Study Protocol

Study Title: Asthma-Tailored Pulmonary Rehabilitation project

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Contents

Abbreviations

ACQ	Asthma Control Questionnaire
AQLQ	Asthma Quality of Life Questionnaire
AT-PR	Asthma Tailored Pulmonary Rehabilitation
CAT	Chronic obstructive pulmonary disease Assessment Test
COPD	Chronic Obstructive Pulmonary Disease
CRF	Cardiorespiratory fitness
CRQ	Chronic Respiratory Questionnaire
DAC	Difficult Asthma Clinic
DEXA	Dual Energy X-Ray Absorptiometry
EQ-5D	Euroqol Questionnaire
ESWT	Endurance Shuttle Walk Test
FeNO	Fractional Exhaled Nitric Oxide
FEV1	Forced Expiratory Volume
FG	Focus Group
GP	General Practice
HADs	Hospital Anxiety and Depression Score
HCPs	Health Care Professionals
HRQoL	Health Related Quality of Life
IC	Inspiratory Capacity
ICE	Incremental Cycle Ergometer
ISWT	Incremental Shuttle Walk Test
ITM	Incremental Treadmill Test with expiratory gas analysis
PA	Physical Activity
PPI	Public and Patient Involvement
PR	Pulmonary Rehabilitation
QALYS	Quality-adjusted-life-years
RCT	Randomised Controlled Trial
UC	Usual Care

1. Scientific Summary

Patients with severe asthma have a high morbidity and healthcare cost despite currently available therapies (1;2). Activity limitation is common leading to reduced health related quality of life (HRQoL) (3). Cardiorespiratory fitness (CRF) is a strong predictor of mortality (4) and asthma has a strong inverse association with CRF (5). Despite this, patients with severe asthma are often excluded from exercise schemes due to perceived higher risks (6). Pulmonary Rehabilitation (PR), with core components of exercise training and multi-professional education, is an integral part of the management of patients with chronic lung disease with grade A evidence for improvements in dyspnoea, exercise tolerance and HRQoL (7). International guidance suggests inclusion of patients with asthma, but there is little published evidence evaluating either existing or tailored regimens in severe asthma leading to few patients being referred. Our patients stated a preference for a PR programme specifically for their disease.

We propose a feasibility study to inform the study design of a large multi-centrerandomised controlled trial (RCT) of asthma-tailored PR (AT-PR) for individuals with severe asthma compared to usual care (UC).

The aims of the proposed study are, in patients with severe asthma, to:

1) Understand the facilitators and barriers to regular physical activity and exercise
2) Understand healthcare professionals' attitudes to exercise for this group
3) Perform a small scale version of the eventual RCT to provide information on a) recruitment rate, retention rate, adverse events, accessibility and acceptability of the AT-PR programme, to assess the feasibility of the proposed study protocol, to design and pilot a suitable patient cost questionnaire to be used in the proposed cost effectiveness economic evaluation in the subsequent RCT and b) identify further barriers or facilitators to participation in a AT-PR programme
4) To facilitate patient involvement, in the design, conduct and dissemination, for the multicentre trial

1.1. Plan of investigation

Each stage will involve patients with severe asthma, who remain symptomatic at steps 4 and 5 of the British Thoracic Society asthma guidelines (27), recruited from the Glenfield Difficult Asthma Clinic (DAC).

1) A qualitative study involving semi-structured interviews will explore attitudes to exercise
2) A qualitative study involving focus groups of healthcare professionals' will explore attitudes to exercise for severe asthma
3) A small scale feasibility study of an RCT of AT-PR versus UC will be performed. A qualitative approach will be used to explore the facilitators and barriers to participation in a AT-PR and the study protocol.

AT-PR, based on our local successful PR programme for COPD, will be exclusively for severe asthma and further modified according to the findings from stage 1 and 2. Usual care (DAC) will include disease education and exercise advice from asthma nurses.

To determine the feasibility of the multi-centre trial, the primary outcomes are recruitment rate, retention rate, and the incidence of adverse events. The outcome measures proposed for the multicentre trial will be included to assess patient acceptability of the tests, study protocol and data completion. They include usual outcome measures for PR (assessed before and after the intervention, and at six months post completion), safety assessments including exercise-induced bronchoconstriction, asthma symptoms, disease activity, healthcare behaviour and cost-effectiveness.

4) The patient involvement during the project will be assessed to make any necessary adaptations for the multicentre trial

1.2. Potential benefits to patients and the NHS

The proposed work will help inform a definitive large RCT of effectiveness of AT-PR that has the potential to provide health benefits for patients with severe asthma nationally. Ultimately, the hypothesis is that the improvement in health status will reduce healthcare utilisation and hence healthcare costs in severe asthma.

2. Background and rationale

Asthma affects over five million people in the UK (1) and estimated UK disability-adjusted life-years for asthma are greater than for both diabetes and breast cancer (8). Much of this disability is in the 10-20% of patients with severe disease despite currently available therapies (9;10) and they consume 50–60% of the health care costs attributed to asthma (2;11). This reflects a considerable unmet need in this patient group, and represents a major economic burden. Novel approaches to treatment are therefore required urgently.

Cardio-respiratory fitness (CRF) is a strong predictor of mortality in both health and disease (4). Improving CRF through regular exercise reduces the prevalence of many diseases which are common in patients with severe asthma (6) and, importantly, reduces the risk of premature death (12). Asthma has a strong independent inverse association with CRF (5). Exercise-induced dyspnoea and activity limitation are very common in patients with asthma (3;13), and may lead to a fear of exercise (14). A progressive loss of CRF (deconditioning) leads to a reduction in the threshold for exercise-induced symptoms and a downward spiral of inactivity. Exercise can induce asthma in some individuals, but this is often a reflection of uncontrolled asthma.

We recently surveyed 60 patients with severe asthma (15). Only 15/60 (25%) reported physical activity within recommended levels. 65% had stopped exercising due to asthma symptoms, 86.7% wanted to be fitter and 71.7% were interested in participating in an exercise programme. Self directed exercise is largely unsuccessful in this group (16). Despite this, patients with severe asthma are often excluded from community-based exercise referral schemes due to perceived higher risks by providers and patients, and perhaps some healthcare professionals. For example, patients with more severe disease were more likely to believe that exercise was not good for asthma (14), and the Department of Health suggests that patients with severe chronic disease require highly adapted, supervised exercise programmes (6;17). These raise potential barriers to exercise in severe asthma.

2.1. Likely benefits of the proposed research to patients

Benefits of physical exercise in asthma

Epidemiological evidence suggests that regular exercise in asthma reduces severe exacerbation rates (18) and improves quality of life (19). A Cochrane review (20) concluded that physical training improves CRF in asthma similar to that seen in non-asthmatic subjects (but the majority of participants were children with mild-moderate asthma). There was no evidence that exercise had adverse effects on lung function or wheeze.

Physical training programmes in asthma

Structured physical training is a key component of pulmonary rehabilitation (PR) schemes (alongside education and self management) which have shown consistent benefits for patients with chronic obstructive pulmonary disease (COPD) (7). The principles are to target the extra-pulmonary manifestations including peripheral muscle dysfunction and mood disturbance (7). Inactivity, deconditioning, and steroid use are likely to be predominant causes of peripheral muscle dysfunction in severe asthma. In addition hyperventilation was found to be the cause of exercise limitation in two-thirds of patients with difficult-to-treat asthma whereas exercise-induced bronchoconstriction was present in <10% (21). Two limited studies in moderate asthma suggest that compared to controls, supervised exercise training improves symptoms, HRQoL, anxiety and depression and aerobic capacity (22;23). However, similar benefits were not replicated following a 12-week self-directed exercise programme suggesting that supervision was a key factor for a positive outcome (16). No adverse events were found with exercise training in moderate-severe asthma (24) and there may be beneficial anti-inflammatory effects (24). However, there was insufficient data regarding the applicability to adults with severe asthma as the majority had moderate asthma.

2.2. Potential anti-inflammatory effect of exercise

In fact, physical exercise may have a beneficial anti-inflammatory effect in asthma. In mouse models, moderate intensity aerobic exercise has been shown to reduce airway inflammation**,** airway hyper-responsiveness, reverse remodelling and improve respiratory mechanic**.** Mendes et al demonstrated significant reductions in eosinophilic airway inflammation in patients with moderate-to-severe asthma given aerobic training, education and breathing exercises but not in a control group given education and breathing exercises only. Obesity is more prevalent in asthma and maybe part of the pathogenesis. Weight loss is associated with improved asthma control in this group (56). A recent paper suggested a differential effect between weight loss achieved through either diet or exercise on neutrophilic or eosinophilic airway inflammation, respectively, in obese individuals with asthma (57).

Since 1994, 111 patients with a diagnosis of severe asthma have completed our local PR programme tailored for patients with COPD. Patients made improvements in dyspnoea, anxiety and depression scores, HRQoL and exercise capacity (25) (assessed by the Incremental Shuttle Walk test (ISWT) and successfully used for the aerobic training exercise prescription). Although the results of PR were positive, there was probably some bias in the referral pattern of our clinicians; patients were not typical of our severe asthma population and had a more COPD phenotype. Importantly, discussions with patients with severe asthma (15) suggest that most would prefer to participate in an exercise programme alongside other patients with severe asthma rather than COPD, with the programme tailored specifically towards asthma. Patients would also prefer to exercise near home, but for safety reasons initially we propose to evaluate a hospital-based programme. We therefore propose

a feasibility study of a randomised controlled trial of asthma-tailored PR (AT-PR) compared to usual care for individuals with severe asthma. We will explore both patient and healthcare professional attitudes towards exercise in severe asthma.

2.3. Implications for the further development of clinical or public health practice

The proposed project will provide useful information for at least three of the areas identified for asthma (physical therapy, psychological interventions, and self management) by the James Lind Alliance. The data from this study will be used to assess feasibility of a multi-centre trial of AT-PR for severe asthma. If a subsequent RCT is positive, this would provide grade A evidence that could be used to inform national and international guidance on exercise programmes in severe asthma. Assuming that subsequent work shows cost-effectiveness, there would be a robust case for the widespread implementation of AT-PR across the UK. Specifically, the proposed work will help further modify all components of PR for patients with severe asthma. We anticipate that with a positive outcome of an RCT, AT-PR could be available across the UK within 24 months, thus leading to a rapid improvement in patient quality of life and a UK-wide reduction in asthma-related healthcare costs.

2.4. Potential impact on local policy-making and improvement in service delivery

If successful, we will aim to alter our local policy to provide, for the first time, an asthma-tailored PR programme. This will improve the quality of the service delivered to patients with severe asthma, enhance access to PR and ensure that local policy more closely reflects the needs of patients.

3. Study design:

This feasibility project has been designed using the Medical Research Council guidelines on developing acomplex intervention (26). It will have three stages and adopts a mixed methods approach. Recruitment for each stage will be separate

3.1. Participants Inclusion and Exclusion Criteria:

Patients with severe asthma (defined as asthma which remains symptomatic at steps 4-5 of the British Thoracic Society asthma guidelines (27)), despite management for >6 months in the Glenfield Difficult Asthma Clinic (DAC), will be recruited. All patients will have a thorough diagnostic work up and a treatment strategy targeting eosinophillic airway inflammation to optimize control (28); exercise-induced asthma is often a reflection of poor control. Exclusion criteria will be 1)a severe exacerbation within a month of entry,2) inability to exercise e.g. due to significant musculoskeletal or neurological abnormalities, 3) admission to ITU within the last year and 4) hospital admission due to asthma within the last 3 months.

3.2. Stage 1

Understanding the barriers and facilitators to exercise in individuals with severe asthma.

The aim of this qualitative stage is to understand the experience of individuals with severe asthma and their attitudes towards physical activity, exercise, and structured exercise programmes. For the current study the data will inform:

1) How to overcome any barriers engaging in exercise and for strategies to encourage exercise behaviour,
2) Acceptability and therefore feasibility of a hospital based programme,
3) Approaches to recruitment,
4) The proposed topics and self management strategies for the education component of the PR programme.

A descriptive study will be undertaken using semi-structured interviews. Basic demographic information will be collected. We have identified the following patient characteristics to be included (based on the literature (14;29;30), research team views, and discussion with patient representatives): age, gender, social class, obesity, employment status, dependents, living arrangements, transport availability. Participants will be recruited until both theoretical saturation and the diversity of the sample required has been met; a sample of approximately 20-30 patients is anticipated.

Audio-recorded interviews (between 30-60 minutes) will be conducted privately face-to-face between the participant and an experienced interviewer. Interviews will be transcribed verbatim by a professional transcriber, with identifiable information removed. Interview questions have been devised based upon relevant literature, experience of the team and consultation with patient representatives and will be piloted before use to ensure validity. Interviews will be analysed using Thematic Analysis (31) supported by Nvivo software (version 9). This approach follows six distinct stages: familiarization with data; generating initial codes; searching for themes; reviewing themes; defining and naming themes and producing the report. The psychologist and the physiotherapist will carry out initial coding and a sample of interviews will be coded by a second member of the team to ensure consistency and to enhance interpretive authenticity. Throughout the data analysis, the team will meet to discuss and review emerging themes and search for accounts that provide contesting views of the same phenomena or identify different phenomena. Our patient representatives will be invited to comment on our (anonymised) initial findings to ensure interpretations made by researchers stay close to the direct experience of patients (32).

3.3. Stage 2

Understanding healthcare professional (HCP) attitudes towards exercise as a therapy for severe asthma

Eight focus groups, of 6-10 HCPs (33) involved in the care of patients with severe asthma will be arranged to explore perspectives on exercise and exercise programmes. This data set will be used to: 1) inform the design of the education for the asthma-tailored PR programme, 2) understand referral behaviours and identify any potential barriers from HCPs to promoting exercise, 3) inform recruitment strategies (including information given to GPs) for the current study and the multicentre trial, 4) inform dissemination strategies. A purposive sample will be employed to ensure a range of professions and seniority are represented including physiotherapists, asthma nurses, respiratory nurses, general respiratory physicians, occupational therapists, general practitioners and managers. Personnel will be

recruited from Glenfield Hospital (n=1), District General Hospitals (n=3) and local GP practices (n=4) to fully explore views across different settings. The FGs will be held in the respective setting to maximize participation. Group discussions will be facilitated by the psychologist and will encourage the exchange of consensus and disagreement on participation in exercise and exercise programmes for this population.

FGs will be audio-recorded and transcribed as per stage 1. Methodology for data-analysis will be as described for stage 1, but will pay close attention to the additional complexity and interaction inherent in focus group data (34). A sample of transcripts will be analysed by all members of the research team to ensure agreement over emerging themes.

3.4. Stage 3

A Feasibility Study of a Randomised Controlled Trial (RCT) of Asthma-Tailored Pulmonary Rehabilitation (AT-PR) versus Usual Care (UC) in individuals with severe asthma.

We will conduct a small scale RCT to assess feasibility of a large multicentre study. **The primary outcome** measures are recruitment rate (incorporating willingness of patients to be randomised and practicality of a hospital-based programme), retention rate (incorporating acceptability of the therapy) and incidence of adverse events. We will record the time to recruit and complete. We will assess the follow up rate at six months as the multi-centre trial will need to establish longer term effects and healthcare utilisation.

We will randomise 2:1 (AT-PR:UC) as retention rate is the primary outcome rather than effectiveness. An RCT is needed to generate recruitment and retention rates under randomisation conditions (allowing for the anxiety about exercise in this population). We aim to assess the feasibility of the study protocol and have therefore included the outcome measures for potential use in the multicentre trial. We have successfully completed PR studies using similarly involved protocols (35;36). Patient experience of the protocol will be used to determine which outcome measures to include for the multicentre trial. Acceptability of the AT-PR programme and study protocol will also be assessed by a qualitative reflection.

The primary outcome measure for the definitive trial will be the Juniper Asthma Quality of Life Questionnaire (AQLQ). Health-related quality of life (HRQoL) is an important patient-centred outcome measure for any chronic disease (37). The AQOL is a valid measure of HRQoL and has an established minimum clinically important difference (38). The results from the multi-centre trial would therefore be directly clinically meaningful and patient-centred.

3.4.1. Intervention (asthma-tailored PR):

The intervention will be based upon our established PR programme, but will be exclusively for severe asthma. It will be undertaken in a hospital setting in case of adverse events. The programme will extend over 12 weeks with two supervised, two-hour sessions per week (one hour of exercise and one hour of multi-disciplinary education) and a well-defined home exercise programme. A rolling programme will be used due to time constraints. The programme duration may have to be extended for return after exacerbations.

Exercise component

Combined endurance and strength training will be based on our local successful PR programme and evidencebased international guidelines for PR (7;39) and health (17;40). An exercise prescription includes intensity, frequency, mode and duration, but there is little specific guidance for asthma (7;17) other than high intensity aerobic training (60-80% of peak oxygen consumption [VO2 peak] or peak heart rate). We propose predominantly high intensity, walking-based (functional) endurance training as our local preliminary data was successful (25). We will aim for an initial walking duration between 6-10 minutes to be increased to 20-30 minutes over 1 – 4 weeks aiming for an end Borg Score for breathlessness of 4-6 (41). The speed of the walk will be recalibrated at four and eight weeks. It is anticipated that fast walking will be high intensity exercise for this population, but cycling or jogging will be prescribed if needed. A home walking diary will be kept and participants advised to walk daily.

Strength training will comprise upper and lower limb exercises: two sets of 6-12 repetitions at 80% one repetition-maximum (1-RM) for knee extensors and flexors on gym equipment and elbow flexion and extension using free weights. The programme above is a preliminary design and any part of this will be adapted for the feasibility study according to the results of stage 1 and 2.

Multi-disciplinary Education and Self Management

The educational component will comprise a series of sessions delivered by health care professionals'. These will be based on the current PR education programme, but will be modified according to the results from stage 1 and 2 of the project. We envisage they will include disease education, inhaler technique, exercise and nutritional advice, breathing control exercises, relaxation techniques, energy conservation, self management and management of symptoms of anxiety and depression. All staff involved have been trained in motivational interviewing to support behaviour change.

3.4.2. Usual Care

All participants will be seen in DAC. They will receive standard asthma management including disease education provided by experienced asthma nurse-specialists; specific advice regarding participation in regular exercise will be given. They will be offered standard PR after participation in the trial.

3.4.3. Outcome measures to be used in the multicentre trial:

The outcome measures to assess the intervention will be collected at baseline, 12 weeks and six months by a blinded investigator (see Appendix A for study schedule). The outcome measures are the same for AT-PR and the UC groups. We have experience in using all proposed outcome measures. Baseline demographics will be recorded including Body Mass Index.

3.4.4. Safety

1) Any adverse events directly or indirectly related to the exercise measurements and training sessions will be recorded. Any severe adverse event will be reported to our Research and Development office immediately. An external respiratory physician has agreed to independently assess any adverse events and stop the trial if necessary.

2) A full cardiopulmonary exercise test with expiratory gas analysis will be performed on a treadmill and also on Cycle Ergometer as an optional choice if participants were willing to perform the additional exercise test. (42). Exercise-induced bronchoconstriction will be assessed by a flow-volume loop, before and after the treadmill test (± Incremental Cycle Ergometer Test (ICE)), before and after 12 weeks.All patients will be included in the programme and excluded only if they have an adverse event. This data will used as an outcome measure not just for safety.

3) Asthma control and disease activity will be assessed by 1) the Juniper Asthma Control Questionnaire Score (ACQ) 2) measuring airway inflammation by induced sputum count before and after the intervention and 3) by comparing the preceeding nine months unscheduled healthcare visits for asthma with nine months after and including the intervention including GP, accident and emergency attendance and hospital admissions.

3.4.5. Cost effectiveness

The Euroqol (EQ-5D) (43) questionnaire will be used to assess quality-adjusted-life-years (QALYs) at baseline, 12 weeks and six months. Costs will be calculated using NHS tariffs. All treatment including medication, adverse events and any over the counter medication will be recorded. Cost effectiveness will be assessed with the help of a health economist using methodology previously described (44).

3.4.6 Outcome measures

Usual PR outcomes, to ensure acceptability of the protocol for the multicentre trial. As exercise rehabilitation is a complex medical intervention there are a number of different outcomes to assess including:

Health Related Quality of Life Questionnaires

- Asthma specific HRQoL using the AQLQ (38;45;46;46) and Chronic Respiratory Questionnaire (47)
- COPD Assessment Tool (CAT)

Pyschological morbidity

- Hospital Anxiety and Depression Scale (48)

Exercise performance

- Incremental treadmill test (ITM)
- Incremental cycle ergometer test (ICE)
- Incremental shuttle walking test (ISWT) (49;50) and the endurance shuttle walk test (ESWT) (51).
- Compliance with the supervised and home training programme

Acceptability and feasibility of other outcome measures that may be used for the multi-centre RCT

- Domestic physical activity measured by bi-axial accelerometers (Sensewear pro 3) (52). This is a validmeasurement of daily activity to assess behaviour change.
- Quadriceps strength assessed by an adapted chair with a strain gauge (53).
- Venous Blood Sampling
- Dexa scanning

Anthropometry and clinical data.
Height and weight will be measured and BMI will be calculated; weight (kg)/ height^2 (m). Gender and age will be recorded, and medication usage and co-morbidity will be obtained from the medical records.

Spirometry
Spirometry will be performed according to standard guidelines using a vitalograph (58).

Physical Activity Monitor
Daily physical activity (daily energy expenditure) will be assessed by a Sensewear accelerometer which is a small lightweight device worn around the triceps brachii bulk of the right arm. Instructions on how to wear it will be given. It should be worn for five days and only removed for showering or bathing. Data will be expressed as total daily energy expenditure (TEE) and the daily profile will be analysed.

Health Questionnaires
Questionnaires will be completed regarding health, the impact of disease upon normal life and how well asthma is controlled. These will be Chronic Respiratory Questionnaire, Hospital Anxiety and Depression Scale, Asthma Quality of Life Questionnaire, Asthma Control Questionnaire, EQ-5D Euroqol and COPD Assessment Test (CAT).

Incremental Treadmill Test
This is a walking test performed on a treadmill to assess level of fitness. If patients have never walked on a treadmill before we will help them to practice. Patients will stand on the stationary treadmill for three minutes and will then walk very slowly for three minutes. The speed and incline will increase every minute and the test usually lasts for about ten minutes. If the patient is unable to perform the test for at least 5 minutes we will repeat the test at a lower intensity either on the same day after 30 mins rest or on a different day. A doctor will be present during the test
Patients will be monitored throughout the test and for at least ten minutes during recovery.

- Heart - ten small monitoring leads are placed on the back and chest
- Breathing - patients will wear a light mask that has sensors that measure air movement to and from their lungs.
- Oxygen in the blood - a small sensor is worn on the finger
- Blood pressure - a blood pressure cuff is wrapped around a patients arm and is inflated briefly before, during and after exercise.
- Airway narrowing – some patients with asthma develop narrowing of the breathing tubes (airways) during exercise. This is not common. To monitor for this, spirometry will be performed before and after the exercise test. A nebuliser (with a bronchodilator) will be available in case it is necessary.

Incremental Cycle Ergometer Test (optional)

Participants from both groups will also be asked if they wish to perform an additional maximal exercise test; Incremental Cycle Ergometer Test. This is a cardiopulmonary exercise test performed on a cycle ergometer to assess level of fitness and also can be used to assess dynamic hyperinflation. Patients will sit on cycle ergometer for three minutes (rest period). Following the rest period they will start unloaded pedalling for three minutes (warm up phase). Then the incremental phase begins and the work load will be increased every minute. Patient will be asked to pedal till exhaustion. If the patient was unable to perform the test for at least 5 minutes we will repeat the test at lower intensity in order to have an accurate maximal test results. A doctor will be present during the test. Patients will be monitored throughout the test and for at least ten minutes during recovery.

Monitoring of heart rate, breathing, oxygen in the blood and blood pressure will be performed as per monitoring for incremental treadmill test.

Dynamic hyperinflation

Presence and severity of dynamic hyperinflation is a useful clinical approach to assess the impact of therapeutic interventions on exercise tolerance. To monitor for this inspiratory capacity (IC) is measured at rest and set intervals thereafter during exercise. The participant will be instructed that after the prompt and at the end of the next normal breath out they should continue the next breath in until their lungs are full then try to give an extra effort to fill up even more and end the manoeuver with a normal, unforced exhalation. They will be asked to do this fairly quickly so as not to interrupt breathing for very long. They will receive verbal encouragement during the IC manoeuvre to inspire maximally.(59;60). Dynamic hyperinflation will be assessed on IMT ± ICE before and after 12 weeks and post 6 months follow up period.

If Participants agree to perform the additional Incremental Cycle Ergometer they will be randomised to perform either ICE or the IMT on the first visit and perform the other modality on the next visit. The same order of the ICE and IMT tests will take place for evaluating participants after 12 weeks (on visits 7 and 8) and post 6 months follow up period (on visits 10 and 11).

Incremental Shuttle Walk Test (ISWT)

Participants will be given standardised instructions on how to complete the test via a CD player. The course is 10m, set with two cones 9m apart giving a turning distance of 1m at either end. Participants are asked to walk along the course at a speed indicated by an audiosignal (bleeps) by the CD player. The aim is to have walked around the cone by the time the audiosignal is given. The pace is very slow to begin with (0.5m/sec) and the speed increases every minute. Participants are advised to continue until they are too breathless or tired to continue or can no longer keep up with the required speed. The distance walked is then calculated. A shuttle is completed if the patient reached within 0.5 m of the cone. The operator gives no encouragement throughout the test. Auxillary measurements of heart rate and oxygen saturation level are monitored continuously throughout the test via pulse oximetry and non invasive blood pressure recorded before and upon completion of the test. The Borg Scale for peak breathlessness [inspiratory effort sensation, but more commonly denoted (BS)] and perceived exertion (PE) are measured at rest and at the end of test.

Endurance Shuttle Walk Test (ESWT)

This is similar to the incremental shuttle walk test but instead the walking speed is constant and it is calculated from the ISWT. The audio signals indicate the required speed. Patients are asked to keep walking around the cones at the required speed until they are either too breathless or are unable to maintain the required speed. The time walked is calculated.

Quadriceps Strength Test
This is performed on an adapted chair with a strain gauge. From a seated position patients are asked to flex their knees at 90° over the end of the chair. A strap is placed around the ankle and connected to a measuring device. Patients are then asked to push as hard as they can against the strap. There are no risks involved in this procedure.

Sputum Collection
Patients that are unable to produce sputum spontaneously are asked to inhale a salty solution for three 5-minute periods. This can cause some chest tightness, wheezing and/or cough. These can all readily be reversed by inhaling a bronchodilator (ventolin). This technique enables sputum collection

Fractional Exhaled Nitric Oxide (FeNO)
This test is done via a small, hand-held and portable device to determine exhaled nitric oxide concentration in a breath sample. The patient needs to exhale through the device for 10 seconds. The last 3 seconds of the 10 second exhalation are analysed by calibrated electrochemical sensor to give a definitive results. The test is indicative of airway inflammation and provides a complementary tool to assess airways in patients with asthma.

Blood Sample
A maximum of 100 ml of blood will be taken three times over nine months.However, the amount usually required is half this 50mls. This may cause some mild discomfort and occasionally some bruising.

Blood and Sputum Analysis
The composition of the samples will be investigated using a variety of analytical techniques to assess for inflammatory cells and potential inflammatory mediators. Serum will be analysed for a variety of proteins and whole blood for fibrocyte number. Some functional assays maybe performed.

DEXA Scan
This is like a chest x-ray, but requires the patient to lie down. It measures the proportion of muscle, fat and bone density in the body. The radiation dose from each DEXA scan is equivalent to radiation from less than $1/10^{th}$ of a chest x-ray. Chest x-rays expose the patient to a minimum amount of radiation.

Post study interview
Participants from both groups will also be asked if they wish to take part in an interview at the end of the study. This will be a semi-structured interview. A semi-structured interview is a flexible interview that allows new questions to be brought up during the interview as a result of what the interviewee says. The questions will be around the experience of taking part inthe trial and pulmonary rehabilitation. The interviews can either take place face-to-face or via telephone. We hope to undertake approximately 30 interviews for this part of the

study. All interviews will be audio-recorded and written up at a later time. All identifiable information, such as your name, will be removed. We may quote some of your comments in the work that is published as a result of this study, but you will not be identifiable from this published work.

3.4.6. Exacerbations of asthma

Patients will be asked to keep a diary of their exacerbations, treatment and unscheduled healthcare visits.Participants in both groups, along with their GPs, will receive a personalised management plan as per standard clinical practice, with guidance about initiating steroids for exacerbations. If participants present to the investigating team they will be reviewed by an independent clinician with the decision to commence treatment with oral prednisolone based on standard clinical guidelines. The patients will be asked to stop coming to the AT-PR sessions for any exacerbation requiring steroid treatment. If they are not recovered enough to start participation within two weeks they will be classified as a dropout. Similarly they will be excluded from the UC limb if they are not back to normal within two weeks to avoid bias.

If a participant is withdrawn from the study or self withdraws from the study then their data collected up until the point of withdrawal may still be used in study analysis.

3.4.7. Sample size calculation

The primary outcomes for the feasibility study are recruitment, retention and incidence of adverse events, to establish the practicality of a definitive multicentre RCT. We plan to recruit 40 patients to the intervention arm and 20 patients to usual care. We estimate conservatively that we will recruit 30% of those invited to estimate the recruitment rate with a precision of at least +/- 7%1. We suggest a conservative dropout rate of 25% (our local PR dropout rate is approximately 15%); recruiting 40 patients to the AT-PR programme, the precision of the estimated retention rate would be at least +/- 14% (54). From experience to date, we are expecting very few serious adverse events relating to the exercise programme. Based on a rate of 2.5%, the rate would be estimated to be less than 13% (55). All precisions are based on two-sided 95% confidence intervals.

The decision to proceed to the definitive multicentre trial will be made on the basis of acceptable rates and time for recruitment, retention and adverse events ≤2.5% related to AT-PR. The proportion of complete data will be reported for all outcomes at baseline, twelve weeks and six months by treatment group to aid sample size calculations for the multi-centre trial.

3.4.8. Qualitative reflection during stage 3

Participants who give consent to take part in stage 3 will be invited to a semi-structured interview at completion or drop out of stage 3 to fully understand the experience of participation in 1) AT-PR and 2) in the RCT protocol. The data will be used to inform further changes to 1) the AT-PR programme and 2) the design of the eventual RCT. Difficulties or concerns encountered will be fully explored with the aim of resolution in the eventual RCT. We will offer a choice of face-to-face or telephone interviews to increase participation. All interviews will be recorded and transcribed as previously described. We anticipate including 20-30 participants to ensure adequate representation and theoretical saturation. Interviews will explore participants' experience of AT-PR and the RCT protocol, and identify factors that

affected recruitment, retention, attendance to AT-PR or subsequent exercise behaviour. The interview schedule will be designed after completion of stage 1. Analysis will be as described for stage 1.

3.5. Stage 4

Assessing the Role of the Patient Representatives in the Project

Our PPI advisory group champion will meet separately with our patient representatives and the co-applicants to gain feedback on the patient representative role in this project to propose adaptations for future involvement.

4. Appendix A –Study Time Table for Stage 3

Week Number	Visit Number	Data to be collected
0	1	Written consent Demographics Spirometry (Spontaneous) Sputum Collection Familiarisation ISWT ITM**† Repeated ITM**† (if duration of the first test was < 5 minutes) Quadriceps Strength Provide Physical Activity (PA) Monitor
1	2	Sputum Sample Induction (if no spontaneous sample provided on visit 1) DEXA Scan ICE (optional)***† Repeated ICE***† (if the duration of first test was < 5 minutes) FeNO Collect the last nine months healthcare utilisation data Collect the PA monitor
2	3	Venous Blood Sampling ISWT1 and ISWT2 ESWT Questionnaires Randomise to AT-PR or UC
Start 12 weeks of AT-PR or UC 1 4 8 12**Finish AT-PR or UC**	 4 5 	 ISWT and ESWT ISWT and ESWT
12	6	ISWT and ESWT Questionnaires Provide PA monitor
13	7	ITM**† Quadriceps Strength Collect PA monitor
13	8	Sputum Induction Venous blood sampling DEXA Scan ICE(optional)***†
Start 26 weeks of follow up (continue unsupervised exercise for PR group)		
39	9	ISWT and ESWT Questionnaires Provide PA monitor Collect the last nine months healthcare utilisation data
40	10	ITM**† Collect PA monitor Quadriceps Strength
40	11	Sputum Induction Venous blood sampling DEXA Scan ICE(optional)***†

*Exercise induced bronchoconstriction will be assessed using FEV1 before and after the treadmill test
†ITM and ICE to be performed in a random order. (Subjects will perform either the ICE or the ITM on the first visit and perform the other one at the next visit. The same order of performing the above tests will take place on visits 7 and 8 (after 12 weeks of starting the study) and during follow up period on visits 10 and 11).

**ITM – Incremental Treadmill Test with expiratory gas analysis
***ICE – Incremental Cycle Ergometer Test with expiratory analysis
ISWT – Incremental Shuttle Walk Test
ESWT – Endurance Shuttle Walk Test
Questionnaires: Asthma Quality of Life Questionnaire (AQLQ), Chronic Respiratory Questionnaire (CRQ), Hospital Anxiety and Depression Score (HADs), Euroqol (EQ-5D), Asthma Control Questionnaire (ACQ)

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