results of this project both locally and nationally. These reports will not include names or other personal details that would allow individual participants to be identified. If you wish, we will send you a copy of the final summary report.

Who is organising and funding the research?
This research is being organised by the University of East Anglia in collaboration with hospitals across East Anglia. The research is being funded by the Department of Health through the NHS Health Technology Assessment (HTA) research funding scheme.

Who has reviewed the study?
The scientific aspects of this project have been reviewed by specialists in the NHS Research & Development funding programme. The Norwich Research Ethics Committee has reviewed the project to make sure this research is ethical and patients' rights are protected. The East Norfolk and Waveney Research Governance Committee has reviewed its suitability to be run in NHS hospitals.

Contact for Further Information
If you need any more information or would like to discuss this project further, you can talk to the researcher who gave you this information sheet, any member of the hospital physiotherapist team or the consultant responsible for your care. If you do decide to take part, whilst you are in hospital you can talk to any of these people about the project.

Once you are back home, if you have any queries or concerns about the project, you can telephone the research team based at the University of East Anglia.
Their telephone number is: **01603 591675**

If you decide to take part, thank you for participating.

Appendix 7

Study consent form

Hospital Number… ……

CONSENT FORM

Title: A Single Blind Randomised Controlled Trial to Determine the Effectiveness and Cost Utility of Manual Chest Physiotherapy Techniques in the Management of Exacerbations of Chronic Obstructive Pulmonary Disease (MATREX).

Name of Chief Investigator: Ms Jane Cross
Name of Principle Researcher at this hospital: Dr S W Watkin.

Please initial box

1. I confirm that I have read and understand the information sheet dated September 2006 (version 5) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the University of East Anglia or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I understand that when I have left hospital, a researcher will periodically contact me at home and ask me to fill in a number of questionnaires. ☐
5. I understand my General Practitioner will be informed of my participation in this study and I give permission for researchers from the University of East Anglia to access information held at the GP Practice on my use of health care services. ☐
6. I agree to take part in this study. ☐

Name of Patient	Date	Signature

Researcher	Date	Signature

1 copy for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 8

St George's Respiratory Questionnaire

Trial ID……

Date……

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE ORIGINAL ENGLISH VERSION

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please tick in one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

P.W. Jones, PhD FRCP
Professor of Respiratory Medicine,
St. George's Hospital Medical School,
Jenner Wing,
Cranmer Terrace,
London SW17 ORE, UK.

Tel. +44 (0) 20 8725 5371
Fax +44 (0) 20 8725 5955

continued…

St. George's Respiratory Questionnaire
PART 1

Questions about how much chest trouble you have had over the past 4 weeks.

Please tick (✓) *one box for each question*:

	most days a week	several days a week	a few days a month	only with chest infections	not at all
1. Over the past 4 weeks, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 4 weeks, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 4 weeks, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 4 weeks, I have had attacks of wheezing:	☐	☐	☐	☐	☐

5. During the past 4 weeks, how many severe or very unpleasant attacks of chest trouble have you had?

Please tick (✓) *one*:

- more than 3 attacks ☐
- 3 attacks ☐
- 2 attacks ☐
- 1 attack ☐
- no attacks ☐

6. How long did the worst attack of chest trouble last?
(Go to question 7 if you had no severe attacks)

Please tick (✓) *one*:

- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 4 weeks, in an average week, how many good days (with little chest trouble) have you had?

Please tick (✓) *one*:

- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day is good ☐
- every day is good ☐

8. If you have a wheeze, is it worse in the morning?

Please tick (✓) *one:*

- No ☐
- Yes ☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your chest condition?

Please tick (✓) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problem ☐

If you have ever had paid employment.

Please tick (✓) *one*:

- My chest trouble made me stop work altogether ☐
- My chest trouble interferes with my work or made me change my work ☐
- My chest trouble does not affect my work ☐

Section 2

Questions about what activities usually make you feel breathless <u>these days</u>.

Please tick (✓) in ***each box*** that applies to you ***these days***:

	True	False
Sitting or lying still	☐	☐
Getting washed or dressed	☐	☐
Walking around the home	☐	☐
Walking outside on the level	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or games	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 3

Some more questions about your cough and breathlessness <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough hurts	☐	☐
My cough makes me tired	☐	☐
I am breathless when I talk	☐	☐
I am breathless when I bend over	☐	☐
My cough or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

Questions about other effects that your chest trouble may have on you <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough or breathing is embarrassing in public	☐	☐
My chest trouble is a nuisance to my family, friends or neighbours	☐	☐
I get afraid or panic when I cannot get my breath	☐	☐
I feel that I am not in control of my chest problem	☐	☐
I do not expect my chest to get any better	☐	☐
I have become frail or an invalid because of my chest	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

Questions about your medication, if you are receiving no medication go straight to section 6.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My medication does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My medication interferes with my life a lot	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your breathing.

	Please tick (✓) in ***each box*** that applies to you ***because of your breathing***: True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time	☐	☐
I walk slower than other people, or I stop for rests	☐	☐
Jobs such as housework take a long time, or I have to stop for rests	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	☐	☐

Section 7

We would like to know how your chest <u>usually</u> affects your daily life.

	Please tick (✓) in ***each box*** that applies to you ***because of your chest trouble***: True	False
I cannot play sports or games	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do housework	☐	☐
I cannot move far from my bed or chair	☐	☐

continued…

St. George's Respiratory Questionnaire

Here is a list of other activities that your chest trouble may prevent you doing. (You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect you):

Going for walks or walking the dog

Doing things at home or in the garden

Sexual intercourse

Going out to church, pub, club or place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your chest trouble may stop you doing:

. . . . . .

. . . . . .

. . . . . .

. . . . . .

Now would you tick in the box (one only) which you think best describes how your chest affects you:

It does not stop me doing anything I would like to do ☐

It stops me doing one or two things I would like to do ☐

It stops me doing most of the things I would like to do ☐

It stops me doing everything I would like to do ☐

Thank you for filling in this questionnaire. Before you finish would you please check to see that you have answered all the questions.

Please enter the date you fill in this questionnaire ……/……/……

Appendix 9

Breathlessness, Cough and Sputum Scale

Trial ID……

Breathlessness, Cough and Sputum Scale

PLEASE COMPLETE IN THE EVENING BEFORE GOING TO BED

Please enter the day: ☐

Please record the date: ☐

HOW MUCH DIFFICULTY DID YOU HAVE BREATHING TODAY? (circle one)

None – unaware of any difficulty	0
Mild – noticeable during strenuous activity (e.g. running)	1
Moderate – noticeable during light activity (e.g. bed making)	2
Marked – noticeable when washing or dressing	3
Severe – almost constant, present even when resting	4

HOW WAS YOUR COUGH TODAY? (circle one)

None – unaware of coughing	0
Rare – cough now and then	1
Occasional – less than hourly	2
Frequent – one or more times an hour	3
Almost constant – never free of cough or need to cough	4

HOW MUCH TROUBLE WAS YOUR SPUTUM TODAY? (circle one)

None – unaware of any difficulty	0
Mild – rarely caused problem	1
Moderate – noticeable as a problem	2
Marked –caused a great deal of inconvenience	3
Severe – an almost constant problem	4

Appendix 10

Medical Research Council-Dyspnoea scale

Trial ID……. **HOSPITAL LABEL**

Date……

MRC DYSPNOEA (BREATHLESSNESS) SCALE

Please put a cross (X) by the statement that best describes your breathlessness

1	I only get breathless with strenuous exercise
2	I get short of breath when hurrying on the level or up a slight hill
3	I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level
4	I stop for breath after walking 100 yards or after a few minutes on the level
5	I am too breathless to leave the house

Appendix 11

EQ-5D questionnaire

EQ - 5D

Health Questionnaire

(English version for the UK)
(validated for use in Eire)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

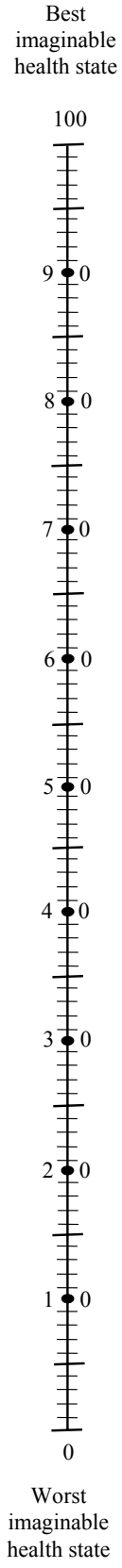
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Because all replies are anonymous, it will help us to understand your answers better if we have a little background data from everyone, as covered in the following questions.

1. Have you experienced serious illness?

	Yes	No
in you yourself	❑	❑
in your family	❑	❑
in caring for others	❑	❑

PLEASE TICK APPROPRIATE BOXES

2. What is your age in years ? ☐

3. Are you:

Male	Female
❑	❑

PLEASE TICK APPROPRIATE BOX

4. Are you:

a current smoker	❑
an ex-smoker	❑
a never smoker	❑

PLEASE TICK APPROPRIATE BOX

5. Do you now, or did you ever, work in health or social services?

Yes	No
❑	❑

PLEASE TICK APPROPRIATE BOX

If so, in what capacity? .....

6. Which of the following best describes your main activity?

in employment or self employment	❑
retired	❑
housework	❑
student	❑
seeking work	❑
other (please specify)	❑ .....

PLEASE TICK APPROPRIATE BOX

7. Did your education continue after the minimum school leaving age?

Yes	No
❑	❑

PLEASE TICK APPROPRIATE BOX

8. Do you have a Degree or equivalent professional qualification?

Yes	No
❑	❑

PLEASE TICK APPROPRIATE BOX

9. If you know your postcode, would you please write it here ☐

Appendix 12

Case report form – randomisation

MATREX: CRF/RANDOMISATION – to be completed for ALL eligible patients

Recruiter initials:

Patient initials ……. Hospital No……... Date ……

	YES/NO ✓ or x	Detail:
Recruiter Checklist completed?		
Physio Checklist completed?		
Patient Info Sheet discussed?		
Informed Consent obtained? If NO, give details:……. …… …… …… In Last Year? No. of days in hospital ☐ No. of admissions ☐		**Consent forms assigned?** To patient? ✓ …….. To hospital notes? ✓ …… To trial folder? ✓ ……
MATREX sticker in patient notes?		
Baseline SGRQ administered?		
Baseline MRC administered?		
Baseline Cost Q administered?		
Baseline EQ5D administered?		
Patient on supported breathing?		**Type of support?** Mask? ✓ ….....% Nasal? ✓ ….... litres/min
Baseline Oxygen sats obtained?		%: .....
Patient Ambulatory?		
NHS Patient sticker verified? Patient phone no: ……... GP phone no:…….. *Affix patient label here*		*Detail if different from NHS record:* …… …… …… …… ……
Name preference and salutation established?		*Detail if different from NHS record:* ……
Patient randomised?		Treatment arm? ✓ …..... Control arm? ✓ ….....
Study Card issued?		
Sputum pots issued?		

Appendix 13

Study arm allocation reminder card – MCP arm

PATIENT STUDY CARD – INTERVENTION ARM

Printed on blue card, 15cm x 10.5cm

Outside:

Front *Fold ↓* *Back*

UEA NORWICH NHS

The MATREX trial
MAnual Therapy for
Respiratory Exacerbations

You have been selected to receive
MANUAL CHEST THERAPY

Thank you for taking part in this trial

If you have any queries or concerns, please contact

Matrex Trial Office
Telephone: 01603 591675

Inside:

Fold ↓

In 6 weeks time we will write to you asking for information on how you have been feeling and what health services you have required. To answer some of the questions, it may be helpful to make a note if you have to …

- Visit your GP, nurse or any other health care professional
- Phone your GP, nurse or any other health care professional
- Pay for medicines (including pre-paid prescriptions)
- Buy any non-prescribed medicines (i.e. over-the-counter)
- If you are in paid employment, the number of days taken off sick
- If applicable, the number of days someone else has taken off work to help you

Appendix 14

Study arm allocation reminder card – control arm

PATIENT STUDY CARD – CONTROL ARM

Printed on blue card, 15cm x 10.5cm

Outside:

Front *Fold ↓* *Back*

UEA NORWICH NHS

The MATREX trial
MAnual Therapy for
Respiratory Exacerbations

You have been selected to receive
ADVICE FROM THE PHYSIOTHERAPIST

Thank you for taking part in this trial

If you have any queries or concerns, please contact

Matrex Trial Office
Telephone: 01603 591675

Inside:

Fold ↓

In 6 weeks time we will write to you asking for information on how you have been feeling and what health services you have required. To answer some of the questions, it may be helpful to make a note if you have to …

- Visit your GP, nurse or any other health care professional
- Phone your GP, nurse or any other health care professional
- Pay for medicines (including pre-paid prescriptions)
- Buy any non-prescribed medicines (i.e. over-the-counter)
- If you are in paid employment, the number of days taken off sick
- If applicable, the number of days someone else has taken off work to help you

Appendix 15

Case report form – MCP arm

MATREX: CRF/INTERVENTION – to be completed EACH time patient receives MCT

Recruiter initials: ☐

Patient initials …… Hospital No…….. Trial ID number ……

Treatment date: ……..

Treatment Positions	1st ...……	2nd ...……	3rd ...……	4th ...……
Oxygen Sats at Start	.....%	on air ……	mask ……%	nasal …….%
Start Time *(hands on)*	……..			
Lowest Oxygen Sats	……..%			
Stop Time *(last cough)*	……..			
Total Time *(nearest min)*	……..			
	YES/NO (✓ or x)	**Detail:**		
Adverse Event? *(see checklist overleaf)*		If ✓ AE Report Form completed? (✓ or x) ……..		
Physiotherapist switch arm?		If ✓ give detail …… …… ……		
Would Physiotherapist normally perform MCT on pt ?		…….. ……..		
Next physiotherapy visit established?		If ✓ date visit planned? …… ……..		
7 x BCSS administered?		*Note: applies to EACH hospital episode*		
Patient Advice Leaflet issued?		*Note: applies to first visit for EACH hospital episode*		
MATREX sticker in patient notes?		*Note: provide new sticker each time patient is re-admitted*		
Sufficient sputum pots provided?				
Sputum pots collected?		Weight? …… g Colour? ……. (1-5) Time? ……		

Date of discharge *(complete when known)* …….....

ADVERSE EVENT	OBSERVATION
Increased intracranial pressure	• Disorientation • Loss of consciousness • Enlarged pupils • Headache • Vomiting
Acute hypotension	• Pallor • Sweating • Reduced consciousness
Pulmonary haemorrhage	• Visible loss of blood
Dysrhythmia	• Pallor • Sweating • Chest pain • Reduced consciousness
Vomiting & aspiratation	• Visible vomit • Harsh breathing • Oropharyngeal sounds • Prolonged coughing
Hypoxia	• Falling O_2 sats • Tachpnoea • Blue lips • Tachycardia • Confusion
Bronchospasm	• Tight chest • Audible wheeze • Abdominal paradox
Pain or injury to muscles, ribs, or spine	• Patient response
Other event you, the physiotherapist or other clinician consider adverse to the patient	Record detail in Adverse Event Report Form

Appendix 16

Advice leaflet on chest clearing

A GUIDE TO CLEARING YOUR CHEST

This leaflet is a reminder of what your physiotherapist has shown you.

It should not be hard work to clear phlegm off your chest. So any shortness of breath or wheeze should not be made worse.

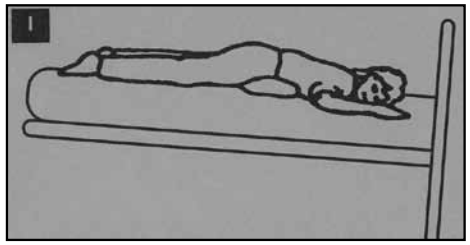
GENERAL POINTS

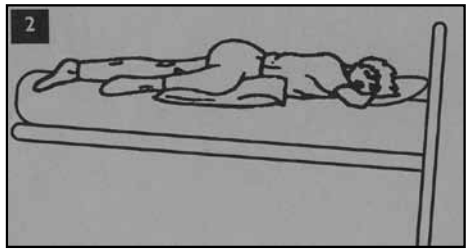
1. **Choose a good time …**

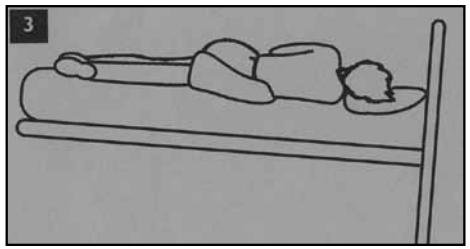
   - when you cough up most phlegm
   - when you are not too wheezy, breathless or tired
   - not when you are in a hurry
   - and not straight after a meal

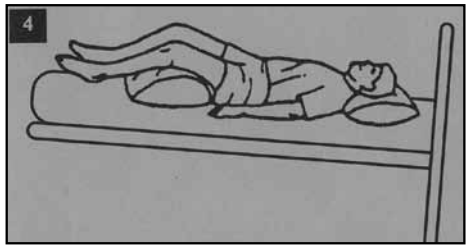
2. **Do your physiotherapy about 15 minutes after your inhaler or nebuliser**

POSITIONS
to help drain the phlegm.
Your physiotherapist will select the one for you.









Position _____ daily for _____ minutes

Use pilows to raise your hips if the bed can't be tilted.

BREATHING TECHNIQUES

to help clear the phlegm …

1. **Rest in the first position while your breathing settles.**

2. **Take _____ slow, deep breaths. Then breathe normally until settled again. Repeat this until the phlegm feels ready to clear.**

3. **To shift the phlegm do _____ strong huffs. A huff is a short, sharp breath out with your mouth open.**

Remember to rest inbetween each huff.

4. **Repeat steps 1 – 3 until your chest feels clear**

PHYSIO TIPS

- **If you have more phlegm to clear, increase the times you do the technique**

- **To help clear phlegm with little effort you should complete this cycle**

  _____ times, combining it with your drainage position

REMEMBER

- **Try not to cough for too long. This can leave you tired and breathless.**

- **Drink plenty of fluids, especially when you are more chesty, to make clearing your chest easier.**

NOTES

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The MATREX trial
MAnual Therapy for Respiratory EXacerbations

ISRCTN13825248

A GUIDE TO CLEARING YOUR CHEST

ADVICE LEAFLET FOR PATIENTS PARTICIPATING IN THE MATREX TRIAL

MATREX TRIAL Office
Telephone: 01603 591675

DOI: 10.3310/hta14230

Health Technology Assessment 2010; Vol. 14: No. 23

Appendix 17

Case report form – control arm

CONTROL ARM – to be completed for each hospital episode

Recruiter initials: ☐

Patient initials ……. Hospital No……... Trial ID number ……

Admission date: ……...

	YES/NO (✓ or x)	Detail:
MATREX sticker in patient notes?		*Note: provide new sticker each time patient is re-admitted*
Physiotherapist seen patient?		Physiotherapist intending to revisit patient? (✓ or x) …….. If ✓ date planned? ……..
Physiotherapist switch arm?		If ✓ give detail …… …… …… ……
Adverse Event? *(see checklist overleaf)*		If ✓ AE Report Form completed? (✓ or x) ……..
7 x BCSS administered?		*Note: applies to EACH hospital episode*
Patient Advice Leaflet issued?		*Note: applies to first visit for EACH hospital episode*

SPUTUM	**Pots issued?**	**Collected?**	**Weight?**	**Colour?**
Day 1 Date : …… Time : ……				
Day 2 Date : …… Time : ……				
Day 3 Date : …… Time : ……				
Day 4 Date : …… Time : ……				
Day 5 Date : …… Time : ……				
Day 6 Date : …… Time : ……				
Day 7 Date : …… Time : ……				

Date of discharge *(complete when known)* …….....

ADVERSE EVENT	OBSERVATION
Increased intracranial pressure	• Disorientation • Loss of consciousness • Enlarged pupils • Headache • Vomiting
Acute hypotension	• Pallor • Sweating • Reduced consciousness
Pulmonary haemorrhage	• Visible loss of blood
Dysrhythmia	• Pallor • Sweating • Chest pain • Reduced consciousness
Vomiting & aspiratation	• Visible vomit • Harsh breathing • Oropharyngeal sounds • Prolonged coughing
Hypoxia	• Falling O_2 sats • Tachpnoea • Blue lips • Tachycardia • Confusion
Bronchospasm	• Tight chest • Audible wheeze • Abdominal paradox
Pain or injury to muscles, ribs, or spine	• Patient response
Other event you, the physiotherapist or other clinician consider adverse to the patient	Record detail in Adverse Event Report Form

Appendix 18

Adverse Event Report Form

MATREX TRIAL - ADVERSE EVENT REPORT FORM

PATIENT DETAILS

Recruiter initials:	Patient initials:	Hospital Number:	Trial ID:	Trial arm:

DETAILS OF ADVERSE EVENT (see overleaf for checklist)

Description / diagnosis	Date of onset	Resolution date	Did AE occur during treatment?	In the opinion of the physiotherapist, was the event related to the therapy Name of Physio:_____

Brief description of the course of the AE and the outcome, including details of any investigations and treatments:

……

……

……

……

……

……

……

Details of follow-up action (see reporting procedure overleaf): ……

……

……

ADVERSE EVENT	OBSERVATION
Increased intracranial pressure	• Disorientation • Loss of consciousness • Enlarged pupils • Headache • Vomiting
Acute hypotension	• Pallor • Sweating • Reduced consciousness
Pulmonary haemorrhage	• Visible loss of blood
Dysrhythmia	• Pallor • Sweating • Chest pain • Reduced consciousness
Vomiting & aspiratation	• Visible vomit • Harsh breathing • Oropharyngeal sounds • Prolonged coughing
Hypoxia	• Falling O_2 sats • Tachpnoea • Blue lips • Tachycardia • Confusion
Bronchospasm	• Tight chest • Audible wheeze • Abdominal paradox
Pain or injury to muscles, ribs, or spine	• Patient response
Other event you, the physiotherapist or other clinician consider adverse to the patient	• Record detail

ACTION	BY WHOM
Report AE in line with individual Trust's Incident Reporting Procedures	Trial Recruiter
Provide Trust R&D Manager with copy of Adverse Event Report form	Trial Recruiter
Report AE to Trial Manager	Trial Recruiter
Report AE to Site Lead Investigator	Trial Recruiter
Consider individual AEs and report any concerns to Trial Manager	Site Lead Investigator
Collate and report monthly AEs to Trial Management Group (TMG)	Trial Manager
Consider monthly AEs and report any concerns to DMEC & TSC	TMG
Collate and report bi-annual AEs to Data Monitoring & Ethics Committee (DMEC)	Trial Manager
Consider bi-annual AEs and report to Trial Steering Committee (TSC)	DMEC
Consider DMEC report on AEs and report to funder	TSC

ADVERSE EVENT REPORTING PROCEDURE:

Appendix 19

COPD cost questionnaire – baseline

COST QUESTIONNAIRE – BASELINE

Questionnaire to be completed by researcher

Patient ID ☐☐☐ Times previously completed ☐ Date ☐☐/☐☐/☐☐

We want to find out how your COPD affects your use of health services and how much your COPD costs you and your family. The following questions are about this.

Hospital visits

1. In the last 3 months, have you attended (name of hospital)

because of your COPD? No ☐ Yes ☐	***If yes**, obtain details:*	
for other reasons? No ☐ Yes ☐	***If yes**, obtain details:*	

2. When you **travel** to (name of hospital) how do you normally get there?

Walk or cycle	☐		
Hospital or community transport	☐	Charge for this:	£
Car	☐	Parking cost:	£
Public transport or taxi	☐	Cost of return fare:	£

3. Around how much time would an ordinary **outpatient visit** to this hospital normally take out of your day? (prompt to including travelling, waiting and consultation time)	hour(s)

4. Do you have to take **time off** work to attend your hospital appointments? Yes ☐ No ☐
   If yes, do you: Lose pay ☐ Get full pay ☐ Get sick pay ☐

5. Does somebody else usually **accompany** you to the hospital? Yes ☐ No ☐
   If yes, do they: Not work ☐ Lose pay ☐ Get full pay ☐

6. Do you need to arrange care for someone else (e.g. dependent, child) when you go to the hospital?

Yes ☐ No ☐	***If yes***, obtain details of cost involved:	

Community health and social services

7. In the last 3 months how many times have you consulted your **GP**

		because of your COPD?		for other reasons?
at the surgery				
at home				
over the phone				

8. In the last 3 months, how many times have you consulted a **nurse** from your local surgery

		because of your COPD?		for other reasons?
at the surgery				
at home				
over the phone				

9. When you **travel** to the GP surgery how do you normally get there?

Walk or cycle	☐		
Hospital or community transport	☐	Charge for this:	£
Car	☐	Parking cost:	£
Public transport or taxi	☐	Cost of return fare:	£

10. Around how much **time** would a visit to the GP surgery normally take out of your day? (Prompt to including travelling, waiting, consultation and treatment time)	hour(s)

11. Do you have to take **time off** work to attend appointments at the GP surgery? Yes ☐ No ☐
If yes, do you: Lose pay ☐ Get full pay ☐ Get sick pay ☐

12. Does somebody else usually **accompany** you to the GP surgery? Yes ☐ No ☐
If yes, do they: Not work ☐ Lose pay ☐ Get full pay ☐

13. Do you need to arrange care for someone else (e.g. dependent, child) when you go to the GP surgery?

Yes ☐ No ☐	***If yes***, obtain details of any cost involved:	

14. In the last 3 months, have you had contact with any of the following NHS **health professionals** outside of the hospital:

	for COPD?		for other reasons?		For each, obtain number of: surgery/practice visits		home visits		phone calls
Health visitor		☐		☐					
Physiotherapist		☐		☐					
Occupational therapist		☐		☐					
Chiropodist/podiatrist		☐		☐					
Other *Specify*		☐		☐					

15. In the last 3 months, how many times have you had contact with someone from **social services** or used any of their services? *e.g. social worker, home help, care attendant, meals-on-wheels, occupational therapist*

Person or service	for COPD?		for other reasons?		For each, obtain number of: office visits		home visits		phone calls
		☐		☐					
		☐		☐					
		☐		☐					

Private health care

16. In the last 3 months, how many times have you seen a complementary therapist or alternative medicine practitioner? *e.g. acupuncturist, homeopath, chiropractor, osteopath, reflexologist, naturopath*

Type of practitioner/service		no. for COPD?		no. for other reasons?		For each, obtain total amount spent on treatment in past 3 months
						£
						£

17. In the last 3 months have you paid for any **private health care**? *e.g. doctor, physiotherapist*

Type of practitioner/service		no. for COPD?		no. for other reasons?		For each, obtain total amount spent on treatment in the past 3 months
						£
						£

Medications and equipment

18. In the last three months, have you paid for any **non-prescription medications** or complementary remedies? *e.g. painkillers, cold remedies, vitamins, minerals, herbal remedies*

Name of product		Total spent on product over last three months
		£
		£
		£
		£

19. In the last 3 months have you been issued with or bought any **health aids, devices or equipment?** e.g. *special chair or bed, walking aids, mobility scooter, portable oxygen cylinders, aids to help get up stairs/ outside, aids to help your breathing such as a nebuliser or humidifier)*

	item		own cost	OR from: GP	Social services	Hospital
for your COPD?			£	☐	☐	☐
			£	☐	☐	☐
			£	☐	☐	☐
for other reasons?			£	☐	☐	☐
			£	☐	☐	☐

20. Do you use oxygen at home?

Yes ☐ No ☐	***If yes***, how many hours a day?	☐
	cylinder?	☐
	concentrator?	☐
	portable?	☐

21. Do you pay for your own prescriptions?

Yes ☐ No ☐	***If yes***, do you use a season ticket?	☐
	pay each time?	☐

Days off

22. In the last 3 months, around how many days have you been **off work** or unable to perform your normal duties:

because of your COPD?	days	for other reasons?	days

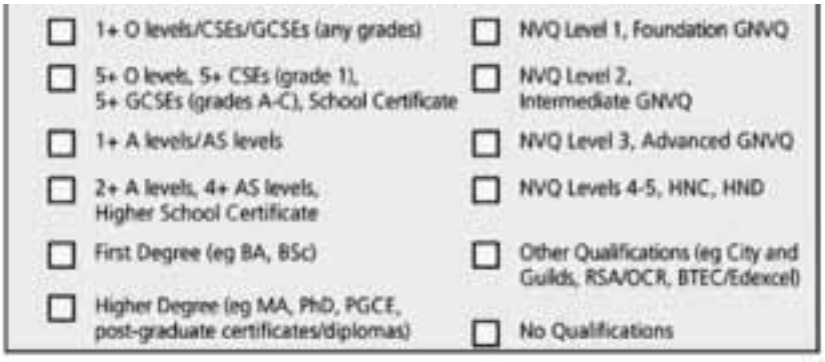
23. When you are unwell, does someone else usually give up time to **look after you**?	Yes ☐ No ☐

If yes, do they: Not work ☐ Lose pay ☐ Get full pay ☐

Educational attainment

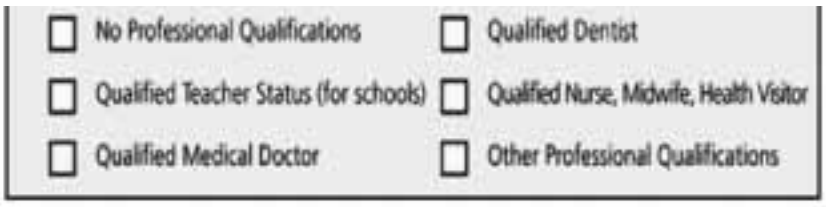
24. Which of these qualifications do you have?

Tick all those that apply. If patient specifies a qualification not listed, tick the nearest equivalent



25. Do you have any of the following professional qualifications?

Tick all boxes that apply



Thank you for your time

Appendix 20

COPD cost questionnaire – follow-up

THE MATREX TRIAL

Completed by researcher:

Patient ID ☐☐☐ Times previously completed ☐ Date ☐☐/☐☐/☐☐

COPD COST QUESTIONNAIRE

This questionnaire is designed to help us learn more about how COPD affects people's use of health services and the financial costs of managing their condition.

1. Since you last completed this questionnaire on …../…../….., have you visited the **Accident and Emergency Department?**

YES ☐ **NO** ☐ Please tick (✓) *one box*

If YES: Please put a number *in each box* (including zero)

How many times? ☐	How many visits were due to COPD? ☐	How many were For other reasons? ☐

For any of these visits, did you **call an ambulance** to get to the hospital?

YES ☐ **NO** ☐ Please tick (✓) *one box*

If YES: how many times did you call one? ☐ Please put a number in the box

---

2. Since you last completed this questionnaire on …../…../….., have you had **contact with your GP?**

YES ☐ **NO** ☐ Please tick (✓) *one box*

If YES: Please put a number in *each box* (including zero)

How many times? ☐	How many were due to COPD? ☐	How many were home visits? ☐

3. Since you last completed this questionnaire on …../…../….., have you seen **a nurse** from the GP Practice**?**

YES ☐ **NO** ☐ Please tick (✓) *one box*

If YES: Please put a number in *each box* (including zero)

How many times? ☐	How many were due to COPD? ☐	How many were home visits? ☐

We would like to find out whether people with COPD see **other NHS health care professionals** and what types of contact they have.

Examples of other NHS health care professionals include: district or community nurse, hospital outreach nurse, health visitor, physiotherapist, occupational therapist, dietician, psychologist, chiropodist, mental health team.

Types of contact include: hospital, GP surgery, home visit, private practice, telephone.

4. Since you last completed this questionnaire on …../…../….., please list **any other health care professionals** you have seen (if none – leave blank)

Person	Due to your COPD?	For other reasons?	What type of contact?
	☐	☐	
	☐	☐	
	☐	☐	

We would like to find out whether people with COPD see anyone from **Social Services** and what types of contact they have.

Examples of Social Service workers include: social worker, home help, care attendant, meals on wheels, occupational therapist, mental health team.

Types of contact include: home visit, council offices, community centre, telephone.

5. Since you last completed this questionnaire on …../…../….., please list **anyone from Social Services** that you have seen (if none – leave blank)

Person	Due to your COPD?	For other reasons?	What type of contact?
	☐	☐	
	☐	☐	
	☐	☐	

---

6. Since you last completed this questionnaire on …../…../….., have you been issued with oxygen at home?

YES ☐ **NO** ☐ **Already using** ☐ Please tick (✓) *one box*

---

7. Since you last completed this questionnaire on …../…../….., have you been issued with or bought any **other health aids, devices or equipment**?

*(**Examples of other health aids include:** special chair or bed, walking aids, mobility scooter, portable oxygen cylinders, aids to help get up stairs/ outside, aids to help your breathing such as a nebuliser or humidifier)*

YES ☐ **NO** ☐ Please tick (✓) *one box*

If YES: please provide details

	Details	Time had it	Cost to you
For your COPD			
For other reasons			

8. Since you last completed this questionnaire on …../…../….., have you paid for any **private health care?**

*(**Examples of private health care include:** chiropodist, physiotherapist, acupuncture, homeopathy and any complimentary therapies you have paid for)*

YES ☐ **NO** ☐ Please tick (✓) *one box*

If YES: please provide details

Details	Number of treatments / sessions	Cost to you

---

9. Since you last completed this questionnaire on …../…../….., how many days have you been **off work** or **unable to perform your normal duties**?

Please put a number in *each box* (including zero)

Days due to your COPD ☐	Days for other reasons ☐

---

10. Do you pay for your own prescriptions?

YES ☐ **NO** ☐ Please tick (✓) *one box*

If YES: do you use a pre-paid prescription 'season ticket' or pay each time?

Please tick (✓) *one box*

I pay for a season ticket ☐	I pay each time ☐

THANK YOU FOR YOUR TIME

Appendix 21

MATREX Trial Management Group

The Chief Investigator (Dr Jane Cross) was responsible for the day-to-day management of the trial. A TMG was established to assist with this function.

Meetings were held monthly with minutes circulated to each member. TMG members included:

Dr Jane Cross – Chief Investigator
Senior Lecturer in Respiratory Physiotherapy
School of Allied Health Professions
University of East Anglia
Tel.: 01603 593315
E-mail: j.cross@uea.ac.uk

Professor Ian Harvey – study design, project management
Professor of Epidemiology and Public Health
School of Medicine, Health Policy and Practice
University of East Anglia
Tel.: 01603 593605
E-mail: ian.harvey@uea.ac.uk

Professor Max Bachmann – study design, project management
Professor of Health Care Interfaces
School of Medicine, Health Policy and Practice
University of East Anglia
Tel. 01603 591220
E-mail: m.bachmann@uea.ac.uk

Dr Garry Barton, health economics
Lecturer in Health Economics
School of Medicine, Health Policy and Practice
University of East Anglia
Tel.: 01603 591936
E-mail: g.barton@uea.ac.uk

Professor Lee Shepstone – study design, medical statistics
Senior Lecturer in Medical Statistics
School of Medicine, Health Policy and Practice
University of East Anglia
Tel.: 01603 592100
E-mail: l.shepstone@uea.ac.uk

Dr Allan Clark – medical statistics
Lecturer in Medical Statistics
School of Medicine, Health Policy and Practice
University of East Anglia
Tel.: 01603 593629
E-mail: allan.clark@uea.ac.uk

Dr Frances Elender – Project Manager
MATREX Trial Manager
School of Allied Health Professions
University of East Anglia
Tel.: 01603 591675
E-mail: frances.elender@uea.ac.uk

Appendix 22

Trial Steering Committee

TSC membership

Name and address	Current position	Current member (Yes/No)
Professor David Price, GPIAG Prof of Primary Care Respiratory Medicine, Department of General Practice and Primary Care, University of Aberdeen, Foresterhill Health Centre, Westburn Road, Aberdeen AB25 2AY E-mail: d.price@abdn.ac.uk.	Chairperson	Yes
Professor Max Bachmann, Professor Health Care Interfaces, Department of Health Policy and Practice, University of East Anglia, School of Medicine, University Plain, Norwich NR4 7TJ E-mail: m.bachmann@uea.ac.uk	Ordinary	Yes
Ms Judy Close, Independent NHS Advisor – Allied Health Professions, Norfolk and Norwich University Hospital NHS Trust, Colney Lane, Norwich, NR4 7UY E-mail: judy.close.nnuh.nhs.uk	Ordinary	Yes
Dr Jane Cross, Senior Lecturer in Respiratory Physiotherapy, School of Allied Health Professions, University of East Anglia, Queen's Building, University Plain, Norwich NR4 7TJ E-mail: j.cross@uea.ac.uk	Ordinary	Yes
Dr Frances Elender, Trial Manager, MATREX trial, University of East Anglia, Queen's Building, University Plain, Norwich NR4 7TJ E-mail: frances.elender@uea.ac.uk	Ordinary	Yes
Dr David Ellis, Consultant Physician, Department of Respiratory Medicine, James Paget Healthcare NHS Trust, Lowestoft Road, Gorleston, Great Yarmouth NR31 6LA E-mail: david.ellis@ukdoctor.org	Ordinary	No
Dr Venkat Mahadevan, Consultant Physician, Department of Respiratory Medicine, James Paget Healthcare NHS Trust, Lowestoft Road, Gorleston, Great Yarmouth NR31 6LA E-mail: venkat.mahadevan@jpaget.nhs.uk	Ordinary	Yes
Ms Rachel Ellis, Superintendent Physiotherapist, Department of Physiotherapy, Norfolk and Norwich University Hospital NHS Trust, Colney Lane, Norwich NR4 7UY E-mail: rachel.ellis@nnuh.nhs.uk	Ordinary	Yes
Dr Garry Barton, Lecturer in Health Economics, School of Medicine, Health Policy and Practice, University of East Anglia, University Plain, Norwich NR4 7TJ E-mail: g.barton@uea.ac.uk	Ordinary	Yes
Professor Ian Harvey, Professor of Epidemiology and Public Health, Health Policy and Practice, University of East Anglia, University Plain, Norwich NR4 7TJ E-mail: ian.harvey@uea.ac.uk	Ordinary	Yes
Ms Kathryn Andrews, R&D Manager, R&D Office, Norfolk and Norwich University Hospital NHS Trust, Colney Lane, Norwich NR4 7UY E-mail: kathryn.andrews@nmuh.nhs.uk	Ordinary	Yes

Name and address	Current position	Current member (Yes/No)
Ms Katherine Jones, R&D Manager, R&D Office, Norfolk and Norwich University Hospital NHS Trust, Colney Lane, Norwich NR4 7UY E-mail: kathryn.jones@nmuh.nhs.uk	Ordinary	No
Ms Julia Kerrigan, Respiratory Physiotherapist, Queen Elizabeth Hospital, Gayton Road, King's Lynn, Norfolk PE30 4ET E-mail: julia.kerrigan@gehkl.nhs.uk	Ordinary	No
Ms Rachel Mathews, Senior Respiratory Physiotherapist, James Paget Healthcare Trust, Lowestoft Road, Gorleston, Great Yarmouth NR31 6LA E-mail: rachel.mathews@jpaget.nhs.uk	Ordinary	No
Ms Sandra Olive, Respiratory Nurse Specialist, Department of Respiratory Medicine, Norfolk and Norwich University Hospital NHS Trust, Colney Lane, Norwich, NR4 7UY E-mail: sandra.olive@nnuh.nhs.uk	Ordinary	Yes
Paula Brown, Respiratory Nurse Specialist, Department of Respiratory Medicine, Norfolk and Norwich University Hospital NHS Trust, Colney Lane, Norwich, NR4 7UY E-mail: paula.brown@nnuh.nhs.uk	Ordinary	Yes
Dr Anna Pawlowicz, Consultant Physician in Respiratory Medicine, Department of Respiratory Medicine, Queen Elizabeth Hospital, Gayton Road, King's Lynn, Norfolk PE30 4ET E-mail: anna.pawlowicz@qehkl.nhs.uk	Ordinary	Yes
Professor Lee Shepstone, Senior Lecturer in Medical Statistics, School of Medicine, Health Policy and Practice, University of East Anglia, University Plain, Norwich NR4 7TJ E-mail: l.shepstone@uea.ac.uk	Ordinary	Yes
Dr Simon Watkin, Consultant Physician, Department of Respiratory Medicine, Norfolk and Norwich University Hospital NHS Trust, Colney Lane, Norwich NR4 7UY E-mail: simon.watkin@nnuh.nhs.uk	Ordinary	No

TSC terms of reference

1.0 Summary functions

1.1 To monitor and supervise trial progress towards its interim and overall objectives.
1.2 To review relevant information from other sources (e.g. other related trials).
1.3 To consider recommendations of the DMEC.
1.4 To inform NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), HTA on the progress of the trial.
1.5 To advise NETSCC, HTA on publicity and the presentation of all aspects of the trial.

2.0 Membership composition

2.1 Independent Chairperson (no direct trial involvement other than as TSC member).
2.2 Two additional independent expert members.
2.3 Chief Investigator (CI).
2.4 MATREX trial HTA grant holders.
2.5 Lead Investigator at each participating site.
2.6 Patient/lay representative.
2.7 Trial Manager.
2.8 In attendance:
  2.8.1 HTA representative.
  2.8.2 Trial recruiters.

3.0 Meetings

3.1 The inaugural meeting will take place:
  3.1.1 After Research Ethics Committee/NHS R&D approval.
  3.1.2 Prior to recruitment of the first patient.
3.2 The TSC will meet at 6-month intervals for the duration of the trial (×6).
3.3 Meetings will be organised by the Chief Investigator.

3.4 Papers for the meeting will be circulated in advance.
3.5 An accurate minute will be prepared by the Chief Investigator and:
  3.5.1 Agreement sought by all the members.
  3.5.2 A copy sent to NETSCC, HTA.

4.0 Trial steering and management
4.1 The role of the TSC is to provide supervision of the trial on behalf of NETSCC, HTA.
4.2 The TSC will concentrate on:
  4.2.1 Trial progress.
  4.2.2 Adherence to trial protocol.
  4.2.3 Patient safety.
  4.2.4 Consideration of new information.
4.3 Day-to-day management of the trial is the responsibility of the Chief Investigator:
  4.3.1 A trial management group will assist with this function.

5.0 Good clinical practice
5.1 The TSC will endeavour to ensure that the trial is conducted at all times to the standards set out in the Guidelines for Good Clinical Practice (GCP).

6.0 Patient safety
6.1 In all the deliberations of the TSC, the rights, safety and well-being of trial participants are the most important considerations.
6.2 The Chief Investigator will provide the TSC with sufficient information to enable it to assess the quality of the patient consent process.
6.3 The TSC will advise the investigators on the continued completeness and suitability of the patient information provided.

7.0 Progress
7.1 It is the role of the TSC to monitor the progress of the trial and to maximise the chances of completing the trial within the agreed time scale.
7.2 At the first TSC meeting targets for recruitment, data collection, compliance, etc. will be agreed with the Chief Investigator.
7.3 Targets will be used to compile a template for presentations to all further meetings.
  7.3.1 The Chief Investigator will submit biannual reports to NETSCC, HTA based on this template.
  7.3.2 These reports will be endorsed by the TSC prior to submission.

8.0 Adherence to protocol
8.1 The full protocol will be presented and agreed at the first TSC meeting.
8.2 Subsequent changes to the protocol will require approval from the TSC.
  8.2.1 The Chief Investigator will inform REC, NHS R&D and HTA of any changes.

9.0 Data Monitoring and Ethics Committee
9.1 The DMEC will meet regularly to review the data and results of any interim analyses.
9.2 Members of the DMEC will be independent of both the trial and the TSC.
9.3 The DMEC will produce summary reports after each meeting for consideration by the TSC.

10.0 Consideration of new information
10.1 The TSC will consider new information relevant to the trial (including DMEC).
10.2 It is the responsibility of the Chief Investigator, the Chairperson and other independent members to bring results from other studies that may have a direct bearing on the future conduct of the trial to the attention of the TSC.
10.3 On consideration of such information, the TSC will recommend appropriate action such as changes to the protocol, additional patient information, or stopping the trial.
10.4 The rights, safety and well-being of the trial participants will be the most important consideration in this regard.
10.5 It is the responsibility of the Chief Investigator to notify the TSC, DMEC and relevant regulatory authority immediately of any unexpected serious adverse events occurring during the course of the trial.

Suggested template for Trial Steering Committee agendas and reports

The list below outlines the information that will be provided by the Chief Investigator at each meeting. This list will be used as a basis for the agenda of TSC meetings and a template for biannual reports to NETSCC, HTA:

- trial progress (with respect to targets)
- recruitment to date (with respect to targets)
- follow-up to date (with respect to targets)
- AEs
- DMEC report
- issues/problems (specifically since last report)
- new information
- changes to protocol.

Appendix 23

Data Monitoring and Ethics Committee – membership and terms of reference

DMEC membership

Research expertise – Chairperson
Professor Richard Lilford
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No longer a current member
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DMEC role

The DMEC is the only body involved in the trial that has access to the unblinded comparative data. Its role is to monitor these data and make recommendations to the TSC and NETSCC, HTA on whether there are any ethical or safety reasons why the trial should not be continued.

All members of the DMEC are independent of the trial they are monitoring.

The DMEC Chairperson organises work related to the trial. The DMEC includes a statistician and a clinically qualified specialist in the field of physiotherapy.

The Chief Investigator and the Chairperson of the TSC will agree with the DMEC Chairperson a timely mechanism for reporting to the DMEC. With the help of the trial statistician, the Chief Investigator will provide blinded data, in strict confidence, to the DMEC as frequently as the members of the DMEC request. A template for reporting interim data will be used by the Chief Investigator (Appendix I).

The DMEC discusses the data on AEs and efficacy data, either in a meeting or by teleconference. If necessary, it may request further data from the Chief Investigator and trial statistician. In the light of interim data, and other evidence from relevant studies (including updated overviews of the relevant randomised controlled trials), the Chairperson of the DMEC informs the Chairperson of the TSC if, in its view, the trial should proceed or be terminated.

Unless cessation of the trial is recommended by the DMEC, the TSC, Chief Investigator and Trial Manager will remain in ignorance of the results of the interim analysis of efficacy.

The DMEC may also advise the TSC on modification of the protocol.

DMEC terms of reference

1. To meet at least once a year during the course of the trial (either at a meeting or by teleconference).
2. To set up and maintain direct communication with the Chief Investigator and Chairperson of

the TSC. The Chairperson of the TSC will be made aware of all communication between the Chief Investigator and DMEC.
3. To receive a copy of the trial protocol and any plans for interim analysis as early as possible in the conduct of the trial.
4. To receive reports (as per the template in Appendix I) during the trial at intervals agreed with the TSC and Chief Investigator.
5. To consider data from interim analyses, unblinded if considered appropriate, plus any additional safety issues for the trial and relevant information from the template and other sources.
6. To report to the TSC and recommend on the continuation of the trial.

DMEC output and reporting

1. The first meeting of the DMEC is an open meeting with the Chief Investigator. The output of that meeting includes agreement on the relevant material that needs to be reported subsequently.
2. The report of the trial statistician to the DMEC is seen only by DMEC members. Each meeting is summarised in the form of brief minutes.
3. The Chairperson of the DMEC provides a brief summary of the recommendations of each meeting to the TSC, Chief Investigator and NETSCC, HTA.

Appendix 1 Template for Chief Investigator's report to DMEC

Date of report:

1. Title of trial:

2. Trial progress
   - 2.1 Trial recruitment
     - 2.1.1 Plan of recruitment
       - Start date of recruitment
       - End date of recruitment
       - Recruitment period
       - Expected average monthly recruitment
       - Recruiting centres
     - 2.1.2 Recruitment to date
       - Recruitment period to date
       - Total recruitment to date
       - Observed average monthly recruitment
       - Recruitment stratified by centre
       - Expected recruitment period (based on current recruitment rate)
       - End date of recruitment (based on current recruitment patterns)
       - Graph showing the planned and actual recruitment rates
     - 2.1.3 Recruitment based on eligibility
       - Inclusion/exclusion
       - Number ineligible
       - Non-consent
       - Protocol violation
   - 2.2 Internal validity
     - 2.2.1 Comparability of selected baseline characteristics between the treatment groups
   - 2.3 External validity
     - 2.3.1 Selected baseline characteristics of subjects in high and low recruiting centres
   - 2.4 Protocol compliance
     - 2.4.1 Number of patients withdrawn from treatment but continued being followed up
     - 2.4.2 Number of patients who have been lost to follow-up
     - 2.4.3 Number of patients with missing follow-up data
     - 2.4.4 Number of patients who have crossed over to alternative treatment

3. Safety data – to be presented overall and by blinded group
   - 3.1 Serious adverse events*
   - 3.2 Other adverse events

4. Details of new information since start of trial/last report
   - 4.1 Publications
   - 4.2 National or international guidelines on the treatment of the disease

*A serious adverse event (SAE) is defined as any untoward medical occurrence or effect that:

- results in death
- is life-threatening (i.e. with an immediate, not hypothetical, risk of death)
- requires hospitalisation or prolongs existing hospitalisation (excluding hospitalisation for elective treatment of a pre-existing condition)
- results in persistent or significant disability or incapacity

or any other important medical condition which may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above (e.g. bronchospasm requiring intensive emergency treatment).

Appendix 24

Action plan to improve questionnaire response rates

1. Trial recruiters to assess at baseline whether the patient may have particular difficulties that might lead to a non-response (e.g. literacy level, very poor eyesight, changing home circumstances). For these patients, alternative methods/routes for data collection are to be negotiated (e.g. identifying a relative/friend to help with completion, large-type questionnaires, telephone call, home visit).
2. Compile a follow-up database containing information on follow-up due dates and questionnaire returns. Include information on patients with special needs and routinely update database when new information becomes available. Scrutinise database before questionnaires are sent out.
3. Conduct a weekly audit to identify overdue questionnaires (i.e. 3 weeks after sending). For overdue returns, check hospital/GP records to establish patient status (i.e. still alive, still at the same address). If all is well, telephone the participant to enquire whether they received their questionnaires and/or whether they require help to complete them.
4. Where it is not possible to contact the patient by telephone, issue a reminder letter that offers support if required.
5. If/when a 'non-responder' is readmitted to hospital, trial recruiters are to offer help to complete duplicate questionnaires. (Note: this tactic is dependent on the admission being within 2 weeks of the planned follow-up date.)
6. When undertaking follow-up strategies, priority is to be given to completion of the primary outcome measure (SGRQ) at the primary end point.

A 3-month audit conducted in October 2007 indicated the following action plan activities:

- 49 reminder telephone calls conducted
- six reminder letters issued
- four patients identified as deceased
- three follow-ups administered in hospital
- two nursing home visits to help complete questionnaires
- one patient identified as having moved.

Appendix 25

Data quality audit (conducted February 2009)

Total participant record set *N* = 526	**Paper record check[a] *n* = 26 (5% sample)**			**Double data entry[b] *n* = 125 (23% sample)**		
Data	**Cells checked**	**Errors found**	**% Error**	**Cells checked**	**Errors found**	**% Error**
MRC-D score	26	0	0	121	2	1.6
SGRQ score	3900	11	0.2	6032	45	0.7
BCSS score	1124	2	0.2	5775	121	2.0
EQ-5D score	671	3	0.4			
Other participant data[c]	585	5	0.8			
Use of hospital services	891	22	2.4			
Total	7197	43	0.59	11,928	168	1.40

a Paper record check: electronic database entries crosschecked against original paper records. Sample comprises 5% random sample from full data set (*N* = 526).
b Double data entry: questionnaire data entered twice on electronic database and compared. Sample comprises all questionnaire returns from participants recruited before 1 January 2007.
c Includes treatment episodes and participant demographics.

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We look forward to hearing from you.

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