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| The PRACTICE Trial |
| Pulmonary Rehabilitation and ACTIvity after COPD Exacerbations: A multi-centre, randomised, pilot, factorial (2x2: in-hospital exercise versus no in-hospital exercise and in-home rehabilitation plus usual care versus usual care alone), parallel arm (allocation 1:1 for each factor) trial to evaluate the feasibility of a full scale trial in terms of patients recruited in a 7 month window) randomised controlled trial |
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| **Version 1.2; 04 August 2015** |
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| Chief Investigator: Rodney Hughes  Sponsor: Sheffield Teaching Hospitals NHS Foundation Trust  Sponsor reference: 18013 HTA reference: 13/24/03  University of Sheffield reference: 138144 REC reference: 15/YH/0259 |
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# Abbreviations

|  |  |
| --- | --- |
| 1RM | One Repetition Maximum |
| 2RM | Two Repetitions Maximum |
| AACVPR | American Association of Cardiovascular and Pulmonary Rehabilitation |
| ACCP | American College of Chest Physicians |
| AE | Adverse event |
| AECOPD | Acute Exacerbation of Chronic Obstructive Pulmonary Disease |
| ATS | American Thoracic Society |
| AUH | Aintree University Hospital |
| BTS | British Thoracic Society |
| CI | Chief Investigator |
| CAT | COPD Assessment Test |
| COM-B | Capability, Opportunity, Motivation, Behaviour |
| CONSORT | Consolidated standards of reporting trials |
| COPD | Chronic Obstructive Pulmonary Disease |
| CRF | Case Report Form |
| CTRU | Clinical Trials Research Unit |
| DMEC | Data Monitoring and Ethics Committee |
| ERS | European Respiratory Society |
| FEV1 | Forced Expiratory Volume |
| GCP | Good Clinical Practice |
| HTA | Health Technology Assessment |
| ICER | Incremental Cost Effectiveness Ratio |
| LCADL | London Chest Activity of Daily Living scale |
| MAU | Medical Assessment Unit |
| MRC | Medical Research Council |
| NICE | National Institute for Health and Clinical Excellence |
| NIHR | National Institute for Health Research |
| NHS | National Health Service |
| NHSFT | NHS Foundation Trust |
| PE | Pulmonary Embolism |
| QALY | Quality Adjusted Life Year |
| R&D | Research and Development |
| RCT | Randomised Control Trial |
| REC | Research Ethics Committee |
| SAE | Serious Adverse Event |
| ScHARR | School of Health and Related Research |
| SOP | Standard Operating Procedure |
| SSC | Service Support Costs |
| STH | Sheffield Teaching Hospitals |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| UK | United Kingdom |
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# 1. Project Details

## 1.1. Investigator details

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## 1.3 Title of project

Pulmonary Rehabilitation and ACTivity In COPD Exacerbations

#### Acronym: The PRACTICE Trial

## 1.4 Sheffield Teaching Hospitals project reference number

18013

## 1.5 Protocol version number and date

Version 1.0; 24 March 2015

## 1.6 Sheffield Teaching Hospitals Directorate affiliation

Directorate of Respiratory Medicine and Professional Services Directorate

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# 2. Research Question

Main research question: Is a full scale randomised controlled trial (to test the hypothesis that early initiation of pulmonary rehabilitation is more clinically and cost-effective in AECOPD compared to standard care) feasible?

# 3. Abstract

Chronic Obstructive Pulmonary Disease (COPD) is a progressive lung condition that affects a person's ability to exercise and undertake normal physical function due to breathlessness, poor physical fitness and muscle fatigue. Patients with COPD often experience exacerbations due to chest infections, which result in worsening of their symptoms, more loss of function, and may require hospital treatment. Recovery from such exacerbations is often slow, and some patients never fully return to their previous level of activity. This can lead to permanent disability and premature death.

The purpose of this project is to assess the whether it is possible to undertake a larger trial of exercise training in patients who have been admitted to hospital with Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD). We aim to find out whether patients will be willing to participate and undertake exercise both during their time in hospital, and then immediately after they get home, to see if this will allow patients to recover more quickly, and get back to their previous level of activity without needing to stay in-hospital for a prolonged period.

The study will look at two different sorts of exercise: 1) a bedside bicycle based activity that can be undertaken whilst the patient it sat at the edge of their bed in hospital, and 2) a supervised exercise program to be undertaken during the first two weeks after they have been discharged. Both forms of exercise will be supervised by a physiotherapist (or physiotherapy assistant for the hospital exercise).

Participants will be randomly assigned to receive: (i) in-hospital exercise and home exercise; (ii) in-hospital exercise but not home exercise; (iii) home exercise but not in-hospital exercise; (iv) neither in-hospital nor in-home exercise. The additional exercises in the research will be given alongside usual care which is group pulmonary rehabilitation in the community.

The study will look at whether participants will be prepared to undertake measurements of activity by means of a walking test and an activity monitor that patients will wear at home. They will also be asked to complete several questionnaires that ask about their activities at home and how their breathing problems are affecting their quality of life. Whilst they are in hospital a measurement of their muscle size will be done to see whether then exercise helps stops the muscles from wasting away when they are unwell.

Additionally, the study hopes to see whether undertaking some form of exercise during a flare up of their COPD will help motivate patients with this condition to attend further exercise and rehabilitation classes once they have recovered.

Finally, we will assess whether or not exercising participants early after a hospital admission has any affect in preventing further chest infections or flare ups of COPD, or reduces the number of re-admissions to hospital occurring within 3 months of discharge.

# 4. Aims and Objectives

## 4.1 Aim

To assess the feasibility of a definitive randomised controlled trial which will test the hypothesis that, compared to current practice, early initiation of pulmonary rehabilitation is more clinically and cost-effective in AECOPD.

## 4.2 Objectives

i) An external pilot randomised controlled trial to determine:

* The availability of eligible patients and the likely rates of participant recruitment and attrition;
* Whether data of acceptable quality can be collected;
* Whether the research interventions can be delivered per protocol; and,
* Key design features including the best primary endpoint and sample size for the main trial.

ii) Fully-integrated qualitative research to determine, in line with the MRC Framework [1]:

* Potential barriers to recruiting participating centres in the main trial;
* Reasons for patient refusal of consent and data on whether the baseline characteristics and adherence to routine treatment of non-recruiters differs from consenting participants;
* Reasons for participant attrition; and,
* The acceptability of the research and intervention procedures to participants and health professionals.

iii) Fully-integrated health economic modelling to:

* Identify key drivers of NHS, social care and societal costs;
* Pilot data collection strategies in advance of the definitive trial; and,
* Quantify the net benefit from running the definitive trial.

# 5. Background

## 5.1 Burden of disease

Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) is associated with accelerated disease progression and increased mortality [2], and patients with frequent episodes have a more rapid decline in lung function [3], quality of life [4] and decreased exercise performance [5]. A recent study also demonstrated a 5 to 10% loss of quadriceps force and muscle mass between the third and eighth day of hospitalisation following AECOPD [6]. Loss of muscle function is in turn associated with poor exercise tolerance [7], [8] and quadriceps muscle strength and mass in particular appear to be significant predictors of mortality, independent of change in lung function [9], [10]. Mechanisms contributing to this acute muscle weakness include physical inactivity [11], oral corticosteroids [12], systemic inflammation [6], negative nutritional balance [13], [14], increased resting metabolism [13], hypoxia [13], [14], and hypercapnia [15]–[17].

## 5.2 Standard care

Pulmonary rehabilitation has become a cornerstone in the management of patients with stable COPD [18]. The British Thoracic Society (BTS) recommends post-exacerbation rehabilitation, commencing within one month of hospital discharge, consisting of a minimum of twice-weekly supervised sessions lasting between 6 and 12 weeks. Exercise should combine progressive muscle resistance and aerobic training. [19]. Systematic reviews have shown large and important clinical effects of pulmonary rehabilitation and benefit for patients in terms of quality of life and daily functioning, but only if they adhere to the rehabilitation programme [20], [21]. Despite the established benefits and widespread availability of pulmonary rehabilitation, many patients are reluctant to attend due to misconceptions about the nature of the exercise training, social isolation or transportation difficulties. A recent UK audit found that <10% of all hospital discharges for AECOPD complete early post-hospitalisation rehabilitation [22]. In those patients with recent hospitalisation, and those receiving long term oxygen therapy, completion of the full programme can be especially poor [23].

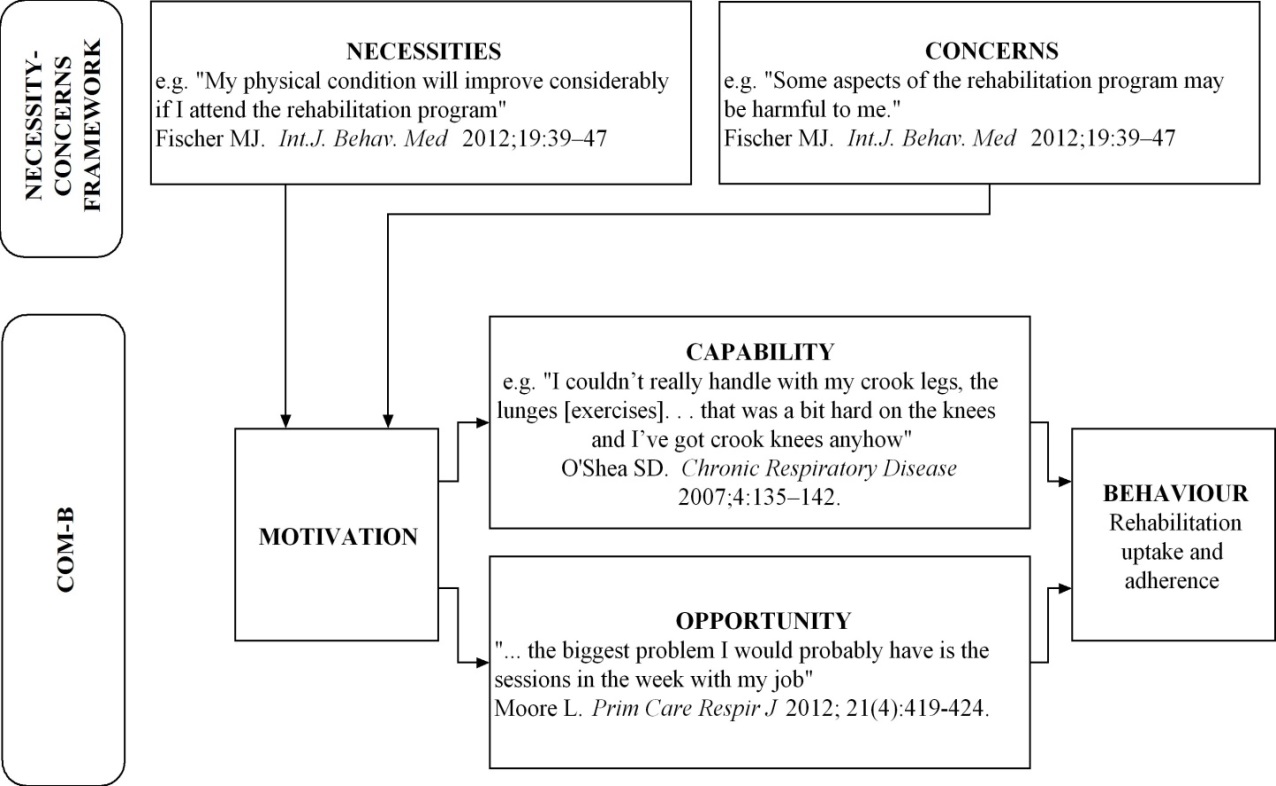
## 5.3 Potential impact of early initiation of pulmonary rehabilitation

Starting rehabilitation whilst in hospital or immediately after discharge may improve the rate of recovery of both peripheral muscle strength and overall physical function [24], [25]. Neuromuscular stimulation [26] and resisted quadriceps exercise [27] delivered to patients admitted with AECOPD have been shown to reverse the significant muscle dysfunction normally seen during hospitalisation, without increasing systemic inflammation (see Section 6.8). Few studies have assessed the impact of pulmonary rehabilitation and exercise training during and soon after the onset of AECOPD, as many patients are too unwell to exercise vigorously or attend group-based sessions [28]. Combining an in-hospital exercise training regime during an exacerbation, followed by an immediate in-home community based exercise programme, has the potential to minimise hospital length of stay whilst allowing the patient to recover function in their own home. The purpose of this study is to investigate the effect of an acute exercise training programme during, and immediately following, an AECOPD, in reducing loss of muscle mass, and improving exercise tolerance, function and quality of life. It is also anticipated that introducing the concepts of exercise training early will motivate more patients to subsequently attend group based rehabilitation sessions.

Early intervention may increase uptake of and adherence to, rehabilitation. Specifically, initiation of rehabilitation immediately following an AECOPD, when the adverse experience is still salient, strengthens belief in the necessity (potential benefits) to participate in and adhere with rehabilitation [29], [30], negating concerns (perceived costs or risks) about exercise which are negatively related to treatment response [31]. In this study we use two theoretical frameworks to understand this process. In the Necessity-Concerns Framework, an extension of the Common Sense Model of self-regulation [32], [33], the motivation to initiate or adhere to, a treatment depends on its perceived necessity of the treatment and concerns patients may have about it [34]. By influencing treatment adherence, patients’ beliefs about treatment are often related to health outcomes [35]. We consider necessity and concerns within the Capability, Opportunity, Motivation, Behaviour (‘COM-B’) system (Figure 1), in which capability (psychological and physical capacity to engage with a target behaviour), opportunity (external factors that make possible or prompt), and motivation interact to generate a target behaviour associated with desirable clinical outcomes. Reflective motivation can be achieved through increasing knowledge and understanding, eliciting positive feelings about behavioural target [36]. When motivation is high, ‘enablement’ interventions, such as bringing supervised rehabilitation to a patient’s hospital bedside (before discharge) or home (immediately after discharge) increase the capability and opportunity to initiate and adhere to a rehabilitation programme (the behavioural target).

There also remain concerns that early pulmonary rehabilitation may be neither feasible nor beneficial: Patients in an unstable pulmonary condition may require more supervision than those in a stable state [37] and in a recent randomised controlled trial (RCT) comparing early pulmonary rehabilitation with standard care in patients with exacerbation of chronic respiratory disease, no benefit was demonstrated overall, and, more worryingly, 12 month mortality was higher in the intervention group [38], though the trial was not powered to detect change in mortality and the authors state the finding cannot be explained directly by the results. They accept that this may have happened by chance but suggest that the intervention may have changed the participant’s behaviour as those in the intervention group had lower uptake of outpatient pulmonary rehabilitation that may have mediated the effects. None of 9 studies included in a recent Cochrane review evaluating pulmonary rehabilitation within 3 weeks of an AECOPD associated excess adverse events with intervention [20]. However, documented risks associated with exercising during and immediately after AECOPD include: aggravating respiratory symptoms, increased ventilatory demand, dynamic hyperinflation [39], muscle fatigue [28], aggravation of local inflammatory and oxidative stress to the muscle, and exacerbation of the catabolic state that exists during AECOPD [14]. On the other hand, an in-hospital exercise programme has recently been shown to be safe, feasible [40] and well-tolerated by patients admitted with AECOPD [30].

### 5.3.1 Figure 1. The Necessities-Concerns Framework [34] within the COM-B system [36]



## 5.4 Evidence explaining why this research is needed now

There is currently insufficient evidence to recommend inpatient rehabilitation for patients hospitalised with AECOPD. Only two studies have directly compared ‘early’ post-exacerbation pulmonary rehabilitation with standard post-exacerbation pulmonary rehabilitation [37], [38]. One study, which randomised only 15% of its planned sample size, found no significant between-group differences in health-related quality of life or exacerbation rates [37]. Importantly, this study’s ‘late’ rehabilitation intervention occurred 6 months post-exacerbation, which does not reflect current guidance or routine clinical practice in the UK [18], [19]. Greening et al. [38] randomised patients with an acute exacerbation of chronic respiratory disease (82% had COPD) and found no significant difference in physical function, or readmission rates over 12 months between the intervention group and those receiving standard care, though did find enhanced physical fitness at 6 weeks . This trial tested a six week intervention delivered initially in hospital and then at home. Importantly the home rehabilitation programme was not directly supervised and patient reported adherence to the programme was low (61%) [38].

The MRC recommend a stepwise approach to the development and evaluation of complex interventions, those with several interacting components such as rehabilitation programmes [1]. In terms of the initial developmental step, the process and outcomes of evidence- and theory-based interventions have been modelled and their components are standardised by national and international guidance. Early intervention has a physiological basis for improved clinical outcomes, which may also be mediated by psychological factors related to the temporal proximity of the exacerbation and disease severity. This feasibility study is an essential preliminary to a definitive RCT assessing the effectiveness and cost-effectiveness of early initiation of pulmonary rehabilitation compared to current practice in AECOPD.

## 6. Plan of Investigation

## 6.1 Methodology

The trial will be co-ordinated from the Clinical Trials Research Unit (CTRU) in the University of Sheffield’s School of Health and Related Research (ScHARR). Delegated study staff located at individual centres will identify and consent potential participants.

Participants will be recruited from two participating hospitals following admission for AECOPD. Eligible patients will be identified by physicians and physiotherapists in the clinical care team and research nurses will work with these teams to provide the participant information sheet and discuss the trial with potential participants. Following this, patients will be given a one hour cooling off period; this will be a sufficient amount of time for the patient to consider whether they want to take part in the trial. Patients must be entered into the trial within 48 hours of admission in order to have the time to complete the in-hospital intervention and therefore if the patient requires more than one hour to make a decision, this will be accommodated within this 48 hours window.

Written informed consent will be obtained from every participant by the Principal Investigator (PI) or someone delegated by the PI (physician, physiotherapist or research nurse) who has been suitably trained. Randomisation will be completed by the physician or physiotherapist who can then make the arrangements for the appropriate intervention to be provided. Participants will be informed of their allocation in two stages: they will be told about in-hospital exercise following randomisation and they will be told about the in-home exercise prior to discharge. Trial physiotherapists will deliver both the in-hospital and in-home interventions (as well as aspects of usual care). Outcome data will be collected by research nurses who will be blind to the group allocation of the participants.

## 6.2 Trial Design

Parallel group, randomised pilot 2x2 factorial trial (equal allocation ratio for each of the four groups), comparing in-hospital exercise versus no in-hospital exercise, and in-home rehabilitation plus usual care versus usual care alone (delayed community-based group rehabilitation).

Integrated qualitative research and economic analysis will be conducted alongside the randomised pilot trial.

### 6.2.1 Allocation

Following consent, participants will be allocated in equal proportions to one of the four groups using a computer generated pseudo-random list, stratified by centre, with random permuted blocks of varying sizes, created and hosted by the Sheffield CTRU in accordance with their standard operating procedures and will be held on a secure server. Access to the allocation sequence will be restricted to those with authorisation. The sequence will be concealed until recruitment, data collection, and analyses are complete.

### 6.2.2 Blinding

The care team and the participant will not be blinded to the intervention. The research nurses who will be collecting the outcome data will be blinded to the treatment allocation for the participant, though we will record if they become unblinded for individual patients during the trial.

# 6.3 Statistical and health economic analyses

1. A full statistical analysis plan will be developed prior to database lock. It is not anticipated that any interim analyses will be performed for efficacy.

### 6.3.1 Quantitative analysis

#### 6.3.1.1 Statistical methods

1. As the trial is a pragmatic parallel group RCT data will be reported and presented according to the CONSORT statement [41]. As a pilot study the main analysis will be mainly descriptive and focus on confidence interval estimation and not formal hypothesis testing. No significance testing will be conducted.
2. We will report rates of consent, recruitment and follow-up by centre and by randomised group. Outcome measures will be summarised (as final value) overall and by randomised group, to inform sample size estimation for the main trial. We will use the data from this feasibility study to estimate the consent rate, attrition rate, and the variability of the continuous outcomes in the trial population and use this information to inform the sample size calculation for the definitive RCT.
3. We will also include, as part of the feasibility analysis, estimation of the effect size for the 3-month 6MWD outcome (the probable primary endpoint for the definitive study) for:

* each of the 2 factors (in hospital exercise vs. no in hospital exercise and in home rehabilitation vs. no in home rehabilitation)
* the interaction between the two factors
* each of the two factors adjusted for other variables.(e.g. centre)

1. We will compute confidence interval estimates to check that the likely effect is within a clinically relevant range (as confirmation that it is worth progressing with the full trial). Although this pilot study will not be powered to detect an interaction of the two factors, we will estimate a confidence interval for its size and direction which will inform the design of the future definitive trial.

This information along with the acceptability of the study design and protocol to patients; the safety of the intervention; patient recruitment and consent/retention rates will enable us to determine whether or not the definitive RCT is feasible within a satisfactory timescale and cost envelope using UK centres alone.

#### 6.3.1.2 Health economic methods

1. Health, social care and societal resource use data will be recorded and combined with unit cost information from standard published sources to produce cost estimates for each patient within the pilot trial. EQ-5D responses will be used to estimate Quality Adjusted Life Years (QALYs). We will estimate incremental cost effectiveness ratios though since this is a pilot trial, we would not expect definitive economic results regarding early pulmonary rehabilitation after an exacerbation. The uncertainties in the data will be fully reflected in the estimated Incremental Cost Effectiveness Ratios (ICERs) and Cost Effectiveness Acceptability Curves constructed. The analysis will provide information on the key drivers of cost, the magnitude of expected additional benefits and indicators of data robustness, in particular the extent of missing data. Value of Information methods will be considered in order to estimate the potential benefits that might be expected to accrue from additional future research that would be expected to reduce the degree of uncertainty in relevant parameters related to cost and health benefits.

### 6.3.2 Qualitative analysis

The methodological approach for the qualitative research is realist, interpretivist and pragmatist [42]. Analysis of the qualitative data will use the National Centre for Social Research ‘Framework’ approach [43]: familiarisation; identifying a thematic framework; indexing; charting; and, mapping and interpretation. The theoretical framework for understanding intervention uptake and adherence will be Necessities-Concerns framework [34] within the COM-B system [36]. The theoretical framework for understanding non-participation in the trial will be that developed by Kanarek and colleagues [44]. The theoretical framework for understanding whether wider implementation of the intervention and trial is likely to be feasible will be Normalisation Process Theory, as articulated by Murray and colleagues [45]. The data will be independently coded, firstly with a sample of the transcripts, before conferring with each other and the study patient representatives to confirm the working coding tree. Themes of a priori interest relating to intervention acceptability and moderators of adherence will be identified in advance through the literature (Section 6.4.3) and consultation with our service-user representatives and physiotherapists on the research team. Themes of a priori interest relating to the acceptability of the research protocol will be based on similar Sheffield CTRU topic guides on the subject and will include participant and health professional views on: being approached for participation at a difficult time; randomisation; the burden of research procedures, especially the battery of outcome assessments; and, which outcome assessments participants feel best reflect their concerns. Subthemes within umbrella categories will be derived inductively from reading the transcripts. Analysis of participant themes will take place using NVivo (QSR International). Participants will not provide feedback on the findings. Quotations will be presented, with age and gender characteristics, to illustrate the themes. Qualitative data from primary and secondary sources will be combined with descriptive feasibility data (e.g. reasons for attrition) and quantitative assessments (e.g. Necessities-Concerns framework results) to understand the how motivation, opportunities and capabilities affect rehabilitation uptake and adherence.

## 6.4 Outcome Measures

### 6.4.1 Feasibility outcomes

Sheffield CTRU will aggregate study data to assess the feasibility of the research and intervention protocols based on the following outcomes.

#### 6.4.1.1 Primary feasibility outcome

1. **Feasibility of recruitment to main trial:** defined as recruitment of 76 participants recruited in a seven-month recruitment window at two centres (**objective stop-go *criterion).***

#### 6.4.1.2 Secondary feasibility outcomes

1. **Recruitment and attrition rates (CONSORT data** [41]**):** number of patients assessed for eligibility; reasons for exclusion; number of physiotherapists in each group as well as the number of patients treated by each; numbers lost to follow-up; numbers discontinuing intervention (with reasons); numbers analysed and excluded from the analysis. Recruiting staff will not prompt, but will record on the screening log reasons for refusal of consent when spontaneously stated by patients. No personal health identifiers will be identified on the log. Statements on refusal of consent will be independently reviewed by two researchers and classified into seven-categories (where appropriate) [46]. Research staff will invite participants who withdraw from intervention or research procedures to give a reason.
2. **Number of missing values/incomplete cases:** Acceptable rates of missing values for each questionnaire prospectively defined as 0.5% in line with industry standards for phase I-III clinical trials. Unacceptably high error rates will trigger staff re-training and, where refractory, consideration by Trial Steering Committee of exclusion of the instrument from the battery.
3. **Intervention adherence:** Defined objectively as the number of exercise sessions attended divided by the number of exercise sessions prescribed at the start of rehabilitation.
4. **Intervention fidelity:** Subjective description of case notes by study team. The case notes of 10 participants who received in-hospital rehabilitation and 10 who received in-home rehabilitation will be reviewed by MC and CO’C to assess physiotherapist fidelity of implementation. Health professionals will not know which participants will have their case notes reviewed during the implementation period.
5. **Participant views on acceptability of research procedures and intervention** (see Section 6.4.3);
6. **Therapist views on intervention/research protocol acceptability** (see Section 6.4.3);
7. **Feasibility of recruiting participating centres:** CTRU study manager field notes will record problems with project approvals and set-up at participating sites; target sites for the main study will be screened for suitability, by interviewing R&D officers and potential principal investigators;
8. **Decision on primary endpoint for main trial:** descriptive assessment based on the above as well as participant feedback on assessments (Section 6.8.3) and sample size estimation (Section 6.6.2).

### 6.4.2 Data collection for clinical and cost components

#### 6.4.2.1 Baseline only measures

1. **Dyspnoea, Eosinopenia, Consolidation, Acidaemia and Atrial Fibrillation (DECAF) Score:** validated clinical tool for the prediction of mortality in patients hospitalised with an exacerbation of COPD [47];
2. **Malnutrition Universal Screening Tool (MUST)** (routinely in clinical use): Screening tool for identifying patients who are malnourished or at risk of malnutrition [48];
3. **Demographics:** bespoke, study-specific questionnaire to collect medical history, smoking history, previous exacerbations, age, gender, length of diagnosis, cognitive impairment.

#### 6.4.2.2 Primary clinical outcome

1. **Six-minute walk distance (6MWD)**: validated objective evaluation of functional exercise capacity [49]. Primary outcome at 90 days post-randomisation; secondary at 30 days post-randomisation;

#### 6.4.2.3 Secondary outcomes (see Section 6.10 for time-points)

1. **London Chest Activity of Daily Living scale (LCADL):** standardised, reliable and validated assessment tool measuring the limitation in activities of daily living (ADL) in patients with COPD which is responsive to change after pulmonary rehabilitation [50], [51];
2. **EuroQol EQ-5D-5L:** generic health status measure for health economic analysis [52];
3. **COPD Assessment Test (CAT):** validated self-report multidimensional assessment of global impact of COPD on health status (cough, sputum, dyspnoea, chest tightness) [53];
4. **Rectus Femoris muscle Cross-Sectional Area (RFcsa):** effort-independent and radiation-free method of using ultrasound to measure quadriceps muscle cross-sectional area in patients with COPD that relates to strength [54];
5. **MRC Breathlessness Score** [55]**:** Score quantifying disability associated with breathlessness by identifying that breathlessness occurs when it should not or by quantifying the associated exercise limitation;
6. **Activity Monitor:** sensitive and well tolerated method of measuring energy expenditure and activity, validated in people with COPD, the MoveMonitor will be used and anonymised data is uploaded and analysed using web-based software from McRoberts;
7. **Written activity diary:** daily diary of activity kept by patients
8. **Serious Adverse events:** death; hospitalization (initial or prolonged); disability or permanent damage; other important medical events. Elicited from participant, carers, health professionals or notes;
9. **Health and social care resource use:** bespoke, study-specific questionnaire for health economic data, which will also capture carer time, travel to appointments and time away from work or other usual activities. Questionnaire will draw on data collection tools developed in ScHARR and those collated by the Database for Instruments for Resource Use Measurement [56];
10. **Perceived Necessity and Concerns:** COPD-specific self-reported beliefs regarding exercise that shape a person’s motivation to initiate and adhere to rehabilitation [31]. Validated for use in cardiac rehabilitation research [57] and reliable for use in COPD [31];
11. **FEV1:** standardised spirometry as a measure of COPD severity [58];
12. **Exacerbations:** based on self-report and hospital records;
13. **Readmission:** based on self-report and hospital records.

### 6.4.3 Data collection for qualitative component

The acceptability of the research procedures and, in particular, the outcome measures are of primary interest in the interviews (see Section 6.4.1). We will elicit feedback from participants and physiotherapists in the trial on how research procedures could be improved and which outcomes seem to be the most relevant. If the qualitative researchers think feedback to the trial team is required, this will be reported via the TSC to ensure that changes are not made to the intervention or trial arbitrarily. All interviews will be recorded on encrypted digital recorders and fully transcribed. Field notes will be taken during and after interviews as required. Initial semi-structured interviews with participants and physiotherapists are expected to average 40 minutes. Follow-up telephone interviews no more than 20 minutes. Transcripts will not be returned to participants for correction

#### 6.4.3.1 Patient Interviews

Semi-structured interviews will take place around a week after hospital discharge when those allocated to in-hospital or in-home rehabilitation will have received intervention. For their comfort and convenience, interviews with participants and physiotherapists will take place in their own homes/workplaces, by telephone or Skype at their discretion. Non-participants will not be invited by the research team, but permitted where requested by participants.

Topic guides will contain questions about the acceptability of intervention and research protocols and will be piloted with study team service-user representatives and physiotherapists. The topic guide will cover *a priori* themes identified in the published qualitative research on early in-hospital [30] and delayed community-based rehabilitation [29], [59]–[62] programmes for people with COPD, re-classified using the Necessities-Concerns [34] and COM-B [36]: e.g. *Capabilities:* inability to exercise due to co-morbidities [59]; *Opportunities*: access to location; difficulties in prioritising rehabilitation [29], [59]–[62]; *Motivation | Necessities:* the hope of reducing breathlessness and regaining function [61]; the experience of an exacerbation immediately prior to referral [29]; *Motivation | Concerns:* beliefs that exercise might be harmful; fears social aspect of group rehabilitation programmes [29], [61].

Brief follow-up telephone interviews will be undertaken at around 90 days to elicit views about the study procedures, usual care (community group rehabilitation) and intervention adherence.

#### 6.4.3.2 Physiotherapist Interviews

We have not identified any published qualitative research studies interviewing physiotherapists on the implementation of new programmes with this or similar patient groups. We will use Normalisation Process Theory (NPT) as a theoretical framework to better understand the conditions necessary to support the introduction and embedding of protocolised early intervention as a routine element of care [63].

#### 6.4.3.3 Interviews with non-participants

The topic guide will cover the same topics as for participants, but also explore their perceptions of the trial reasons for non-recruitment. We will also ask non-recruiters to fill out the Perceived Necessity and Concerns questionnaire (see Section 6.10).

### 6.4.4 Measurement of outcomes

1. Eligible patients who have given written informed consent to participate in the study will undergo a baseline assessment (LCADL, EQ-5D, CAT score, DECAF score, RFcsa, Perceived Necessity and Concerns, MUST, demographics). Five days after randomisation, whilst in hospital, the participants will complete another set of assessments (LCADL, EQ-5D, CAT score, RFcsa, Perceived Necessity and Concerns, 6MWD MRC breathlessness score, SAEs) and at discharge they will be fitted with an activity monitor and be given an activity diary to complete. Seven days after discharge either a telephone call or visit will take place to make two assessments (Perceived Necessity and Concerns and SAEs). Participants that are taking part in the qualitative research will have their interviews at this point and the activity monitor should be returned to the participating site (by taxi if there is no visit).
2. Participants will attend a research specific clinic appointment 30 days after randomisation to collect further outcome data (LCADL, EQ-5D, CAT score, RFcsa, Perceived Necessity and Concerns, 6MWD, MRC breathlessness score, Activity Diary, Health and social care resource use questionnaire, SAEs), and finally at a routine clinic visit further data will be collected at 90 days post-randomisation (LCADL, EQ-5D, CAT score, RFcsa, 6MWD, MRC breathlessness score, Activity Diary, Health and social care resource use questionnaire, SAEs, Record of most recent FEV, Exacerbations over last three months, Readmission over last three months). A brief telephone interview will be conducted with participants of the qualitative research again at 90 days post-randomisation.
3. All of these time points for assessment may vary +/- 2 days, and the date of completion will be recorded as part of the feasibility assessment.

### 6.4.5 Participant timeline

Participants will be in the trial for three months in total. Participants will decide whether they want to take part, provide consent, complete a baseline questionnaire and be randomised following AECOPD. If allocated to in-hospital exercise, this will take place for 5 days whilst in hospital, and if allocated to in-home exercise this will take during four visits in a two week period in the patient’s home.

All participants will be followed-up at 5 days post-randomisation, 7 days post-discharge, 30 days post-randomisation and 90 days (3 months) post-randomisation. All participants should be offered group based pulmonary rehabilitation as part of their standard care, which will take place 4-6 weeks post-discharge.

### 6.4.6 Study Flow Chart (Outcome Measures detailed in 6.4) N:\projects\PRACTICE\3 Ethics\Application\Re-submission June 2015\Flow chart v1.1.jpg

## 

## 6.5 Project Setting

Sheffield Teaching Hospitals (STH) NHS Foundation Trust (NHSFT) will be the Sponsor for the trial and the trust will be the ‘clinical co-ordinating centre’. Coordination of the trial will be by the CTRU. STHNHSFT and Aintree University Hospitals (AUH) NHSFT will be the two centres taking part in the trial, and patients will be approached and recruited here.

The interventions will take place in the participating hospitals (In-hospital exercise) and in the participant’s homes (in-home exercise) which may be covered by the participating trusts or community NHS services. The clinical teams involved in the research are employed by the hospital trusts.

## 6.6 Participants

### 6.6.1 Eligibility

The target population will be patients admitted to collaborating centres with exacerbation of COPD.

To date a definition of AECOPD has been difficult to standardise. NICE defines an exacerbation as “a sustained worsening of the patient’s symptoms from their usual stable state which is beyond normal day-to-day variations, and is acute in onset. Commonly reported symptoms are worsening breathlessness, cough, and increased sputum production and change in sputum colour. The change in these symptoms often necessitates a change in medication” [19]. Since no subset of patients admitted to hospital with an exacerbation and more at risk of developing muscle dysfunction has been identified, this study aims to target all patients with AECOPD who are identified as requiring a hospital admission of at least five days duration.

#### 6.6.1.1 Inclusion criteria

* Patients 35 and over with known COPD admitted to hospital with a primary diagnosis of an exacerbation of their COPD, as clinically determined by the treating physician;
* pH >7.35;
* Maintaining SpO2 within prescribed target range (as prescribed by the treating physician) with or without controlled oxygen at rest [64];
* Glasgow Coma Scale (GCS) ≥ 15.

#### 6.6.1.2 Exclusion criteria

* Predicted length of hospital stay <5 days;
* Acute MI / heart failure within last 6 weeks;
* Suspected / confirmed Pulmonary Embolism (PE) within last 6 weeks;
* Known Abdominal Aortic Aneurysm >5.5cm (or >4.5cm if ultrasound is over three months old);
* Known cardiovascular instability: Heart Rate of greater than 120 bpm and/or a systolic blood pressure of less than 100mmHg at the time of screening, or the requirement for inotropic support;
* Extensive pulmonary fibrosis;
* Absolute contraindications to exercise / musculoskeletal conditions limiting exercise capacity as assessed by trained physiotherapist.;
* Unable to give full informed consent
* Non-English speaker (to allow fully informed consent and the completion of questionnaires).

#### 6.6.1.2 Withdrawal criteria

Patients may be withdrawn from the trial at their request and data collected up to that point will be kept in line with the Data Protection Act.

If participants are re-admitted to hospital during their time in the trial, they will be withdrawn from treatment and be managed under the usual care pathways. If participants’ conditions change so that they meet the exclusion criteria following randomisation or if the care team thinks they should not continue with the intervention they will also be withdrawn from treatment. We will still collect outcome data from these participants at the follow-up points where possible.

### 6.6.2 Proposed sample size

The study is an external pilot trial intended to explore the feasibility of conducting a future definitive trial. The sample size for a feasibility study should be adequate to estimate the uncertain critical parameters (Standard Deviation for continuous outcomes; consent rates, event rates, attrition rates for binary outcomes) needed to inform the design of the full RCT with sufficient precision. A sample size of 60 patients with 3 month outcome data (76 randomised with 20% drop out) allows a standard deviation to be estimated to within a precision of approximately ±19% of its true underlying value with 95% confidence. This estimate will be synthesised with standard deviations observed in other published studies and ongoing trials to provide a robust estimate for use in the sample size calculation for the full trial. Preliminary estimates suggest the definitive RCT would need to have between 350 and 500 patients, in total, to detect a small standardised effect size of 0.35 at conventional levels of power (90%) and significance (5% two-sided).

In the trial participant interviews, with a relatively homogeneous patient group, 24 interviews (8 from each randomised group) should be adequate to understand common perceptions and experiences of 12 people who receive in-hospital exercise, 12 who receive in-home rehabilitation as well as 8 people receiving neither, thereby achieving thematic saturation [65] (as distinct from other forms of saturation [66]) on both intervention and study procedures. All physiotherapists working on the trail will be invited to be interviewed in the physiotherapist interviews. Formal assessment of whether saturation has occurred or stopping criteria for qualitative data collection will not be employed [67]. In the non-recruiters interview group, we will recruit six participants and then continue to recruit either until we have reached data saturation, prospectively defined as six interviews since the last new theme arose (minimum n=12), or until we recruit a maximum of 24 individuals.

## 

## 6.7 Recruitment

### 6.7.1 Patient pathway

Patients attending the STH and AUH NHSFT with AECOPD, will be assessed by the Medical Assessment Units (MAU) in each centre and may be recruited from MAU or from a respiratory or general medical ward.

### 6.7.2 Expected throughput of eligible patients

The pilot trial will be undertaken at two centres (STH and AUH). Both centres have identified a sufficient pool of eligible patients. In a small audit of potential participants over a 4 week period, 28 of 40 screened would have fulfilled the inclusion criteria. We assume 75% screening ineligibility on grounds of health; refusal of consent; immediate dropout which would leave around 7 eligible and consenting patients per centre per month. With a 7 month recruitment period at 2 sites we need to recruit 5.5 patients per centre per month; just over 1 patient/centre/week.

### 6.7.3 Non-recruited Data Collection

In order to follow CONSORT guidelines for reporting RCTs we will collect aggregate anonymised data on non-recruited patients. These patients will fall into three groups: eligible patients refusing consent, eligible patients not recruited by the clinician and ineligible patients.

To satisfy the requirements of the CONSORT we will collect basic baseline data (non-identifiable: age and gender) for eligible patients along with a reason for their non-recruitment (if offered by the patient). To complete the CONSORT diagram, we will collect baseline data and reasons for ineligibility for patients admitted for treatment of AECOPD. This non-recruited data will be available to site staff and the study team and may be discussed at committee meetings in regards to recruitment strategies.

In addition to this baseline data, patients who do not consent to participate in the trial will be asked whether they would be willing to receive information about a non-recruiters qualitative study which aims to include a number of people who are not taking part in the trial. Previous studies of this nature indicate that the circumstances of recruitment will necessitate an opportunistic approach to sampling [68]. Those agreeing to be interviewed for the non-recruiters qualitative study will sign a consent form or provide formal verbal consent prior to their interview. Consent will include optional boxes allowing the research team to collect baseline data from the care team and to contact the participant and their care team three months after discharge to assess the extent of their take-up of community-based pulmonary rehabilitation (usual care). This data will be available to the interviewer and the research team and will be combined with feasibility data for designing the main trial.

### 6.7.4 Participant interviews

A sub-sample of participants will be invited to take part in the interviews for the trial. The interviews are detailed in the participant information sheet and an optional tick box is included on the consent form to identify those willing to participate. These participants will be follow-up by the qualitative interviewers to discuss their participation further and make arrangements for the interview to take place.

### 6.7.5 Health professional interviews

Physiotherapists involved in delivering the intervention will be given the associated information sheet by the two co-applicant physiotherapists, and be asked to contact the trial manager if they are willing to take part in the interviews. This is so that their colleagues do not know whether they have opted to take part or not; one reminder email may be sent by the trial team if required.

## 6.8 Intervention

### 6.8.1 In-hospital exercise

#### 6.8.1.1 Underlying theoretical considerations

The in-hospital exercise intervention is based on the known mechanism of action that resistance training during AECOPD improves muscle power [27] and successfully counteracts the skeletal muscle dysfunction and functional decline widely reported during hospitalisation for AECOPD. Resisted quadriceps exercises performed daily during an exacerbation is safe, results in a significant and sustained increase in muscle force, and also promotes increased functional exercise tolerance after discharge [27]. The in-hospital intervention is based on national and international guidance [18], [19], and has been developed through focus group discussions and pilot work at STH.

#### 6.8.1.2 Intervention components

The intervention will be delivered in hospital at the patient’s bedside on the MAU, Respiratory Ward or General Medical Ward, depending on the stage of the patient pathway. It will be delivered by physiotherapists experienced in managing patients with AECOPD and delivering exercise prescription in this setting. A manual describing the intervention will be produced and all staff will be trained to deliver the specific intervention by the lead physiotherapist at each site.

Resistance training will be delivered using a Motomed Viva 2 (Medimotion Ltd, UK) combined upper and lower limb cycle ergometer. This allows resistance training to be delivered to both upper and lower limbs with multiple muscle groups targeted. The intervention comprises an initial assessment of maximal muscle strength, 2 revolutions maximum (2RM), to determine the participants training workload. The 2RM is the maximum resistance against which participants are able to complete two pedal revolutions and is based on a published study in healthy older adults in which this intervention been successfully tested [69]. Participants will be seated on the edge of the bed or in a chair with the cycle ergometer positioned in front of them. The participant will be asked to cycle against the maximum level of resistance (20kg). The resistance will be gradually reduced in 1kg increments until the patient is able to complete two pedal revolutions. To ensure a maximal load, participants will be asked to perform further attempts with the resistance increased by 1kg loads. This assessment is repeated for both upper and lower limbs.

Those randomised to in-hospital exercise will perform a single intervention repeated in three sets of sixteen daily upper and lower limb revolutions at 80% of the 2RM, a resistance and repetition previously described to have a training effect in patients hospitalised for AECOPD [27] and healthy elderly adults [69]. At the end of each set of exercise small adjustments in load will be made based on symptoms (Modified Borg Dyspnoea Scale) [70] to maximise the number of revolutions that participants are able to complete and minimise respiratory symptoms. Exercise will be continued on each subsequent day of the hospital admission for 5 days.

This is a largely inflexible experimental intervention. The only adjustments that can be made by practitioners involves adjusting the load to maximise the number of repetitions that can be undertaken without increasing symptoms of breathlessness or fatigue.

#### 6.8.1.3 Rationale for selection of the intervention

Modalities and intensity of training delivered during AECOPD need to be chosen with careful consideration for the markedly increased dyspnoea and fatigue experienced during exacerbations. In order to avoid excessive respiratory symptoms, ventilatory requirements and dynamic hyperinflation should be kept to a minimum [39]. Exercise training during or following exacerbations may also aggravate local inflammatory and oxidative stress to the muscles and high-intensity exercises performed until exhaustion are associated with increased muscle oxidative stress in stable patients with COPD [71]. High intensity resistance training has been shown to be effective in counteracting the deleterious effects of inactivity-induced skeletal muscle atrophy, has a relatively low ventilatory burden, and is well tolerated during AECOPD [27].

#### 6.8.1.4 In-hospital control condition

During the hospital admission, participants not randomised to in-hospital exercise will receive usual care according to NICE guidance [18]. Physiotherapy will be limited to mucous secretion clearance techniques and breathing exercises. Patients will not be restricted in their physical activities but no formal exercise therapy will be offered.

#### 6.8.1.5 Compliance monitoring

Physiotherapists delivering the in-hospital exercises will record the number of rotations undertaken at each session and any adverse events that may occur, where possible they will record reasons for not taking part in a session (for example patient choice, illness or at another appointment).

### 6.8.2 In-home exercise

#### 6.8.2.1 Underlying theoretical considerations

The in-home rehabilitation programme is based upon on the known mechanism of action that structured rehabilitation programmes incorporating interval training and continuous exercise following AECOPD increase exercise capacity and improve symptoms and quality of life [19], [20], [72]. Both interval and continuous exercise have been shown to improve function under stable conditions [19]. The in-home exercise program intervention offers a combination of interval training and continuous exercise training in the form of a structured rehabilitation program, and a daily walking plan respectively. The training incorporates cardiovascular, resistance and flexibility exercises of the major muscle groups of the upper and lower limb in keeping with current guidelines [19], [72], [73]. Traditionally early rehabilitation following AECOPD has taken place in a hospital inpatient or outpatient setting, rather than a domiciliary setting [20], [72]. The advantages of the domiciliary setting for the acutely unwell are that participants do not have to travel whilst recovering from an exacerbation. This may be more convenient and less distressing for participants and may promote adherence. The intervention is structured in such a way as to initiate exercise training within 72 hours of hospital discharge, thereby limiting the physical deconditioning that occurs post exacerbation [74] whilst also allowing participants to take part in group rehabilitation 4-6 weeks post discharge so that training may be optimised whilst stable. The components of the intervention are based on current BTS [19], American and European (ACCP/AACVPR [73], and ERS/ATS [75]) pulmonary rehabilitation guidelines. The protocol is in routine use by community physiotherapists working from STH and close to that delivered at AUH.

#### 6.8.2.2 Intervention components

The in-home rehabilitation intervention, including routine clinical assessment and observations, will take place in the domiciliary setting and will be carried out by a qualified physiotherapist with previous experience in delivering both group pulmonary rehabilitation and individual exercise prescription.

Participants will be seen at home within 72 hours of discharge, receiving a total of four visits no more than 5 days apart (over approximately two weeks). In addition to twice weekly supervised sessions, participants will be asked to complete at least one prescribed unsupervised session per week [19], a daily walking plan and an exercise diary [76]. Session duration will initially be 20 minutes increasing to 40 minutes as tolerated [24]. The intervention will incorporate a warm-up and cool-down period of low intensity exercise [77] and interval training at moderate to high intensity including aerobic and resistance exercises [19], [75] involving the major muscle groups of the upper and lower limbs [19], [73], [75]. Cardiovascular exercise prescription will be standardised using the Modified Borg Breathlessness Score [70] aiming for a score between 4 and 6 [75]. Post exacerbation resting Borg score may be elevated and that the resting Borg score may therefore already be within this range [78]. Furthermore, individual participant’s interpretation of Borg values may vary [79]. For these reasons pulse oximetry will also be used to monitor exercise prescription, aiming for a moderate to high intensity of exercise with oxygen saturation (SpO2) maintained above 84% at all times. Supplemental oxygen will not be provided unless the patient fulfils the local criteria for long term oxygen therapy prescription at rest. In order to avoid injury in this susceptible group the one repetition maximum (1RM) measurement using free weights will not be performed. Resistance exercises will commence with 2-4 sets of 10-15 repetitions aiming for muscle fatigue, not failure [19], [77]. Exercises using equipment will be kept to a minimum in order to encourage unsupervised continuation of resistance exercise [19].

The exercise programme will be detailed in a manual which will be used for training and will be available to the physiotherapists throughout the trial. Participants will be provided with a home exercise booklet on the first supervised exercise session detailing the exercises undertaken and giving general advice on undertaking the exercise programme at home. This booklet will include an activity diary for recording the exercises undertaken each session.

Interventions are multifactorial (individual combination) and exercises may be individualised depending on the ability of the participant. However the intensity of the exercise session and major muscle groups exercised should remain constant.

Participants will be encouraged to undertake at least one unsupervised exercise session in addition to a home walking plan whilst receiving supervised home rehabilitation. After completion of the four supervised sessions (two weeks) the participant will be encouraged to continue at least three unsupervised sessions per week until the commencement of the group program.

Following the in-home rehabilitation participants will be advised to continue exercising at home with a minimum of three sessions per week until their attendance at the group rehabilitation sessions four to six weeks following discharge from hospital.

The participant will then attend eight supervised group pulmonary rehabilitation sessions incorporating eight exercise sessions and four to six education sessions each lasting approximately 45 minutes over a period of four weeks (see Section 6.8.3). This should be arranged by the clinical care team as per usual care pathways.

Application of the intervention will require a degree of flexibility, with physiotherapists prescribing exercise according to the ability of the participant. Prescription will be based on the Borg score supported by respiratory rate and pulse oximetry. Minor musculoskeletal conditions will also be considered when prescribing specific exercise. The experimental intervention will be by experienced physiotherapists in practice settings where the care delivery system and providers are highly experienced in managing pulmonary rehabilitation groups. The intervention will be closely monitored during supervised sessions so that exercise prescription can be optimised and side effects minimised.

#### 6.8.2.3 Rationale for selection of the intervention

Structured rehabilitation programmes incorporating interval training and continuous exercise following AECOPD have proven benefits. Current recommendations are that rehabilitation should begin no later than one month post discharge from hospital [19], however, there are potential benefits from moving this intervention closer to the point of discharge including prevention of muscle wasting before pulmonary rehabilitation begins. This experimental intervention utilises the proven components of pulmonary rehabilitation but delivers them in the participants own home with close supervision. This method of delivery has been chosen to account for the acute nature of the participants who will start the intervention within 72 hours of discharge from hospital and are likely to remain symptomatic.

#### 6.8.2.4 In-home control condition

This will be standard care as described in 6.8.3 below. Participants allocated to in-home exercise will receive 8 sessions of community rehabilitation, and those who are not will have 12 sessions.

#### 6.8.2.5 Compliance monitoring

Physiotherapists delivering the in-home exercises will record the exercises undertaken at each session and any adverse events that may occur, where possible they will record reasons for not taking part in a session (for example patient choice, illness or at another appointment).

### 6.8.3 Standard care

This section describes the standard care following AECOPD in the NHS, though the care offered may differ across trusts.

#### 6.8.3.1 Underlying theoretical considerations

The standard care rehabilitation programme is based upon on the known mechanism of action that structured rehabilitation programmes incorporating interval training and continuous exercise following AECOPD increases exercise capacity and improves symptoms and quality of life [19], [20], [72]. The exercise training program offers a combination of interval training and continuous exercise training in the form of a structured rehabilitation program and daily walking plan respectively. The training incorporates cardiovascular, resistance and flexibility exercises of the major muscle groups of the upper and lower limb in keeping with current guidelines [19], [72], [73]. Both interval and continuous exercise have been shown to improve function under stable conditions [19]. The components of the intervention are based upon current pulmonary rehabilitation guidelines [19], [72], [73].

#### 6.8.3.2 Intervention components

Participants not randomised to early exercise training will attend 12 sessions of group exercise, four –six of which will be supplemented with education. These sessions will take place once the participant is considered stable, four to six weeks post discharge, and will be delivered at existing community venues in Sheffield and Liverpool. In addition to twice weekly supervised sessions participants will be asked to complete at least one prescribed unsupervised session per week [19] and complete an exercise diary [76] and daily walking plan. The intervention is multifactorial (individual combination) and exercises may be individualised depending on the ability of the participant, however the intensity of the exercise session and major muscle groups exercised should remain constant.

Group exercise sessions will last approximately 50 minutes and include a 10 minute warm up, 30 minutes of core exercises and a 10 minute cool down. The 30 minute core exercise will incorporate interval training at moderate to high intensity including aerobic and resistance exercises [19], [75] involving the major muscle groups of the upper and lower limbs [19], [73], [75]. Participants will be instructed how to self-assess their exercise progress by using the modified Borg breathlessness score [70] and cardiovascular exercise prescription with a Borg score of between 4 and 6 [75]. It is appreciated that individual participant’s interpretation of Borg values may vary [79]. For this reason pulse oximetry will be used to monitor exercise prescription using the Borg score aiming for a moderate to high intensity of exercise whilst maintaining a SpO2 greater than 89%. In order to avoid injury in this susceptible group the 1RM measurement using free weights will not be performed. Resistance exercises will commence with 2-4 sets of 10-15 repetitions aiming for muscle fatigue not failure [19], [77]. Exercises using equipment will be kept to a minimum in order to encourage unsupervised continuation of resistance exercise [19]. Supplemental oxygen will not be provided unless the patient fulfils the local criteria for long term oxygen therapy prescription.

Warm up will include seated and standing low intensity aerobic exercise (no greater than two increments above resting Borg score).

Cardiovascular exercise will aim for Borg score 4-6 as described above, and duration will increase according to the ability of the patient commencing at 15 seconds with increments of 15-30 seconds as able per session. Between exercises participants will perform periods of active recovery (for example low intensity exercise such as foot tapping) consistent with the principles of interval training. Cardiovascular exercises will include: walking, static exercise bike, marching on the spot, shoulder punches, sit to stand, arm lift, wall press and step ups.

Resistance exercises commence with 2-4 sets of 10-15 repetitions aiming for muscle fatigue not failure (equating to approximately 65-75% of the one repetition maximum (1RM)) [19], [77]. This aspect of the intervention involves: bicep curls, squats and cool down exercises.

At least one unsupervised exercise session in addition to a home walking plan is encouraged whilst receiving supervised group rehabilitation. The daily walking plan will be progressed by 5 minutes each week depending on the ability of the participant. After completion of the supervised sessions the participant will be encouraged to continue at least three unsupervised sessions per week.

In addition to exercises, there will be four-six education sessions each lasting approximately 45 minutes over a period of four weeks. Education sessions will cover: pathophysiology of lung condition, exacerbation management, pacing, stress management, relaxation and inhaler technique and medication

## 6.9 Safety Assessments

We will collect data on the Adverse Events (AEs) which are considered related to the study treatment including but not limited to those listed below as expected events on the case report forms (CRFs).

All Serious Adverse Events (SAEs) will be recorded and will be reported in accordance with the CTRU’s Standard Operating Procedures (SOPs). These SOPs have been developed to comply with guidance from the Health research Authority (HRA), and Good Clinical Practice (GCP). Site staff will be responsible for reporting all SAEs; on identification they will complete an SAE form and send it to the CTRU and ensure that the local Principal Investigator has been informed. SAEs which are related and unexpected will be reported to the Sponsor and we will expedite these to the REC within 15 days of becoming aware.

### 6.9.1 Possible Expected Outcomes for pulmonary rehabilitation (Interventions)

There are possible risks associated with pulmonary rehabilitation, particularly following AECOPD. Evidence has shown the following possible outcomes: fatigue (physical, mental and general) [80], aggravating respiratory symptoms, increased ventilatory demand, dynamic hyperinflation [39], and muscle fatigue [28].

Details of any of the AEs listed above will be recorded on the CRFs and participant completed questionnaires and reported periodically to the Sponsor, Data Monitoring Committee (DMEC) and the Trial Steering Committee (TSC). The blinding of data for presentation to different stakeholders will be detailed in the DMEC charter.

SAEs will be reviewed by the DMEC and TSC periodically. Any SAEs occurring during the intervention will be reviewed by the DMEC.

## 6.10 Outcome Assessment Instruments

1. Six-minute walk distance (6MWD) [49];
2. London Chest Activity of Daily Living scale (LCADL) [50], [51];
3. EuroQol EQ-5D-5L [52];
4. COPD Assessment Test (CAT) [53];
5. Rectus Femoris muscle Cross-Sectional Area (RFcsa) [54];
6. MRC Breathlessness Score [55];
7. Active Wear Armband;
8. Activity diary;
9. Adverse Events and Serious Adverse Events;
10. Semi-structured interview;
11. Health and social care resource use;
12. Perceived Necessity and Concerns [31];
13. FEV1 [58];
14. Exacerbations;
15. Readmission;
16. Dyspnoea, Eosinopenia, Consolidation, Acidaemia and Atrial Fibrillation (DECAF) Score [47];
17. Malnutrition Universal Screening Tool (MUST) [48];
18. Demographics.

### Table 1: Outcome assessments

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Baseline** | **5 days** | **Discharge + 7 days** | **30 days** | **90 days  (3 months)** |
| London Chest Activity of Daily Living scale (LCADL) |  |  |  |  |  |
| EuroQol EQ-5D-5L |  |  |  |  |  |
| COPD Assessment Test (CAT) score |  |  |  |  |  |
| Dyspnoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation (DECAF) Score. |  |  |  |  |  |
| Rectus Femoris muscle Cross-Sectional Area (RFcsa); |  |  |  |  |  |
| Perceived Necessity and Concerns |  |  |  |  |  |
| Malnutirion Universal Screening Tool (MUST); |  |  |  |  |  |
| Demographics. |  |  |  |  |  |
| Six-minute walk distance (6MWD); |  |  |  |  |  |
| MRC Breathlessness Score |  |  |  |  |  |
| Activity Monitor |  | \* |  |  |  |
| Activity diary |  |  |  |  |  |
| Serious Adverse events (SAEs) |  |  |  |  |  |
| Semi-structured qualitative research interview |  |  |  |  |  |
| Health and social care resource use questionnaire |  |  |  |  |  |
| Record of most recent FEV1 |  |  |  |  |  |
| Exacerbations over last three months |  |  |  |  |  |
| Readmission over last three months |  |  |  |  |  |
| Brief qualitative research telephone interview |  |  |  |  |  |

\* Fitted at discharge and returned at discharge + 7 days

## 6.11 Quality Control & Assurance

1. The trial will be conducted in compliance with the protocol, GCP and regulatory requirements.

The study will be registered with the local R&D department of each centre and STHNHSFT will act as the Sponsor for the trial. Three committees will be established to govern the conduct of this study:

* the Trial Steering Committee (TSC);
* an independent Data Monitoring and Ethics Committee (DMEC);
* Trial Management Group (TMG).

These committees will function in accordance with Sheffield CTRU SOPs. As a minimum, the TSC will consist of an independent chair, a respiratory physician, a physiotherapist with clinical and research expertise and a patient representative. The Committee will meet approximately every 6 months from the start of the trial. The DMEC will consist an independent statistician, an independent respiratory physician and an independent physiotherapist. The TMG will comprise of a Trial Manager who will be jointly supervised by the CI and the Assistant Director of the Sheffield CTRU and will liaise with the whole study team. The trial manager will contact the CI and meet with the Assistant Director of the CTRU regularly.

Trial monitoring procedures and site monitoring will be undertaken at a level appropriate to a risk assessment performed by the Sponsor and the CTRU according to CTRU SOPs.

# 7. Project Management

STHNHSFT will act as the Sponsor for the trial, and therefore will have overall responsibility for the trial along with the Chief Investigator (who holds an honorary contract with STH). The study will be registered with the local R&D department of each participating centre and a Principal Investigator will be responsible for the study at their site. The CTRU will be responsible for project management for the trial.

Data management will be provided by the CTRU in line with SOPs relating to all aspects of data management including data protection and archiving. The study will use the CTRU’s in-house data management system (Prospect) for the capture and storage of participant data. Prospect uses industry standard techniques to provide security, including password authentication and encryption. We will also seek the patient’s permission to inform their general practitioner that they are taking part in this study. Essential documentation relating to the trial will be archived for 5 years in line with the Sponsor’s requirements.

# 8. Expertise

The research team has the expertise to cover all aspects of the research and the right blend of multidisciplinary skills – physicians, physiotherapists, experienced trialists, statisticians, health economists, data managers and trial managers.

* Dr Rodney Hughes is a Consultant Respiratory Physician and an experienced trialist [81]–[83]. He is responsible for the clinical management discharge planning and immediate post-discharge care of hospitalised COPD patients at Sheffield.
* Terry Schofield has experienced exacerbations of COPD and has used different rehabilitation methods.
* Matthew Cox is an Extended Scope Respiratory Physiotherapist with extensive experience in the management of patients with acute on chronic respiratory disease in the hospital setting at Sheffield.
* Catherine O’Connor is a Clinical Specialist Physiotherapist with extensive experience in the Physiotherapy management of patients with chronic respiratory disease in the community setting at Sheffield.
* Dr Paul Albert is responsible for the clinical management, discharge planning and immediate post-discharge care of hospitalised COPD patients at Aintree. He is an academic member of staff at Liverpool University’s Institute of Ageing and Chronic Disease.
* Dr John O’Reilly proposed the initial research question as Clinical advisor to the NICE COPD Guideline Group. He is a Consultant Respiratory Physician at Aintree, co-author of National BTS COPD intermediate care guidelines, Chair of National RCP Map of Medicine project for COPD, National Clinical Advisor to the NICE COPD guideline and NICE COPD Clinical Standards Group, was Chair of National BTS COPD Specialist Advisory Group 2007-2010, and co-author of National COPD Resources and Outcomes Project (NCROP) re-survey 2010.
* Julie Channell is a Rehabilitation Physiotherapist who organises pulmonary rehabilitation physiotherapy at Aintree who will serve on the TMG.
* Dr Daniel Hind is an experienced trial manager, qualitative researcher and Assistant Director of the Sheffield Clinical Trials Research Unit; he will supervise the trial management and qualitative research.
* Professor Stephen Walters is medical statistician with extensive experience of the design, management, analysis and reporting of pragmatic RCTs.
* Professor Allan Wailoo is Professor of Health Economics and Director of the NICE Decision Support Unit.
* Katie Biggs is an experienced trial manager, a Research Associate in the Sheffield CTRU.

# 9. Ethical Issues

The ethical issues in this trial are related to patient safety, the identification and recruitment of patients, the procedure for gaining fully informed consent, and data protection arrangements.

The trial documentation, including this protocol, has been submitted to South Yorkshire Research Ethics Committee (REC). The patient information leaflet, patient consent form, and any other patient facing documentation are included in the ethics application. Any substantial amendments to the approved documentations will be approved by the REC prior to use in the trial, and they will be informed of minor amendments as per Health Research Authority (HRA) guidance.

Due to the unknown risks of early pulmonary rehabilitation and the recent trial showing increased mortality in the intervention group [38] we will be establishing a DMEC for the trial which will include one member was a part of the Greening research team. In addition, qualified physiotherapists will be delivering the intervention and will be monitoring the participants as they exercise.

# 10. Involvement of Service Users

We are committed to involving service users at each stage of our research, from design to dissemination. Prior to our outline grant application we consulted 14 people with COPD in regards to the research question and study design. One these patients is a co-applicant on the trial and will be invited to TMGs and another patient is on the TSC. They have helped to develop and review the patient information sheet, consent procedures and protocol. They will help disseminate the research findings via local support groups and the British Lung Foundation.

# 11. Methods of Dissemination of Results

We expect several manuscripts prepared from this research to be published in high impact peer-reviewed journals. We will publish the results and a lay summary on the study website upon study completion. Findings will be disseminated through the British Lung Foundation.

# 12. Costing the project

## 12.1 Service support costs (research nurses)

Each site will require service support funding for the research nurses that will consent participants; across two sites 76 patients will be recruited at a cost of £56.58 each, total £4,300.00

The research grant will provide each site with 0.6WTE of a Band 6 research nurse for data collection and other research related activities.

## 12.2 Treatment costs (cost of the interventions)

The in-hospital exercise intervention will require additional physiotherapy time and the excess treatment costs arising from this activity will be funded by the participating trusts.

The in-home exercise will also require additional physiotherapist time and the excess treatment costs arising from this intervention will be funded by the Clinical Commissioning Groups (CCGs) who currently commission pulmonary rehabilitation in the community.

# 13. Funding Source

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**Protocol amendments since initial REC approval**

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| **Version number** | **Changes made** | **Date of REC approval** | **Amendment number** |
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