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The MATREX trial
MAnual Therapy for
Respiratory EXacerbations

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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).

1 Research objectives

1. a) To estimate the effect, if any, of physiotherapy interventions involving the manual techniques of chest percussion and vibration, administered to COPD (Chronic Obstructive Pulmonary Disease) patients with infective exacerbations during consecutive hospital admissions for 6 months, on respiratory status, quality of life and total number of hospital days during follow-up.
1. b) To undertake a pre-specified sub group analysis comprising separate analysis of subjects producing ≥ 15 mls and <15 mls of sputum per 24 hour period during hospitalisation period.
2. To compare costs incurred by the patient, the NHS and society between patients who either receive, or do not receive manual chest physiotherapy whilst in hospital.
3. To estimate the incremental cost-utility ratio comparing manual chest physiotherapy with no manual chest physiotherapy.

2 Background

While manual respiratory physiotherapy techniques have long been used in the treatment of respiratory conditions, strong evidence for the benefits of this intervention is lacking. The Cochrane Airways Group reported on the evidence for these techniques in both COPD and Bronchiectasis[1]. Their report looked at seven randomised controlled trials and found a paucity of usable evidence. The available studies were heterogeneous (both statistically, in terms of the interventions delivered and the setting in which they were delivered) and generally of low quality. The evidence that does exist reports mixed effects for manual techniques – both negative (i.e. falls in arterial oxygen saturation/ tension and falls in lung function measures) and positive (i.e. sputum removal).

In 2001, this study's Principle Investigator (J Cross) led a comprehensive review of the literature regarding manual techniques[2]. The project was commissioned by the Association of Chartered Physiotherapists in Respiratory Care and its remit was to identify and critically review the literature relating to the use of manual techniques (i.e.

chest percussion and vibration) in relation to mobilisation and clearance of secretions in respiratory physiotherapy. The review focused on patients with compromised respiratory function and impaired mucocillary 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 emerge from this literature review and these are reported below.

Eight papers report designs which separately evaluated a specific manual technique, using secretion clearance as the main outcome. 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. Of these eight studies, four found no evidence that manual techniques conferred greater efficacy. The remaining four found that; manual percussion was associated with sputum mobilisation[3], vibrations and percussion were associated with an increased wet weight of sputum[4], a significant increase in sputum clearance at 60 minutes post treatment with mechanical vibration but no difference over 24 hours[5], and a significant increase in sputum with manual percussion (with fast manual percussion producing the greatest sputum volume 60 minutes after treatment) [6]. Chest physiotherapy, including manual techniques appeared inappropriate in acutely ill patients with little or no sputum and on occasion was associated with oxygen desaturation, V/Q (ventilation/perfusion ratio) mismatch, a decrease in FEV_1 (forced expiratory volume in one second) and bronchospasm. In patients with copious secretions movement of sputum was more likely to relieve airway obstruction.

In many studies the effect of manual techniques independent of encouragement to cough was not separately determined. However, Rossman[7] reports that cough alone appeared as effective as manual techniques whilst De Boeck[8] finds no clear benefit of chest physiotherapy over cough alone. The long term benefit of increased short term sputum clearance is still under debate as studies show an increase in volume following treatment which is not maintained over 24 hours[9].

Lung Volume measures
Manual techniques have sometimes been reported as producing falls in lung volumes. Campbell[10] compared two groups of patients with chronic bronchitis and applied chest percussion in a postural drainage position. They report 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, this study does not report how much sputum these subjects were producing and whether they had been tested for airway reversibility prior to the study.

Newton and Stephenson[11] consider 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. They find no change in

FEV_1, vital capacity, specific conductance or arterial blood gases (ABGs). However, Functional Residual Capacity (FRC) and airway conductance and resistance were all seen to increase after these manoeuvres. Whilst this study does support the view that manual chest therapy may not be appropriate in small sputum producers, the precise physiotherapy techniques used are inadequately described. May and Munt[12] suggest that FVC increases with both chest physiotherapy and cough alone, though neither technique shows an advantage over the other.

Feldman and Traver[13] used a mixed group of patients with either chronic bronchitis or Cystic Fibrosis (CF) characterised by chronic copious sputum production. They found chest physiotherapy produced a significant improvement in lung function, predominately at low lung volumes, and that the effect can persist for 45 minutes after treatment. However, the heterogeneous nature of their study group raises the possibility that these benefits may be confined to higher sputum-producing CF patients.

Rivington-Law[14] conducted a cross-over study of 12 patients, all with chronic bronchitis according to the ATS classification. 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.

De Boeck[4] performed a cross-over 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.

Sputum Clearance

Bateman[15] 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 100mls 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[16] also studied six patients with Chronic Obstructive Airway Disease (COAD)/Bronchiectasis (3 female), in a repeated measures design. Researchers compared control (no cough), with cough alone and with chest physiotherapy (CPT) and cough. They report significantly greater clearance of radioactive aerosol for both intervention modalities compared with control. However, only CPT produced a significant difference in clearance from the peripheral areas of the lungs. ($p<0.05$). Sputum weights for CPT were also significantly greater ($p<0.05$).

Wollmer[17] undertook a study in which inhalation of radio-labelled particles (aerosol scintigraphs) was employed to measure particle deposition and clearance during chest physiotherapy. Although there was no overall affect on the deposition and clearance of radio-labelled particles, two patients with the highest sputum production (100ml 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[18] investigated the effect of manual percussion as a single procedure as well as in combination with postural drainage (PD), coughing and breathing exercises on tracheo-bronchial clearance in patients with chronic airflow obstruction (CAO) and excessive tracheo-bronchial secretions. Again the study was small (only nine subjects) but PD and coughing, with or without manual percussion, did appear to improve mucocillary 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
Connors[19] is often quoted to substantiate the claim that chest physiotherapy produces hypoxaemia. However, this study has significant methodological and analytic weaknesses. May and Munt[12] report no significant effect (clinical or statistical) of manual techniques on either O_2 or CO_2 levels. Buscaglia[20] presents a well designed study of a homogenous group of patients, supporting the evidence that patients' response to CPT in terms of oxygenation depends on the amount of sputum produced. Wollmer[17] finds no significant difference in arterial oxygen saturation (SaO_2) between pre and post treatment values, either with or without percussion.

Summary
The numbers of patients investigated in the studies described above are small and the focus is on very specific groups of patients. As a consequence, it is difficult to generalise these findings to the total population of patients with acute exacerbation of COPD. In consequence, it is reasonable to suggest that there is a clear state of clinical equipoise as to whether manual physiotherapy techniques actually confer even short term benefits upon patients with COPD. Cross-over 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.

The literature presents a clear case for the need for further rigorous research. Recently published clinical guidelines from the National Institute of Clinical Evidence (NICE) on the management of COPD reiterate this view[33]. A parallel group randomized controlled trial allows the evaluation of the effectiveness and cost effectiveness/utility of manual techniques in COPD patients. Sufficient numbers of patients are required to confer adequate statistical power and maximise generalisability to the target population.

3 Rationale for trial outcome measures

Quality of Life (QOL)

COPD is a life limiting condition with considerable effect on quality of life. A recent study of 141 COPD patients admitted to a District General Hospital for exacerbations (mean age 70) when compared with patients in the non-exacerbated state, reports a considerable loss of health utility with the majority of patients indicating a state regarded as 'worse than death' (mean Health Utility: - 0.21) [26]. The adverse impact on health utility appears to be greater with increasing severity of COPD.

The choice of outcome measure appropriate for a trial of this type is contentious due 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 which has often not been addressed. The choice of outcome measures in this study is therefore predicated on the assumption that long term effectiveness must be based largely on quality of life considerations. Physiological measures may however provide useful short term indicators of effectiveness and are therefore included as secondary measures in this study.

The quality of life outcome measures chosen for this trial include the St George's Respiratory Questionnaire (SGRQ)[21] and the Breathlessness, Cough and Sputum Scale (BCSS)[22].

The SGRQ is the primary outcome measure selected for this study on which the sample size Power calculation is based. It is a self-completed questionnaire containing 76 items divided into 3 domains. These are:

1) Symptoms: frequency of cough, sputum production, wheeze, breathlessness and duration and frequency of attacks
2) Activity: physical activities that either cause or are limited by breathlessness
3) Impact: employment, being in control of health, panic, stigma, need for medication and side-effects, health expectations, disturbances in daily life

The SGRQ was developed specifically for patients with COPD. It provides valid and reliable measures of respiratory symptoms and is sensitive to changes in objectively measured respiratory function. It has been extensively used in randomised trials of rehabilitation and early discharge of COPD patients[23] and has been rated as easy to use by 90% of subjects[24]. It correlates well with the Quality of Life measure SF36 but not with the EuroQol (EQ-5D) [25] thereby providing a degree of independence in QOL assessment.

The 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 new scale has demonstrated strong correlation with cough-specific items from the SGRQ[22]. Validation of this tool suggests that the BCSS is able to demonstrate sensitivity to within-group change and between-group differences.

The EuroQol five dimensional instrument (EQ-5D) will be used in a complementary fashion with the other outcome measures to determine health-related quality of life

changes occurring in both groups. The EQ-5D is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and well validated single index value of health status. It is suitable for both clinical and economic evaluations of health care as well as population health surveys. The current 3-level, 5-dimensional format of the EQ-5D is unlikely to be changed in the immediate future. EQ-5D is designed for self-completion by respondents and is ideally suited for use in postal surveys, in clinics and face to face interviews. It is cognitively simple, taking only a few minutes to complete.

Cost Effectiveness/utility
Hospital admissions have a demonstrable effect on the quality of life of a person with COPD. Additionally, there are cost implications for what are after all prolonged and repeated hospital stays. Costs include the direct treatment costs both in the hospital, out-patient and community setting. There are also costs to society including lost working days and working days lost by carers; personal costs incurred by patients and family in their treatment (e.g. 'over the counter' medications, travel to health services and pharmacists, costs of running oxygen concentrators at home, adaptations to homes for chronic sufferers and hire of other equipment etc.).

Data will be collected on both direct and indirect costs incurred during the initial hospitalisation. Patient costs post-discharge will be collected via a self-complete questionnaire detailing on-going use of health services and wider social support received. Analysis of the total and disaggregated SGRQ scores will be made and combined with costings data to compile cost-effectiveness ratios and cost per functional improvement scores.

Physiological impact
With regard to the physiological impact of manual physiotherapy techniques for COPD, useful indicators suggested by the literature are the short term impacts on sputum volumes and oxygen saturation[18]. As some research suggests lung function measures are useful predictors of morbidity but of little value in predicting quality of life, this outcome is not included other than as a baseline indicator of severity of disease.

With respect to longer term physiological impacts, The 6 Minute Walk Test[28] (6MWT) is easy to administer, tolerated well by patients and more reflective of daily living than other walk tests and is regarded as the most useful functional walk test for research purposes[29]. The 6MWT will be completed at 6 months post intervention on a sample of subjects.

4 Research design
A single blind, parallel group, non-superiority, randomised controlled trial (RCT)

5 Setting
A multi-centre trial involving 4+ teaching /district general hospitals across the UK

6 Target Population
Patients admitted to participating hospitals with infective exacerbations of COPD.

7 Sample selection
All patients admitted to the participating hospitals with an infective exacerbation of COPD will be potentially eligible. Patients fulfilling the eligibility criteria for the trial and giving written informed consent will be randomly allocated to either experimental or control group. Randomisation will be blocked (block length 6) and stratified by hospital.

Inclusion Criteria:

1. Diagnosis of COPD as defined by the British Thoracic Society[35]; namely,
   a) progressive, predominantly irreversible airflow obstruction in which
   b) the forced expiratory volume in the first second (FEV_1) is <80% of the predicted value
   c) and FEV_1/FVC (forced vital capacity) is less than 0.7
2. A COPD exacerbation as set out by the British Thoracic Society[35]; namely,
   a) a sustained worsening of the patient's symptoms from his or her usual stable state that is beyond normal day-to-day variations,
   b) The exacerbation is acute in onset
   c) symptoms may include worsening breathlessness, cough, increased sputum production and change in sputum colour

Exclusion Criteria

1. Cognitive impairment, rendering patients unable to give fully informed consent
2. Contraindications to the use of manual techniques[34]; namely,
   a) Osteoporosis
   b) Frank haemoptysis
   c) Bronchial hyper-reactivity
   d) Known respiratory system malignancy
   e) Raised intracranial pressure
   f) Uncontrolled hypertension (diastolic > 110)
   g) Pulmonary Embolism
   h) Coagulopathy (platelets <50 and/or INR ≥3)
   i) Bronchopleural Fistula
   j) Subcutaneous Emphysema
   k) Left Ventricular Failure as primary diagnosis
3. No evidence of excess sputum production after examination (i.e. the patient does not report excess secretions and no signs of excess secretions on auscultation).

8 Planned interventions

Intervention arm

Participants will receive the respiratory manual techniques of percussion and vibration. A standard treatment protocol manual, in accordance with normal NHS clinical care, will be followed by all the participating hospitals (Appendix 1). This manual has been developed with the clinical staff involved in the trial in order to minimise variation in practice and optimise compliance. It comprises an amalgam of current practice and best research evidence to date. Treatment will be applied with the patient positioned according to an agreed protocol for optimal drainage of secretions. The chest will be percussed whilst the patient performs thoracic expansion exercises with vibration applied on expiration. Treatment will be interspersed with periods of relaxed abdominal breathing and directed coughing to enable chest clearance.

Participants will also be given an information sheet giving advice on positioning, managing cough and mobilisation (Appendix 2). The content, number and duration of treatments will be at the discretion of the physiotherapist applying treatment, within the bounds set by the manual and will be varied according to clinical need. The precise nature of each therapeutic intervention will be recorded. Oxygen saturation will be monitored and recorded during treatment. Once the patient has returned to his/her normal stable saturation, monitoring will stop. Sputum produced in each 24 hour period will be collected and its volume measured throughout each hospital admission.

Control arm

Participants will receive no manual chest physiotherapy. They will be given the same information sheet giving advice on positioning, managing coughing and mobilisation by a physiotherapist. 24 hour sputum volumes will be measured as for the intervention group.

Group allocation protocol

The Medical Research Council Scale for dyspnoea[31] will be administered to compare levels of severity of COPD in patients across the two arms of the trial. Usual sputum volumes will also be ascertained by self report. In both trial arms, usual volume of sputum produced will be ascertained during the baseline physiotherapy assessment based on the patient's own estimate.

Once randomised to an arm, each patient will remain in that arm for the duration of the study. Patient medical records will be marked, identifying the arm of the trial to which they have been randomised. Patients will be issued with a card containing the same information. For patients in the control arm who show severe deterioration due to sputum retention, additional physiotherapy including manual techniques will be permitted. Such movement between trial arms will be monitored closely. Movement between arms will occur where there is clear clinical evidence of sputum retention (auscultation/ chest x-ray evidence) in conjunction with a pH of less than 7.26, a rising CO2 in patients already receiving supportive treatment and controlled oxygen therapy [27]. The primary analysis will be intention to treat. A per protocol analysis will be performed as a secondary analysis, with adjustment for baseline differences.

9 Outcome measures

Primary

1 Quality of Life: St George's Respiratory Questionnaire(SGRQ)
Administered at randomisation and at 6 weeks and six months.

Secondary

2 Breathlessness, Cough and Sputum Scale (BCSS)
Administered daily for one week post completion of SGRQ
3 EuroQol five dimensional instrument (EQ-5D)
Administered at randomisation and at 6 weeks and six months
4 Sputum volume and oxygen saturation
Compiled for each 24 hour period during hospitalisation
5 Number of days spent in hospital
Total during 6 months post intervention.
6 Cost Questionnaire
Administered at randomisation and at 6 weeks and six months.
7 Incremental cost effectiveness ratio for manual versus no manual chest physiotherapy
Composite measure derived from costing & QOL data
8 The 6 Minute Walk Test (6MWT)
Conducted at 6 months post intervention

A flow diagram summarising the sequence of data collection is provided in Appendix 3. Copies of questionnaire-based outcome measures are provided in Appendix 4.

10 Sample Size

Based on the primary outcome measure, SGRQ: Treating this study as non-superiority, where an Effect Size of 0.3 (typically considered small) is considered 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 is required. Allowing for 15% loss to follow-up a total of 550 patients will need to be randomised.

Sample size required for 6MWT: A sub-group of 114 per trial arm will confer 90% Power (5% significance) to detect a clinically significant difference in mean distance of 54m, assuming a Standard Deviation of 125m [29,30].

11 Integrated Health Economic evaluation

The economic evaluation component of this study will use both the SGRQ and the EQ-5D quality of life (QoL) scores to assess the cost effectiveness of the intervention. This will proceed alongside the clinical evaluation as befits recommended 'best practice[32]. Both instruments are well validated and applicable to COPD patients. Although the EQ-5D could be regarded as a rather 'blunt instrument' to identify small changes in QoL, given its wide usage in health service research it is important to include it in the analysis as there is no *a prior* reason to assume the extent of the intervention's impact. 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 will be compiled and analysed using both total and disaggregated scores.

In both the intervention and control arms, direct inpatient costs will be compiled from information recorded in patient notes (e.g. diagnostic tests, medications etc) and data collected during the trial itself (e.g. hands-on time spent by physiotherapists and other clinicians as a consequence of delivering the protocol etc). Indirect inpatient costs will be inferred from each hospital's cost per day information.

To calculate patient costs post-discharge, a cost questionnaire will be administered to patients alongside QOL instruments at each follow up. Health Service use declared by patients will be cross-checked with the relevant hospital/primary care records (Appendix 5). A menu of 'standard' direct costs (e.g. GP visit) will be derived from published Health Economics literature to ascribe monetary values to each activity recorded.

12 Data management & statistical analysis

All data will be collected and managed in accordance with Good Clinical Practice (GCP) research standards. Details of data management systems and functional specifications are provided in Appendix 6. The analysis will be conducted on an intention-to-treat basis with quality of life as the primary outcome. A regression model will be used to model data obtained from the St Georges Respiratory Questionnaire, with treatment group and hospital assigned as independent factors. Any variables found at baseline to exhibit a disparity between groups will be included in the model. The null hypothesis for the study will be one of superiority. If the upper bound of a 95% confidence limit exceeds an Effect Size of greater than 0.3 then the null hypothesis will be accepted.

Data on the total number of days each patient spends in hospital during follow-up will be ascertained from participating hospital PAS systems and cross checked against self reported episodes of hospital admission. A Poisson regression model will be used to analyse number of bed-days with hospital as a covariate.

A sub-group analysis based on sputum levels will be performed using a similar modelling approach by including a 'sputum level with treatment group' interaction term.

Analysis of the remaining variables will be through linear regression, with or without transformations as appropriate.

13 Consumer involvement

Protocol development has included consultation with the local service-user group 'Breathe Easy' (a charitable organisation affiliated to the British Lung Foundation) In particular, the group have highlighted the need for clarity in establishing precise treatment protocols for each trial arm and the importance of consistency in health care delivered. Random allocation to intervention and control arms is not regarded as unduly problematic providing a clear protocol is provided regarding participants who deteriorate and require more intensive physiotherapy. The Patient Information Sheet has also been developed in conjunction with this user group. Continued consumer involvement regarding trial setup and on-going conduct will be achieved via a service user sitting on the Trial Steering Committee.

With respect to trial publicity, Breath Easy has undertaken to circulate trial information to group members. Local GP surgeries will be asked to display posters about the study and provide information sheets upon request. The study is fortunate in being able to draw upon the expertise of a pilot project being led by Norwich PCT and UEA (Principle Investigator, Amanda Howe, Professor of Primary Care) which is compiling a local research-user register and developing new ways of engaging consumer groups in research design and execution.

14 Ethical considerations

Whilst the evidence for manual chest physiotherapy techniques remains scant, these continue to be used to treat infective exacerbations of COPD. Clinicians, both physiotherapists and respiratory physicians alike, agree that a state of clinical equipoise exists in this issue. Nonetheless, the acceptability of the RCT method, particularly in acute settings, is highly dependent on good communication between researchers, clinicians and patients. Employing defined, reproducible criteria has the advantage of enabling control subjects to receive manual physiotherapy if they deteriorate to a defined extent. Current clinical criteria used for admission of COPD patients to a high dependency unit will be used as the basis for switching between trial arms and the extent of 'contamination' will be assiduously documented.

15 Informed consent procedure

Patients identified as eligible to participate will have the trial introduced to them and given a Patient Information Sheet (Appendix 7). Clinical and research staff will be available to discuss any issues the patient may have before written informed consent is obtained (Appendix 8). This consent will include permission to access hospital and GP records.

16 Trial documentation retention

All documentation relating to the trial will be retained by the host institution for a period of 5years from completion of the study

17 Research Team

The multi-disciplinary project research team has extensive experience of interdisciplinary research in health care settings and includes a wide range of research and clinical skills, specifically clinical trial design, health economics, medical statistics and physiotherapy skills.

Principle Investigator

Jane Cross is nationally recognised as a leader in the field of respiratory physiotherapy and has been Chair of the Association of Chartered Physiotherapists in Respiratory care. She led the review work of this group in the field of manual respiratory physiotherapy techniques and has published in the field of respiratory physiotherapy.

Other grant holders:

- Professor Ian Harvey is currently involved in three large randomised trials; ELEVATE, and BECCA are both funded by the NHS R&D HTA programme and

HEARTMED is funded by the British Heart Foundation. In total, these trials are recruiting 1500 subjects from secondary and primary care. His research team has extensive experience of in-hospital recruitment of older subjects and he has strong clinical links with participating hospitals in this study through the East Anglian Confidential Enquiry into Asthma Deaths.

- Professor Max Bachmann is a clinical epidemiologist with extensive experience of design and analysis of randomised trials, including a WHO-supported trial of integrated management of lung disease in primary care, a randomised trial of smoking cessation and several epidemiological studies of occupational respiratory disease.
- Dr Richard Fordham has undertaken several international economic evaluations in respiratory medicine including; assessments of physiotherapy, sleep apnoea, COPD and asthma interventions.
- Dr Lee Shepstone: Medical Statistician, University of East Anglia.
- Dr Simon Watkin: Consultant Physician, Respiratory Medicine, Norfolk & Norwich University Hospital NHS Trust.
- Dr David Ellis: Consultant Physician, Respiratory Medicine, James Paget Healthcare NHS Trust.
- Rachel Ellis: Superintendent Physiotherapist, Norfolk & Norwich University Hospital NHS Trust.

Trial Management

Our understanding of large and complex hospital based Randomised Controlled Trials has led us to ensure the provision of active recruiters based within the hospitals involved in the trial. The training of these individuals will be based upon our experience of recruiting patients who are unwell and vulnerable into other trials. Research Associates (RAs) will identify, recruit and randomise patients and collect baseline data. In order to maintain assessor blinding, RAs will collect follow up data from a different recruitment site (i.e. an individual will be responsible for recruitment in one hospital and for follow-up in another). Funding also includes provision for a specialist health economics RA to take responsibility for the management of complex health economics data. A full time Trial Manager will co-ordinate the extensive data collection and analysis involved with this project, liaise between the research and clinical teams and oversee the activities of the RAs and a dedicated trial secretary.

18 Trial supervision and monitoring

A Trial Management Group (TMG), comprising academic and clinical leads, will oversee the day to day running of the trial. A Trial Steering Committee (TSC), with terms of reference conforming to MRC/DH standards, will be responsible for the trial's overall quality and compliance with Research Governance principles. A Data Monitoring & Ethics Committee (DMEC), comprising independent experts will evaluate ongoing data quality, assess the need for interim analyses and evaluate ethical issues arising during the conduct of the trial.

The TMG and DMEC will report to the TSC at regular intervals.
The TSC will report to the trial's sponsor (NHS R&D HTA) at regular intervals.

19 Project milestones (achieved to date & planned):

Time frame	Date	Milestone
0-6 months	01/03/2005	Trial protocol development Treatment protocol development Establishment of TSC and DMEC Research staff recruitment and training COREC & NHS R&D approval for pilot
7-12 months		Pilot study- NNUH Baseline assessments and data entry Development of CRFs and data management SOPs
@ 12 months	01/03/2006	Report to Sponsor COREC & NHS R&D approval to extend pilot
12-18 months		Pilot extended - JPH
@ 18 months		Report to Sponsor Study Protocol & Trial documents amended COREC & NHS R&D approval to proceed to main trial
@ 21 months		Main trial starts – NNUH, JPH, QEH
@ 24 months	01/03/2007	Monitoring visit by Sponsor to agree: 1 Trial extended to 4th site to boost recruitment 2 Recruitment timeframe extended by 12 months 3 Follow up timeframe reduced by 6 months
@ 26 months		Trial extended to University Hospital Aintree
@ 30 months		NREC approval for Study Protocol amendments Last patient recruited to be followed up for 1 year
@ 36 months	01/03/2008	Closed to recruitment
@ 42 months		Closed to follow-up
42-45 months		Data analysis
46 - 48 months		Write up & Dissemination
@ 50 months	01/05/2009	Project ends

Abbreviations:
TSC – Trial Steering Committee
DMEC – Data Monitoring & Ethics Committee
CRF – Case Report Form
SOP – Standard Operating Procedure
COREC – Central Office for Research Ethics Committees
NREC – National Research Ethics Service

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