NCCHTA

18th April 2007

01/15/10: A randomised 2x2 trial of community versus hospital rehabilitation, followed by telephone or conventional follow up; impact on quality of life, exercise capacity and use of healthcare resources

1 The change of project since outline proposal submitted

The fundamental design of the project remains as per the original outline proposal. The core remains a 2 x 2 design, with patients randomised to receive rehabilitation in either a hospital or community setting, followed by either telephone or conventional follow up. The following changes have been made;

- In addition, it is proposed to collect additional qualitative data to help clarify the cause of any differences in outcome, together with further patient characteristics to amplify the main outcome data.
- In order to ensure this major study is carried out robustly, we have also planned for additional personnel for trial management and data processing.
- Those playing a major role within the steering and scientific committees are defined as applicants. Others whose skills will be drawn on within an advisory committee are defined separately.

2 Planned Investigation

2.1 Introduction

Chronic obstructive pulmonary disease (COPD) has a high prevalence throughout the world, and is on the increase (1). This has been emphasised in Sheffield by the SHAIPS2 survey, which shows a particularly high prevalence of COPD in the city, where nearly 10 % of the population over 45 years of age have symptoms of the disease. SHAIPS2 also demonstrated a tight association of disease incidence with indices of deprivation and heavy use of healthcare resources (2). In addition to being an important cause of death, the chronic impairment and disability that can result gives rise to both poor quality of life for the individual, and a major economic burden for society (3). By definition, the pulmonary impairment of COPD represents permanent damage that is largely irreversible. Only smoking cessation and long term oxygen therapy (where appropriate) have been shown to have an effect on survival in COPD. The goal of all other therapies is to limit the effects of the disease and endeavour to enhance the patient's quality of life (3).

Three major societies, the British Thoracic Society, the American Thoracic Society and the European Respiratory Society have produce guidelines on COPD. These differ in classification of disease, and in advice in important areas such as use of glucocorticosteroids and theophyllines (4). However, all are agreed that pulmonary rehabilitation is an efficacious treatment that should be widely available. This view was further endorsed by a consensus conference of the Royal College of Physicians held in 2001, the proceedings of which are currently in press, and a meta-analysis of trials has formally confirmed their efficacy in enhancing exercise capability (5).

During the course of COPD, exercise capacity and quality of life are decreased by a number of factors. Although the disease is defined in terms of a test of respiratory function, the FEV_1 (3), this measure actually correlates quite poorly with both quality of life and exercise capacity (6). Often, there is a loss of muscle mass and evidence of detraining (7). A vicious circle is established in which a breathless patient begins to exercise less, so becomes less fit. Exercise is then harder and thus is curtailed further, perpetuating the cycle of decline.

The aim of pulmonary rehabilitation is to arrest this cycle. A key component of the programme is thus an exercise training programme to enhance cardiovascular and muscular fitness. However, the cycle of decline will be re-established after the programme has stopped unless it is successful in engendering a fundamental shift in the patient's lifestyle. To encourage such lifestyle changes it has become conventional to add an educational programme. One key aim of this is to enable the patient to gain a good understanding of their condition, and thereby to play a key self-management role. It is expected that the patient will make positive choices particularly to maintain increased exercise levels.

The Sheffield COPD Group has adopted the following definition of pulmonary rehabilitation in order to emphasise this;

"'Pulmonary rehabilitation' is the process of assisting people with respiratory disease to live their life to their full potential, using individualised exercise training with health and lifestyle education, usually within the context of a group".
That a relatively brief period of pulmonary rehabilitation (6 to 12 weeks) can produce an effect that persists as long as 2 years (8) demonstrates that a change in behaviour is occurring, as the effects of exercise training alone would be expected to have vanished long before. Existing research has tended to focus on direct effects of the exercise programme without examining the wider context in which this exercise occurs takes place. A given exercise could, for instance, be viewed as challenging, frightening, exciting, or impossible, depending on the context in which it is presented, and the willingness to voluntarily repeat the exercise would vary as a consequence. The cost-effectiveness of an intervention will critically depend on the duration of effect, yet this has been little studied. The proposed study intends to examine whether the physical context within which the rehabilitation programme occurs is key in determining future outcome, and whether a simple, low cost continued intervention may prolong the treatment effect. It proposes to examine in detail the cost-effectiveness implications of this.

2.2 Research objectives

This research proposal intends to answer the following questions;

- Is pulmonary rehabilitation delivered in a hospital outpatient or a community setting more efficacious in acute and long term effects on exercise capacity and health related quality of life?
- Is intermittent telephone follow up efficacious in prolonging the beneficial effects of pulmonary rehabilitation on exercise capacity and health related quality of life?
- What is the cost-effectiveness of these interventions in pulmonary rehabilitation services?

2.3 Existing research

Generally, effects of pulmonary rehabilitation decline over one to two years (9). It is reasonable to assume that patients who continue to exercise at the end of a rehabilitation programme will experience sustained benefits. Grosbois et al, who adopted various strategies for continuing exercise after pulmonary rehabilitation, have formally shown this. Only those with a continuing exercise maintenance programme demonstrated continuing benefit at 18 months in this particular study (10), with more vigorous interventions producing greater gains. Nevertheless, the fact that benefit may be detectable 2 years after a relatively brief intervention in some studies suggests patients may modify their behaviour after pulmonary rehabilitation, but factors leading to this change have been little studied. There may be a gender effect, with men being helped more by prolonged exercise programmes than women (11). It has proved difficult to demonstrate the direct effect of education, though this has been studied in terms of quality of life rather than exercise capacity (12).
While there have been examples of randomised trials showing the benefit of pulmonary rehabilitation versus 'standard care' for inpatients, outpatients and at the patient's home, no existing trial randomises patients between different venues. The majority of trials have examined hospital inpatients and outpatients, where resultant benefit is clear, or at the patient's home, where results have sometimes been less favourable (13). Community settings for group rehabilitation have been little studied.
Two of the advisory committee members for the proposed study (Sue Ryan and Jenny Elliot) have run a community-based rehabilitation programme. Audit of 9 patients (all the individuals in a single programme) showed not only that their average shuttle walk distance improved by 73 % at the end of the programme, but remarkably, there was an *additional* 34 % improvement 12 months later. Improvements in breathlessness were likewise maintained over 12 months. Vivienne Gill, a postgraduate student of Sheffield Hallam University (supervised by Nigel Mitchell, a further advisory group member), used focus groups and questionnaires to judge subjective patient response to the pulmonary rehabilitation programme. This clearly indicated the importance of mutual support, friendship and amelioration of isolation previously caused by COPD. The dissertation concluded that these benefits may have been facilitated by meeting in a community rather than a hospital setting, and that this led directly to the objective success of the programme. An analogous suggestion has been made for a home-based programme, in which the closer links to the domestic situation were felt to be important (14).
A long-term change in exercise behaviour will depend, in part, on psychosocial factors. Importantly, anxiety and depression scores have been shown to improve after pulmonary rehabilitation (15). A study of the health impact of COPD in a Leeds population also used qualitative techniques to suggest several important impacts on global well-being. In particular, "Quality of life was seen as mainly depending on family relationships, opportunities afforded locally for neighbourliness and freedom from fear, mobility and independence……" (16). Thus it is possible that a community setting for rehabilitation may be

more efficacious than a hospital one by facilitating feelings of community and neighbourliness, and avoiding the perceived impersonality and encouraged dependence of a large hospital. The development of mutual support and feelings of control could be strong motivational factors in changing behaviour. Our study proposes to test whether there is a recognisable difference in outcome at the different venues, and if so to give some indication as to the reasons why. It will also assess the cost-effectiveness implications of this.
A number of studies have recognised the declining effect of pulmonary rehabilitation with time and sought to prolong its effect by using supplementary exercise. These have tended to use methods that are intensive of time, such as a 6 week intensive course followed by home follow up and 'booster' courses (17), 18 month duration exercise programmes (11), 3 months breathing training and physiotherapy, then 3 months supervised exercise daily, followed by 6 months of weekly supervised exercise (18), or a six month programme of supervised walking at home following a 2 week hospital-based programme of walking (19). Those studies including comparison with less intensive interventions showed some outcome benefit from the greater intervention. However, none performed any cost-effectiveness analysis. That a 6 week pulmonary rehabilitation programme is capable of producing a beneficial net cost-effectiveness has been shown (20). It seems unlikely that expensive interventions will produce sufficient increment in benefit to be favourable overall. However, a cheap intervention may do so. The key to prolonged benefit is changed patient behaviour. As reviewed earlier, support, friendship and amelioration of isolation are likely to be key factors. These are easily addressed by telephone follow up, when encouragement and advice can be given. We propose to test whether telephone follow up prolongs duration of effect of pulmonary rehabilitation, and whether this is a cost-effective strategy.

2.4 Research methods

2.4.1 Recruitment

A current research study underway at the Royal Hallamshire Hospital is recruiting subjects seen during routine medical practice at the hospital to a pulmonary rehabilitation research project. No external advertising to patients or to general practioners has been carried out, but the research project is successfully recruiting numbers equal to those envisaged for the hospital limb of the proposed study. The Northern General Hospital sees greater numbers of patients with COPD and would be expected to be able to recruit at least an equal number in the same fashion.
The Sheffield HAZ has been responsible for training healthcare workers in COPD and more than half general practices now have a nominated lead individual for COPD. Further practice leads are being identified.. Recruitment to the proposed project would occur by advertisement to this lead and subsequent referral for rehabilitation, and by advertisements placed in hospitals, primary care settings and the local press. This would be expected to comfortably yield the additional subjects required in excess of direct hospital referrals.
Prior to the study, patients referred for pulmonary rehabilitation will be reviewed by a respiratory physician (Dr. Rod Lawson at RHH, Dr. Paul Anderson at NGH) unless already reviewed by a respiratory physician within 4 months. This will mirror the pattern of referral likely to be seen outside a trial setting, enabling the results to be generalised confidently. They will confirm the diagnosis and ensure pharmacological treatment is optimal prior to rehabilitation. Spirometry and reversibility, and oxygenation will be assessed, and a physiotherapist will perform a clinical assessment to confirm suitability for rehabilitation. Informed consent will be obtained for enrollment into the sutdy, as detailed below

2.4.2 Patient data

At a baseline visit and at each subsequent assessment visit (immediately post-rehabilitation, and 3, 6, 12 and 18 months post rehabilitation), the following assessments will be made (with an additional practice shuttle walk at baseline):

- Shuttle walk distance
- Health related quality of life measures (CRQ, SF-36, EQ-5D)
- Primary care resource use questionnaire
- Drug use (patients will bring medication for recording)
- BMI, arm circumference and skin-fold thickness (used to assess mid arm muscle circumference)
- Questionnaire on use of social services and time off work

These data will be gathered by a researcher not directly delivering the rehabilitation programme itself.

At each telephone follow up, results of key questions will also be recorded during the structured interview.

2.4.3 Qualitative data

Qualitative data will be obtained from a random selection of 32 subjects, stratified equally between intervention groups. On the basis of previous work (Stevens), and the predicted volume of data capture, it is estimated that response saturation will be achieved with this number of patients. Subjects will be interviewed at baseline, immediately post-rehabilitation, and at 18 months.
The study will employ a qualitative approach using semi-structured interviews to explore and compare respondents' perceptions and experiences of rehabilitation in the two settings. Interviews will be carried out by senior researchers who are used to liasing with clinicians, have experience of conducting qualitative research in sensitive areas and are used to dealing with patients who are severely symptomatic. With the permission of the participant, the interviews will be tape recorded and subsequently transcribed by a professional agency. Tapes will be stored in a locked room, accessible only to researchers working on this project, at the Royal Hallamshire Hospital, Sheffield until analysed. Researchers not directly connected with patient care will handle all the data. If respondents wish, they will be able to inspect the transcript of their own interview. To verify interpretation, transcripts will be read independently by an experienced researcher who is not part of the project team.

2.4.4 Cost data

2.4.4.1 Exercise programme

The purpose is to estimate the cost of the programme for each person in each arm of the trial. This is achieved by multiplying the number of sessions attended by each person by an estimate of the average cost per attendee per session. The costs of running an exercise programme includes recruitment, administration, hire of facilities, payments to the exercise leaders and the nurses engaged in monitoring. The staff time will be recorded and costed using NHS rates, along with local rentals for facilities, office costs and other directly incurred costs from running the programme. Care will be taken to exclude costs related to the research component of the programme.

2.4.4.2 Cost consequences

It is anticipated that the expected health improvements achieved through regular exercise would impact significantly on the use of health service resources by reducing the need for secondary and primary care interventions. The use of resources will be recorded over the 18 months of the follow-up. Use of hospital services in terms of inpatient admission (including the length of stay and speciality), outpatient attendances and A&E visits will be obtained from the Sheffield Health Information Project (a well validated linked data base of all health services use in Sheffield). The use of primary care will be obtained from self-completed resource use items included in the health follow-up questionnaires. Questions will be asked about recent use of primary care services and be extrapolated to the full 18 months. Use of more expensive drugs will be estimated from patient reports and by asking subjects to bring their chronic drugs to their assessment sessions. Resource use will be costed using national average costs (21). To enable a broader based costing, patients will also be asked about their use of social services and time off work.

2.5 Planned interventions

Patients suffering from COPD deemed suitable for pulmonary rehabilitation will be recruited (see section 2.6). The two acute hospitals in Sheffield, the Northern General Hospital and the Royal Hallamshire Hospital, will be paired with the North and West PCT's, and the South Eastern and the South Western PCT's, respectively. Each hospital/paired PCT's will have a joint recruitment list for pulmonary rehabilitation. The venue for the rehabilitation programme (community or hospital) will be allocated at random. Patients in the hospital programme will come from either paired PCT, but in community programmes will attend the programme in their local PCT. The community settings will be leisure centres based in the same geographical part of the city. Representatives of Sheffield City Council have agreed to facilitate their use. Leisure centres have been chosen because of their close ties with the local community who use their facilities, and because of the experience of the NHS Beacon Site community cardiac rehabilitation in Newcastle. Here, 40% of its patients continue to attend the general public exercise sessions after completing the rehabilitation course. Continuing to exercise is also a crucial part of maintaining the effects of pulmonary rehabilitation and this setting may promote

better compliance with post programme exercise than the hospital setting. Leisure centres can provide the same space and equipment as the hospital settings. The hospitals are each large acute teaching hospitals, both part of the Sheffield Teaching Hospitals Trust.

Composition of rehabilitation course

Pulmonary rehabilitation will be delivered, whenever possible, by the same individuals in paired hospital and community settings, to minimise variabilities. Data assessment and collection will be made by individuals who are not involved with the primary interventions.

Each course will be preceded and followed by assessment visits as detailed above. One community rehabilitation course will commence each time a hospital rehabilitation course commences, in either one or the other PCT linked to the hospital. Eleven patients will attend for six weeks for two afternoon sessions a week each of 2-hour duration. A carer or relative is encouraged to attend. Each session has two elements, exercise and education.

Exercise

A circuit of 10 exercises each graded into three levels, easy, moderate and hard.

The level of exercise and treadmill walking speed the patient begins the scheme on is determined, by set criteria, from the shuttle walk test result achieved in the initial assessment. All patients on the first session complete 30 seconds at each station.

Heart rate, oxygen saturation and Borg score are recorded at the end of each station.

At the end of the session the average Borg score is calculated for each patient and their station exercise time adjusted to a set criteria for the next session.

All patients are re-shuttle tested at the end of week 3 to adjust the exercise level, to the set criteria, for the remainder of the scheme.

Education element

Week (session)	Professional	Topic
1(1)	Physiotherapist	Breathing control technique
1(2)	Doctor	What is COPD?
2(3)	Nurse	Medication
2(4)	Physiotherapist	Symptom recognition and sputum clearance
3(5)	Occupational therapist	Activity planning and energy conservation
3(6)	Occupational therapist	Stress reduction and relaxation techniques
4(7)		Open discussion
4(8)	Physiotherapist	Healthy lifestyle advice
5(9)	Dietician	Health eating advice
5(10)	Occupational therapist/Nurse	Managing anxiety
6(11)	Nurse	Benefits advice
6(12)		Open discussion

Inevitably, there will be some patient dropout during this phase, particularly because of exacerbations of COPD occurring during the rehabilitation phase. These are variable, in particular depending on the season of the year. Experience of previous rehabilitation programmes leads us to expect a drop out rate of around 10 %. However, we plan to recruit 20 % above the numbers suggested by power calculations to ensure recruitment is sufficiently robust.

Following the pulmonary rehabilitation programme either in community or hospital settings, patients will be randomised to either routine follow up (i.e. usual patient contact as determined by their usual healthcare professionals) or routine follow up plus telephone follow up. The latter will consist of a structured questionnaire enquiring about exercise participation and general lifestyle. This will be repeated at 1,2 3, 4, 5, 6, 9,12 and 15 months. The initial frequent follow up is intended to consolidate lifestyle changes.

2.6 Planned inclusion/exclusion criteria

2.6.1 Inclusion criteria

- Diagnosis of COPD as defined by British Thoracic Society guidelines (3)
- MRC grade 3 dyspnoea or worse despite optimal medical care
- Clinically stable for 4 weeks prior to commencing programme

2.6.2 Exclusion criteria

- Lack of informed consent
- Unwilling/lack of motivation to make lifestyle changes
- Inability to hear and understand educational talks and exercise instructions (hearing aids and interpreters may be used if appropriate)
- Prognosis under 2 years from any disease
- Long term oxygen therapy or absolute requirement for oxygen therapy on exercise
- Unstable or uncontrolled cardiac disease
- Musculoskeletal problems precluding exercise training

2.7 Ethical arrangements

2.7.1 Risks and benefits for trial participants and society

Patients participating in the study will have the benefit of receiving pulmonary rehabilitation. The level of exercise will be individually adjusted for subjects to a level to which they would be expected to be able to exercise at home. Whilst all exercise carries a theoretical risk of musculoskeletal harm or adverse cardiac events, the risk is greatly exceeded by the potential benefit.
Patients with COPD pose a large burden on society in terms of demands on social services and healthcare resources. More efficacious and cost effective treatment would be to the benefit of society in general. Existing evidence suggests favourable cost-effectiveness analysis for pulmonary rehabilitation (20), but this trial will add to this information, and further inform decisions as to the best use of healthcare resources.

2.7.2 Informing potential trial participants of risks and benefits

All subjects will receive a written patient information sheet when recruitment to the trial is offered, detailing the rationale behind pulmonary rehabilitation, the benefits and risks and what will be expected of them. Subjects will have the opportunity to discuss this with a member of the trial team, and will be asked to sign to confirm they have read and understood the form.

2.7.3 Informed consent

All potential recruits will receive information as discussed above. They will be asked whether they wish to participate in the study. Those expressing a wish to participate in the study will be asked to sign to confirm their free and informed consent. This will be witnessed by at least one member of the study team and one other individual.

2.7.4 Retention of data

Data relating to the trial will be held for at least 15 years following trial completion.
The primary care team for each subject will receive written information relating to the subject's enrolment in the study, and detailing their progress during the treatment phase.

2.8 Sample size

The primary outcome will be the percentage change relative to baseline i.e. {(eight week follow-up – baseline)/baseline} in distance walked (in metres) during the shuttle test. From a study of 20 COPD patients the mean percentage change in distance walked relative to baseline was 188% (SD 343%).

Assuming similar levels of variability, if a difference in mean percentage change of **100%** between the Community and Hospital groups is considered to be of clinical and practical importance. Then to have an 80% power of detecting this difference in means as statistically significant at the 5% (two-sided) level would require **186** patients per group (**372** in total). If 20% of patients are lost to follow-up then we need to recruit and randomise **234** per group (**468** in total).

To recruit **468** patients at **44** (11 subjects each on 4 programmes simultaneously, i.e. 2 hospital and 2 community) per cycle, will take approximately 11 cycles. However, some of these will be staggered extending the number cycles to 12/13.

Table 1: Sample sizes required to detect various differences in % change in distance walked relative to baseline in between the hospital and community groups

Mean difference In change scores	***n per group***	***total***
200%	48	96
175%	62	124
150%	84	168
125%	120	240
100%	186	372
75%	330	660
50%	740	1480

80% Power & 5% two-sided significance.

One of the secondary outcomes which will be used in the economic analysis will be the SF-6D preference weighted single-index utility score post rehabilitation. From a study of COPD patients the mean SF-6D score was 0.60 (SD 0.126). Assuming similar levels of variability, if a difference in mean SF-6D scores of **0.05** between the Community and Hospital groups is considered to be of clinical and practical importance, then to have an 80% power of detecting this difference in means as statistically significant at the 5% (two-sided) level would require **108** patients per group (**216** in total).

Table 2: Sample sizes required to detect various differences in SF-6D score at follow-up between the hospital and community group

Mean difference in SF-6D scores	***n per group***	***total***
0.10	28	56
0.05	108	216
0.04	167	334
0.03	297	594
0.02	665	1330

SD = 0.13
80% Power & 5% two-sided significance.

Table 3: Factorial design

	Community	*Hospital*
Telephone follow-up	1 (n = 117)	3 (n =117)
No telephone follow-up	2 (n = 117)	4 (n= 117)

1: Community rehabilitation and telephone follow-up.

2: Community rehabilitation and no telephone follow-up.

3: Hospital rehabilitation and telephone follow-up.

4: Hospital rehabilitation and no telephone follow-up.

The trial will include a factorial design (see table 3) with the patients randomised to one of four groups. Therefore 468 patients will be randomly allocated to each of the four intervention groups. Utilising the factorial design we will be able to assess community versus hospital rehabilitation by comparing the 234 patients in groups 1 and 2 with the 234 patients in groups 3 and 4. The primary outcome for this comparison will be the percentage change relative to baseline i.e. {(eight week follow-up – baseline)/baseline} in distance walked (in metres) during the shuttle test.

Similarly we will be able to assess telephone follow-up versus no-telephone follow-up by comparing the 234 patients in groups 1 and 3 with the 234 patients in groups 2 and 4. The primary outcome for

this comparison will use the repeated assessments of distance walked during the shuttle test at baseline, 8 weeks, 3, 6, 12 and 18 months.

2.9 Statistical analysis

The statistical analyses will be performed on an intention-to-treat basis. All statistical exploratory tests will be two-tailed with $\alpha = 0.05$. Baseline demographic, physical measurements (e.g. Shuttle walking test), and health-related quality of life data (SF-36, CRQ and EQ-5D) will be assessed for comparability between the treatment groups.

The primary aim is to compare community versus hospital rehabilitation. Secondary aims are to compare telephone follow-up versus no telephone follow-up utilising the factorial design of the trial.

The percentage change relative to baseline i.e. {(eight week follow-up – baseline)/baseline} in distance walked (in metres) during the shuttle test is the primary efficacy response variable. A two independent samples t-test will be used to compare mean changes between the groups (hospital & community) in this parameter. A 95% confidence interval (CI) for the mean difference in this parameter between the community and hospital groups will also be calculated. Secondary outcomes such as the change in health-related quality of life (SF-36, CRQ and EQ-5D) between baseline and week 8 will be analysed in a similar way.

For the repeated assessments at pre- and post-rehabilitation assessments, and 3, 6, 12 and 18 months after completion of rehabilitation a summary measure such as the Area Under the Curve (AUC) will be calculated for each patient. Mean AUC between the two groups (Hospital & Community) will then be compared by a two independent samples t-test. Again a 95% CI for the mean difference in AUCs between the Community and Hospital groups will also be calculated. The AUC will also be used to assess telephone follow-up versus no-telephone follow-up in the factorial design.

2.10 Proposed outcome measures

2.10.1 Shuttle walk distance

Shuttle walk distance is a robust measure of exercise capacity, shown to be sensitive to exercise change produced by pulmonary rehabilitation in patients with COPD (22). Exercise training is the cornerstone to pulmonary rehabilitation. The shuttle walk test is the most direct measurement of exercise outcome and is least subject to further confounding factors, and will thus be used as a measure of exercise capacity. For this reason, this is selected as primary outcome measure.

2.10.2 Health related quality of life using CRQ, SF-36 and EQ-5D

CRQ will be administered by interview at baseline to help respondents select the areas for measuring dyspnoea. It will subsequently be self-completed. This validated disease specific quality of life questionnaire (23) has been shown to be responsive to changes seen after pulmonary rehabilitation, and has been found to be more sensitive than the SGRQ and BPQ (24).
The SF-36 complements the CRQ. It is less sensitive, but provides measures of non-respiratory as well as respiratory consequences of pulmonary rehabilitation. It generates scores on eight dimensions (physical functioning, mental health, social function, pain, physical and emotional role limitations, vitality and general health), summary measures for physical and mental health and a preference-based index (25). It has been shown to be responsive to changes resulting from pulmonary rehabilitation (26, 27). The one page EQ-5D will also be included to provide an additional preference-based measure.

2.10.3 Body composition

Changes in body mass and composition assessed by BMI, arm circumference and skin fold thickness will be measured (28, 29). Tissue depletion is closely linked to quality of life and exercise capability in COPD, and affects on changes in body mass and composition with time are likely to be important (30).

2.10.4 Economic analysis

2.10.4.1 Approach

This economic evaluation aims to help health care commissioners determine whether providing exercise classes in the community is more cost-effective than providing it in hospital and whether

providing formal follow up is cost-effective compared to no formal follow-up. The primary economic analysis has taken an NHS perspective, but data will be collected to allow a societal perspective to be taken in the costing.
The appropriate technique of economic evaluation depends on the outcome of the study in terms of costs and health benefits. The simplest scenario would be for one arm of the trial to dominate the other by either being both cheaper and more effective (in terms of health gain), equivalent in cost and more effective, or cheaper and equally effective. However, more complex scenarios may arise where there are conflicts in terms of the different dimensions of health or between costs and health. In such circumstances, the assessment of cost-effectiveness requires a preference-based single index measure of health gain, and preferably one that can be used to consider how the cost of the gains compare with other interventions purchased by the NHS. This can be done informally, within a cost-consequences framework where the decision-maker is left with task of combining the different benefits and comparing them across programmes (31). The preferred approach in economic evaluation is to attempt some kind of aggregation of the benefits using values obtained from the general public.
The method chosen for doing this is to value the benefit of an intervention in terms of quality adjusted life years (QALYs) and compare the two interventions in terms of cost-effectiveness ratios. Where the more costly intervention is also found to be better in terms of health gain, it is then possible to express it as an incremental cost per QALY, and compare this with other interventions purchased by the NHS. The problems and limitations of this approach are well known, but it provides some guidance to the NHS on the cost-effectiveness. The SF-36 data collected in this study will be converted into health state utility values using a recently estimated preference-based algorithm (25). The area under the curve will be estimated between assessments for each individual in the trial to provide an overall estimate of the QALY difference between the intervention and control arm.

2.10.4.2 Analysis

The main analysis is an intention to treat comparison of the costs of providing exercise in the community compared to hospital, compared to the gains in SF-36 scores at the individual patient level. The final result will be presented as a ratio of the differences in cost and QALY between the arms of the trial, with a 95% confidence interval estimated by bootstrapping. There will be considerable uncertainty in many of the cost estimates and the underlying estimate of benefit. Furthermore, an important consideration in the long-term cost-effectiveness of these interventions is likely to be the longevity of the benefits and cost consequences, particularly of the formal follow-up sub-arms of the trial. It will be important to conduct extensive sensitivity analyses.

2.10.5 Qualitative data

Qualitative interview data will be analysed based on a grounded theory approach (32). Software packages such as QSR NUD*IST will be employed to facilitate analysis. The 'Framework' approach developed by the National Centre for Social Research will be used to identify recurrent themes (33).

2.10.6 Further analyses

Further subgroup analysis will be used. In particular, the effects of disease severity as assessed by FEV_1 and the effects of gender will be examined. These data will be used to generate hypotheses, as the sample size required for formal evaluation within the study would be excessive.

2.11 Independent supervision of trials and management structure

A Data Monitoring and Ethics Committee will be established. It will meet prior to patient recruitment and yearly thereafter. As pulmonary rehabilitation itself is established and known to be safe, its main remit will be to ensure an ethical approach to the large numbers of subjects involve, with correct and safe handling of data. It will consist of three individuals with experience of clinical research from outside Sheffield, and will report to the Trial Steering Committee.
The Trial Steering Committee will be chaired by an independent chair from outside Sheffield, with experience in conduct of clinical trials. There will be two further independent members. Each will have experience in the conduct of clinical trials. At least one will have specific experience in pulmonary rehabilitation. Members of the members of the scientific committee (see below) will also participate in the Trial Steering Committee.
We recognise the importance of involving consumers in research (34, 35). We plan to invite two consumers recruited from local support groups within Sheffield to sit on the Project Steering Group. We will offer training to these consumers. This will be in the form of either the IMPACT programme,

which is operated from the Education Division/CASP from the NHS Public Health Resource Unit or an internal programme operated by the Academic Palliative Medicine Unit at the Royal Hallamshire Hospital. The travel expenses of consumers will be reimbursed and they will be paid on a sessional basis (£15) which is in line with current recommendations issued by the NHS Consumers in Research NHS Support Unit.
The Trial Steering Committee will meet at least once prior to commencement of patient recruitment, and at least a further five times during the conduct of the trial. It will communicate directly with the DMEC, the Study Co-ordinator and the Advisory Committee (see below).
The Scientific Committee will be formed by the applicants. They will be responsible for ensuring the trial is run in a scientifically thorough and rigorous fashion. They will finalise trial arrangements prior to commencing subject recruitment, and be responsible for adequate training of staff to ensure consistent and complete data capture and recording will occur. They will be responsible for continued monitoring of the trial's progress and interim report generation. They will be responsible for final data analysis and dissemination of results in the form of peer reviewed papers in scientific journals and presentations to scientific societies. The Scientific Committee will meet as necessary to discharge these responsibilities.
The Advisory Committee will be a group of individuals with relevant practical expertise that is both broad and deep. They have agreed to contribute this knowledge to help ensure the study runs successfully, but who do not have direct responsibility for it.
A study co-ordinator will providing a key role liasing between the management and implementation groups.
Appendix 1 shows a plan of the proposed management structure.

3 Project timetable and milestones

Timetable (months)	Milestones
1-2	Study set-up • Programme scheduling and resource co-ordination • Training of research staff • Data recording and analysis preparation • Development of database • Early recruitment to rehabilitation programmes
3-20 (26)	Run the rehabilitation programmes • Recruitment to programmes and study • Four rehabilitation programmes: 2 community based, 2 hospital based. Programmes run every 6-8 weeks.
5-37 (43)	• Follow-up telephone calls and assessments
36- 48	• Data collection and analysis • Report writing • Dissemination • Study closure

4 Expertise

Rod Lawson has a background in academic medicine, predominantly in inflammatory biology. His PhD was gained for a thesis entitled, "Neutrophil kinetics in pneumonia". Currently he is a full time NHS Respiratory Physician. He is lead clinician for COPD at the Royal Hallamshire Hospital, and is a member of the COPD Joint Planning Group of Sheffield Health Authority. He has played a strong role in the development of the city-wide initiative for developing COPD services within the Health Action Zone, whilst facilitating research into COPD. Existing research underway for which he is principal investigator include projects on the use of medical gasses to relieve dyspnoea and targeted delivery of inhaled therapy. He is also site lead for multi-centre studies of the genetics of COPD and subcutaneous pulmonary vasodilators. He is co-investigator in an investigation of the role of Chlamydia pneumoniae in exacerbations of COPD and the use of hyper-polarised helium MRI imaging in COPD. He will perform medical assessments at the Royal Hallamshire Hospital, and participate in overall trial supervision.
Paul Anderson is an experienced respiratory physician. He is also a member of the Sheffield Joint Planning Group for COPD. He has research experience in a range of respiratory diseases. He will

perform medical assessments at the Northern General Hospital and help ensure correct standards of medical supervision are available for all study subjects.
John Brazier is Director of the Sheffield Health Economics Group within Sheffield University, which includes 14 trained health economists. His main research interests have been in the measurement and valuation of health outcomes and economic evaluation. He has led research into the first testing of the SF-36 and developing it for use in economic evaluation. He has assisted in economic evaluations of gallstone lithotripsy, minor surgery in general practice, helicopter emergency medical services, screening for osteoporosis, exercise in the elderly, leg ulcer management and the prescription of clodronate to reduce hip fractures in elderly women. He is also involved in a study of the resource and health effects of housing improvement. He teaches and co-ordinates modules on two MSc courses. He will be lead for health economic evaluations.
Stephen Walters is a lecturer in medical statistics at Sheffield University. He has been involved in the design, analysis and reporting of several RCTs, which have compared new and existing health technologies. He also has extensive experience of analysing HRQoL measures such as the SF-36.
Judith Waterhouse has extensive expertise in respiratory technical measurements and use of quality of life measurements. She heads the Respiratory Function Unit at the Royal Hallamshire Hospital. She has extensive experience in the conduct of significant clinical trials, having been involved in the MRC oxygen study and having been a member of the scientific and steering committees of the multi-centre ISOLDE trial of inhaled steroids in COPD. She will be responsible for training in physiological measurements and administration of quality of life and other assessment tools, ensuring quality control.
Tony Stevens is lecturer in the Academic Palliative Medicine Unit at Sheffield University. He has extensive skills in qualitative research techniques, including large scale studies of prisoners and of patients in various healthcare settings. These have included work with difficult subjects with behavioural problems, and with subjects from deprived areas and ethnic minority backgrounds. He has transcribed interviews and analysed transcripts both manually using the 'Framework' approach and with the QSR NUD*IST software package. As a qualified librarian he has experience of storing, retrieving and handling large quantities of information, and has an effective working knowledge of copyright and data protection. He will be responsible for the qualitative aspects of research, and will advise on data handling and protection.
Mandy Higenbottam and **Sarah Warden** are hospital based physiotherapists with experience in establishing, running and maintaining rehabilitation programmes. Sarah Warden is currently employed as a full time researcher on an existing trial of involving pulmonary rehabilitation. **Jenny Elliot** and **Sue Ryan** have together established a successful pulmonary rehabilitation programme, one of a small number successfully running in the United Kingdom. The former is a community physiotherapist. The latter is a practice nurse named Nurse of the Year for her work in pulmonary rehabilitation. **Hazel Horobin** is a physiotherapist and senior lecturer who has extensive experience of pulmonary rehabilitation programmes, who is now involved in teaching and research. **Nigel Mitchell** is a dietician and senior lecturer who also has an interest in qualitative research. He has supervised qualitative audit of rehabilitation programmes. Together, these individuals will form an advisory committee to assist and advise on content and conduct of the rehabilitation course and subsequent follow up.

5 Justification of support required

5.1 Salaries
The rehabilitation programmes and telephone follow-ups require a physiotherapist and nurse team to run 2 programmes (one hospital and one community) every 6 – 8 weeks. The programmes have been scheduled to maximise resources, account for holidays and sickness and permit some degree of flexibility. The hospital programmes will be supported by service funding and we have thus requested salaries for 1.0 WTE additional physiotherapist (Senior 1) and two nurses (Band 8); 0.5 WTE for a period of 41 months and 1.0 WTE for a period of 12 months when the programmes and follow-ups overlap. This will allow new community programmes to be established for the research and appropriate additional facilities.
To separate the rehabilitation programmes from assessments (HRQoL, shuttle walk, etc) we require a research nurse (Band 9) for 42 months; 0.5 WTE for the first 6 months, 1.0 WTE for the following 29 months and 0.5 WTE for the final 7 months.
The data collection and analysis for the cost effectiveness element require the skills of a health economist/statistician (RAII). The work will predominantly take place at the beginning and end of the study, so we have requested 0.4 WTE during the first year and 0.6 WTE during the fourth year.

Although essentially a single site study, the complexity of organisation and detail warrants the skills of an overall study co-ordinator for 0.5 WTE (Band 10) throughout the study. This person in this post will assume day to day responsibility for the running of the trial; they will co-ordinate the study and study personnel, assist with data collection and analysis, co-ordinate the meetings of the study Committees (e.g. DMEC), manage the financial aspects of the study and assist with report writing. Development of the patient database, dietetic advice (part of the rehabilitation programmes) and the qualitative research will be supplied through consultancy.
All other personnel input will be supplied by the applicants and in-house R&D resources.
Please note: There is an additional project cost of £16,150 for 40% overheads associated with the salary of the health economist/analyst who will be employed by the University of Sheffield.

6 Consumables and Equipment

A significant cost of the study is the travel allowance for patients to and from their rehabilitation sessions and for subsequent follow-up assessments. It is anticipated that we will be able to arrange a group collection service wherever possible to reduce costs. For this activity we have requested £9240, and a further £500 has been requested over the four years for refreshments for patients during their rehabilitation exercise. The community settings will charge for use of their facilities and we have been quoted £50 per week. A small sum of £800 (£400 for each of the first two years) has been requested to replenish medical equipment such as oxygen cylinders during the programmes.
We expect that the DMEC will meet four times and the Steering Group six times over the duration of the study. We have allocated £1800 to cover travel and subsistence costs for these meetings.
The use of questionnaires and supply of educational material will cost in the region of £4,600 for the study and the cost of telephone follow-ups has been based on a 10-15 minute telephone call per patient.
The majority of equipment that will be used is already available. The study will however require 11 additional wrist pulse oximeters at a cost of £550 each and 2 skin-fold callipers (£157 each). A docking station and software to allow download of dat from oxymeters has been included.
We have also requested a dedicated computer for the main study databse, with appropriate software.

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6.1 Appendix one – proposed management structure