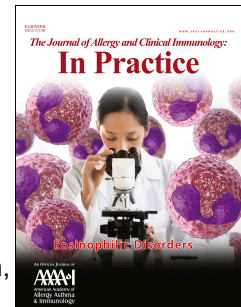


Journal Pre-proof

A feasibility study of a randomised controlled trial of asthma-tailored pulmonary rehabilitation compared with usual care in adults with severe asthma

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Abstract 250

A feasibility study of a randomised controlled trial of asthma-tailored pulmonary rehabilitation compared with usual care in adults with severe asthma

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1. What is already known about this topic?

Adults with severe asthma have lower cardiorespiratory fitness and physical activity levels compared with their healthy peers with an increased risk of heart disease and diabetes despite recent pharmaceutical advances demonstrating a large unmet need.

2. What does this article add to our knowledge?

We report the first clinical trial involving exercise training compared to usual care for adults with severe asthma. Although asthma-tailored pulmonary rehabilitation may be efficacious, the mode of delivery was not acceptable for some patients.

3. How does this study impact current management guidelines?

These initial results support the need for exercise training and education interventions for adults with severe asthma, but the model of delivery needs further development to improve acceptability for this complex group of patients.

Abstract**Background:**

Currently the acceptability and efficacy of pulmonary rehabilitation (PR) for adults with severe asthma is unknown.

Objective:

We investigated the feasibility of performing a randomised controlled trial of asthma-tailored PR (AT-PR) versus usual care (UC).

Methods:

Adults with severe asthma were recruited and randomised 2:1 to AT-PR:UC. The primary outcomes were recruitment, retention and serious adverse event rates (SAE). Secondary outcome measures included those for a future trial assessing the feasibility of collecting data. Assessments were performed at baseline, 12 weeks and nine months including measures of physical performance, health-related quality of life (HRQoL), and asthma control. A recruitment rate of 30% was estimated with 95%CI of $\pm 7\%$, a retention rate of $75\% \pm 14\%$ if we recruited 40 patients to AT-PR, and a SAE rate of 2.5%.

Results:

61/238 (26%) eligible patients were recruited: 38 females, mean (SD) age 54 (13)years, BMI $32 (7)\text{kg/m}^2$, FEV_1 1.9 (0.7)L, FEV_1/FVC 69 (11)%. 51 were randomised to either AT-PR (n=34) or UC (n=17). The retention rates were AT-PR 62%, UC 53% with a SAE rate of 3.3% related to the study visits. Overall collection of the outcome measures was feasible. The results were suggestive of improvements in exercise performance, HRQoL and asthma control with AT-PR compared to UC.

Conclusion:

Both recruitment and retention rates were within the a priori estimated 95%CI. Our results indicate AT-PR may be efficacious for adults with severe asthma but any future intervention and trial design would need further modifications to improve acceptability and retention rate.

ISRCTN: 96143888

Key words:

Severe Asthma, Exercise, Exercise Training, Pulmonary Rehabilitation, Airway Inflammation, Quality of Life, Feasibility Study

Abbreviations:

ACQ Asthma Control Questionnaire

AQLQ Asthma Quality of Life Questionnaire

AT-PR Asthma-tailored Pulmonary Rehabilitation (AT-PR)

BMI Body Mass Index

British Thoracic Society COPD Chronic Obstructive Pulmonary Disease

CPET Cardiopulmonary exercise tests

CRQ Chronic Respiratory Questionnaire

EIB Exercise induced bronchoconstriction

EQ5D Euroqol ESWT Endurance Shuttle Walk Test

FENO fractional exhaled nitric oxide

FEV1 Forced Expiratory Volume in one second

FVC Forced Vital Capacity

HRQoL health-related quality of life

ICE incremental exercise test on a cycle-ergometer

ISWT Incremental Shuttle Walk Test

ITM incremental exercise test on a treadmill

ITU Intensive Care Unit

PR pulmonary rehabilitation

SAE serious adverse event rates

SIGN Scottish Intercollegiate Guideline Network

- 92 UC usual care
- 93 HADS Hospital Anxiety and Depression Scale
- 94

Journal Pre-proof

Introduction

The high burden of disability associated with asthma is similar to many common cancers(1) and originates from those with severe disease: about 5-10% of the asthma population(2). The majority of the high healthcare cost is also associated with severe disease(3). The recent introduction of biological pharmaceutical agents targeting eosinophilic airway inflammation enable reduction in oral corticosteroid use and hospitalisations, but they are often only partially effective at controlling the disease(4, 5). Furthermore, adults with severe asthma have a higher risk of co-morbid conditions such as obesity, diabetes, coronary heart disease and heart failure(6), therefore despite current therapeutic options there remains a high unmet need for these patients.

Cardiorespiratory fitness is one of the strongest predictors of survival in health and disease(7) and regular exercise reduces the risk of many co-morbid conditions associated with asthma. Unfortunately, asthma has a strong independent inverse association with cardiorespiratory fitness(8) and is associated with lower functional capacity and physical activity levels(9). Exercise-induced dyspnoea and fear of worsening asthma prevent regular exercise participation(10).

Despite concerns, studies of exercise training in mild to moderate asthma have shown no detriment in pulmonary function, airway hyper-responsiveness or increase risk of adverse events(11) and show improvements in peak oxygen uptake, the gold standard measure of cardiorespiratory fitness. These results have been replicated in a small study of patients with moderate to severe disease but included only a few patients with severe asthma(12). There are conflicting results regarding effects of exercise training on asthma control, airway hyper-reactivity and inflammation, but there does not appear to be a negative effect(12-16).

For other chronic respiratory diseases, there is extensive evidence that pulmonary rehabilitation (PR) programmes with a core component of exercise training improve exercise

capacity, dyspnoea, health status and psychological well-being(17, 18). Patients with severe asthma may benefit from the structured, individualised approach of PR but modifications to the model of PR may be needed for example to the initial assessment for safety, for the education component, and for the healthcare professionals delivering PR.

To determine whether an asthma tailored pulmonary rehabilitation programme (AT-PR) would be clinically and cost-effective for patients with severe asthma, a large expensive multicentre, randomised controlled trial would be needed. Therefore, we investigated the feasibility of conducting a larger trial in patients with severe asthma by performing a small scale randomised controlled trial of AT-PR versus UC to assess recruitment, retention and adverse event rates and the feasibility of collecting the potential outcome measures for a future larger trial.

Methods

Study Design

We conducted a prospective feasibility study (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4792418/>) of a future multicentre randomised controlled trial of AT-PR versus UC in adults with severe asthma. The study was approved by the National Research Ethics Service Committee of the East Midlands (Ref. 127552) and conducted from September 2014 until July 2017. This study was part of a larger project registered as a clinical trial ISRCTN: 96143888, and the study protocol has previously been published(19).

Patients were randomly allocated 2:1 to AT-PR or UC as retention rate to AT-PR was one of the primary outcome measures. Written consent was obtained from all participants. The trial duration was nine months (Figure 1). The primary outcome measures for the study were recruitment, retention (markers of accessibility and acceptability of the trial and intervention)

and serious adverse event (SAE) rates. The secondary outcome measures were feasibility of collecting data, and the results, to inform outcome measures for the future trial.

Participants

Participants were recruited from patients who were under physicians specialising in the care of severe asthma for at least six months and were symptomatic despite being on step 4-5 treatment according to SIGN/BTS guidelines 2014(20) (high-dose inhaled corticosteroids (>1000 µg beclomethasone equivalent) plus a second controller and/or systemic corticosteroids). Exclusion criteria were:

- ▶ a diagnosis of smoking-related COPD
- ▶ presence of fixed airflow obstruction (FEV1/FVC <70%) and a smoking history of ≥10 pack years
- ▶ unable to exercise for example, due to significant musculoskeletal or neurological abnormality
- ▶ history of significant cardiac disease for example, myocardial infarction (MI) within the last 3 months, unstable angina or heart failure, and/or significant valvular disease
- ▶ a severe exacerbation of asthma in the preceding month prior to entry to the programme
- ▶ a hospital admission due to an exacerbation of asthma within the last 3 months
- ▶ an ITU admission involving intubation within the last year

Of note, our recruitment period was before anti-IL5 or similar biologics pharmaceutical agents were available within the NHS.

Intervention

The AT-PR was exclusively designed for adults with severe asthma using the Medical Research Council complex intervention guidelines and the existing model of PR(21). AT-PR

was delivered by our local PR team but only adults with severe asthma attended the classes following patient consultation(19). The programme duration was 12 weeks with two supervised sessions per week, each lasting for two hours: one hour of exercise training and one hour of multidisciplinary education. The exercise component is described in detail within the protocol(19) and Table 1. The education programme was developed using qualitative interviews(22) with patients and healthcare professionals, patients involved with our research group, consultation with other asthma professionals and experts in patient education. Each week there was interactive session around 12 topics (Figure 2) delivered by relevant healthcare professionals and an individualised session led by a health psychologist to support behaviour modification, and to enable individualised goal setting and action planning.

Both groups were seen by physicians specialising in the care of patients with severe asthma and were under the care of a severe asthma multidisciplinary team.

Safety

Adverse event reporting is described in the study protocol(19). Based on an a priori serious adverse event rate of 2.5% (requiring hospitalisation) the estimated rate would be <13%.

Exercise induced bronchoconstriction (EIB) was assessed post cardiopulmonary exercise tests according to ATS/ERS guidelines(23) by measuring FEV₁ before and repeatedly after at 5, 10, 15, 20 and 30 minutes post exercise. However, patients were allowed to take their regular inhaled medication. EIB severity was defined by the percentage decrease in FEV₁ from baseline : mild $\geq 10\%$ to $<25\%$, moderate $\geq 25\%$ to $<50\%$ and severe if $\geq 50\%$ as per ATS guidelines on EIB.

Assessments (all completed by a blinded assessor)

Cardiopulmonary exercise tests (CPET) were performed using Quark Cart (COSMED-Rome, Italy) and ventilatory and gas exchange data were recorded breath by breath. All patients performed a maximal incremental exercise test on a treadmill (ITM) with an optional test on a cycle-ergometer (ICE). Patients were randomly assigned to ITM or ICE on separate days. Maximum work load for the ICE was estimated(24) with the aim to elicit a test within 8 to 12 minutes. For the treadmill, we used a protocol designed to achieve a linear response(25) using simultaneous changes in speed and grade. The modified Borg Scale for Dyspnoea(26) and rating of Perceived Exertion(27, 28) were used during each CPET. For both tests, patients were advised to take their usual inhalers and were not pre-medicated with extra salbutamol dose. Patients were asked their preferred platform.

Shuttle walk tests. Patients performed a familiarisation modified Incremental Shuttle Walk Test (ISWT)(29) and then two further tests on the same day(30). The highest value was used as the baseline measure, for the speed of the Endurance Shuttle Walk Test (ESWT)(31, 32) and for the exercise prescription.

Quadriceps muscle strength was assessed by isometric knee extensor force production using a Cybex NORM dynamometer (Cybex international, NY, USA). The measurement was repeated until participants had three readings within 5% of each other and the peak value was recorded.

Asthma control was assessed using Asthma Control Questionnaire (ACQ)(33) with a score below 0.75 representing well-controlled asthma and above 1.5 representing inadequately controlled asthma(34). FeNO was measured using a handheld portable NIOX MINO® device (Aerocrine; Solna, Sweden) in accordance with guidelines published by the ATS.

Patients underwent sputum induction using previously described methods(35) if they were unable to provide a spontaneous sputum sample. Prior to testing, patients inhaled 200 mg of salbutamol. Patients were asked to blow their nose and rinse their mouth with water.

Sputum induction was undertaken using normal saline given via an ultrasonic nebulizer, followed by successive concentrations of saline from 3% up to 5% to aid expectoration. The expectorate was processed within 2 hours.

Health-related quality of life was assessed through both Chronic Respiratory Questionnaire (CRQ)(36) and Asthma Quality of Life Questionnaire (AQLQ)(37). Both questionnaires have four domains including dyspnoea, fatigue, emotional function and mastery for CRQ and symptoms, activity limitation, emotional function and environmental stimuli for AQLQ. For both questionnaires, higher scores in each category indicate better health related quality of life. The Euroqol EQ5D-3L(38) was used to assess generic quality of life.

Psychological morbidity was assessed using the Hospital Anxiety and Depression Scale (HADS)(39) which include anxiety and depression domains; a score of 0 to 7 is regarded as normal and a score of ≥ 11 indicates probable presence of a mood disorder.

Statistical analysis

The normality of data was assessed via the Kolmogorov-Smirnov test. For baseline characteristics, an independent t-test was used to compare the parametric data between participants randomised to UC and AT-PR. Categorical data were compared using Chi-squared (χ^2) test. As the study was not powered for the change in secondary outcome measures data only are described. For within group pre to post-intervention results, paired t-test was used for parametric data and Wilcoxon Rank test for non-parametric data. The between group differences pre- to post-intervention (12 weeks) were analysed using two-way analysis of covariance (ANCOVA) to adjust for the baseline differences between groups.

Sample size

We planned to recruit 40 patients to the intervention arm and 20 patients to UC. We estimated to recruit 30% of those invited in order to estimate the recruitment rate with a

precision of at least $\pm 7\%$. We estimated a retention rate of 75% and the precision of the estimated retention rate would be at least $\pm 14\%$ if we recruited 40 patients to AT-PR(19).

Results

61 patients were recruited (62% females, mean [SD] age 54 [13] yrs, BMI 32 [7] kg/m², FEV₁ 1.9 [0.7] L, FEV1 % predicted 69 [19] %, 69% were atopic (defined as the presence of a positive skin test or specific IgE to at least one common aeroallergen), median [IQR] MRC dyspnoea scaled grade 2 [2-3]. The baseline characteristics were similar between the AT-PR and UC groups except for lung function which was better in the usual care group (FEV1 % predicted 77 [13] % vs 65 [21] %). All patients were prescribed high dose inhaled corticosteroids (>1000 μ g beclomethasone equivalent) mean [SD] 1562 [325] mcg, 56% were prescribed oral prednisolone and only 1 was prescribed omalizumab. Sputum eosinophil percentage was <3% in 62.7% of participants.

A study flow diagram is shown in Figure 3. The recruitment rate was 26% which falls within the 95% CI (23% to 37%) estimated for the recruitment rate. The retention rate from visit one to post intervention period was 49% and for nine month follow up was 38%. Retention rates after randomisation to post-intervention period were 62% for AT-PR was and 53% for UC. The retention rate for the AT-PR group fell within the lower limit of 95% CI of the estimated retention rate; 61% to 89%. A comparison of baseline characteristics between completers and non-completers of the study is shown in Table 2.

Thirteen SAEs were reported for the whole duration of the trial, 11 were related to asthma, and seven resulted in dropping out of the study completely. There were the same proportion of SAEs in the intervention and usual care groups and none were directly related to the intervention. Two were directly related to the study visits (3.3%) where two patients

developed EIB after the ITM test requiring observation in Glenfield hospital; one was transferred to intensive care without requiring intubation (and subsequently found to have an illness unrelated to asthma) and the other patient was discharged home after four hours.

Feasibility of assessment for secondary outcome measures

Collection of all outcome measures for the future larger trial was feasible (Table 3). Two patients were unable to perform the ICE test: one patient had leg length discrepancy causing discomfort with cycling and the other was unable to reach the pedals due to short stature. A baseline sputum sample was unavailable in three patients due to either a contraindication of the test (reduced FEV₁ (L)), termination of induced sputum due to a reduction in FEV₁, or no sample produced. Sputum quality was poor for 6/49 patients. Two patients were unable to perform the FeNO test despite several attempts and one did not complete the test due to study withdrawal.

Secondary outcome measures

A comparison of the secondary outcome measures between groups post-intervention period at 12 weeks is shown in Table 4. The trend was for an improvement in exercise performance, asthma control and dyspnoea related health-related quality of life after AT-PR compare to usual care.

Exercise-Induced Bronchoconstriction was elicited more frequently on the ITM (13/51) than the ICE (3/49) at baseline, and overall appeared unchanged after AT-PR and UC.

Our data did not show any reduction in airway eosinophilic inflammation (sputum eosinophil count and FeNO) after 12 weeks of exercise training compared to usual care.

Follow up period

Long term effect of AT-PR after nine months follow up period compared to the baseline measures are shown in Table 5, between AT-PR and UC groups. The numbers are small particularly in the usual care group limiting meaningful interpretation. However, some improvements in exercise capacity, strength, and dyspnoea were potentially sustained in the AT-PR group, whereas the usual care group results were either unchanged or worsened.

Discussion

The primary aim of this study was to assess the feasibility of undertaking a future large multicentre randomised controlled trial comparing AT-PR with UC for patients with severe asthma, focussing on recruitment, retention and adverse event rates. To the best of our knowledge this is the first description of patients with severe asthma participating in exercise training compared to usual care and the first description of asthma-tailored pulmonary rehabilitation. The recruitment rate for the current study was within the 95% CI of the estimated recruitment rate (23% to 37%). The retention rate for AT-PR was only just within the lower limit of the 95% CI of the estimate (61% to 89%) but the retention rate for the usual care group was not any higher. The high hospitalisation rate >10% reflects the instability of adults with severe asthma compared to those with mild-moderate disease highlighting another challenge for this group and supporting the rationale to study solely patients with severe disease. The overall retention rate for the trial was lower than expected 38% and we had more dropouts prior to randomisation than expected.

Work commitments, child care and travel issues were common barriers to participation in the trial and patients who completed the trial were older (58 years) compared to the non-completers (50 years). Overall patients in a severe asthma service are younger than a typical

PR population and more flexible timings such as evening or weekend sessions may be needed to accommodate patients. Provision for an offer of evening classes had been agreed to improve accessibility to AT-PR during the study period, but the group sizes were always too small to provide this highlighting a practical limitation of delivering separate PR programmes for single disease groups.

Non-completers of the trial potentially had underlying psychological co-morbidity reflected in their higher anxiety scores and worse emotional function scores compared to completers. Depression is a recognised predictor of non-adherence to PR programmes in asthma and COPD(40). Hence, offering psychological support and management for patients where needed prior to participation in an exercise intervention may improve acceptability of the service. 10% of dropouts were due to not being able to commit to the study visits. In order to assess the best outcome measures for a future trial there were two to three research visits at each time point which may have negatively impacted retention to the trial. Therefore, we would advocate a single research visit at the relevant time periods in future.

There were no adverse events directly related to the AT-PR sessions. However, two serious adverse events occurred after the treadmill test during a study visit and the higher prevalence of EIB on treadmill compared to cycle ergometer raises a concern regarding the safety of this particular ITM protocol for patients with severe asthma. Achieved peak oxygen uptake and minute ventilation have been reported to be lower on maximal exercise tests performed on a cycle ergometer compared to a treadmill(41, 42) and our data reflects this. It is also of note that testing on the cycle ergometer was preferred to the treadmill by participants. We were also exploring the physiological limitations to exercise so had chosen not to administer short acting beta-agonists immediately prior to the exercise tests, but patient were advised to take their regular prescribed medication which included inhaled long-acting beta-agonists. These

adverse events highlight the need for access to medical support during maximal exercise testing for this population and further preventative measures for EIB prior to ITM for this group of patients, for example variable intensity pre-exercise warm up and use of short acting bronchodilators(43).

We showed that collection of all the selected outcome measures was feasible among patients with severe asthma. However, a high number of the spontaneously obtained sputum samples were poor quality and therefore performing sputum induction where patient characteristics and time allows would likely result in better quality sputum samples.

Our study was not powered to detect differences in the change for any of the secondary outcome measures either intra- or inter-group. However, the trend after three months of the intervention for those who completed was towards a positive effect of AT-PR compared to UC on exercise performance, HRQoL and asthma control; we note the usual care group had higher physical functioning, better health-related quality of life, and lower anxiety and depression scores. Previous studies have shown a beneficial effect of a 12-week exercise training on patients with moderate to severe asthma in terms of exercise performance and health-related quality of life(14, 44), but again the majority of participants had moderate disease. In line with previous studies, our study did not show any changes in lung function after a period of AT-PR(11). However, a recent meta-analysis including individuals with asthma across the severity spectrum showed a slight improvement in lung function with exercise training (45).

In our study, sputum eosinophil count and FeNO levels appeared unchanged with AT-PR compared to UC, and eosinophilic airway inflammation was controlled in the majority of patients at baseline. These results are similar to systematic reviews on the effect of exercise training on airway inflammation(45,46) which showed no overall effect on FeNO with

exercise training. One study showed a decrease in sputum eosinophil count with training(12) but airway inflammation was high at baseline and adherence to medication (not assessed) may have improved during the trial accounting for some of the improvements seen. In contrast a further study (15) also involving patients with moderate to severe asthma showed no overall effect of training on either sputum eosinophil count or FeNO level with exercise training compared to control.

Overall in our study, EIB appeared unaltered after AT-PR or usual care in keeping with a lack of effect on measures of eosinophilic type 2 airway inflammation. However, a higher prevalence of EIB might be expected after training as a higher minute ventilation predisposes the airways to higher degree of water loss and an increase in airway surface osmolarity leading to the release of mediators causing smooth muscle contraction(48). However, two meta-analyses also report no significant change in EIB overall with exercise training in patients with asthma(46,49).

In conclusion, exercise training, education and behavioural modification for improved self-management and adherence to a healthy lifestyle delivered by the model of pulmonary rehabilitation and tailored for patients with severe asthma may be safe and efficacious for those that attend and complete. However, from this small single centre study it is clear that the intervention is not accessible or acceptable for all patients with severe asthma. A future intervention and trial design would need modification to improve accessibility, acceptability and retention rate.

Author contributions

Conception and design: RA Evans, RH Green, P Bradding, SJ Singh, L Apps, N Hudson and E Eglinton; recruitment and conduct of the study: S Majd, S Chantrell, L Apps, B Hargadon, AC Murphy; research analysis and interpretation: S Majd, RA Evans, RH Green, P Bradding; drafting the manuscript: S Majd, R. Evans; Refining and approving the final manuscript: S Majd, RA Evans, RH Green, P Bradding, SJ Singh, L Apps, AC Murphy, B Hargadon, E Eglinton, S Chantrell, N Hudson.

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Table 1. Exercise Component for 12 Week Asthma-Tailored Pulmonary Rehabilitation (AT-PR)

AEROBIC TRAINING	Supervised	Unsupervised
Frequency	Twice weekly	Minimum one additional session at home but daily walk encouraged when not in class and diary kept
Intensity	85% peak VO_2 derived from the ISWT distance, 60-80% peak VO_2 for treadmill walking or additional cycling	As per supervised
Time	20 – 30 minutes	As per supervised
Type	Predominantly continuous endurance training with ground walking. Treadmill walking and cycling also utilised	Ground walking
STRENGTH TRAINING	Supervised	Unsupervised
Frequency	Twice weekly	One additional session at home
Intensity	80% one repetition maximum (1-RM) progressed using ratings of perceived exertion (Borg Scale)	As per supervised
Time	Two sets of 6-12 repetitions	As per supervised
Type	Knee extensors and flexors using gym equipment Elbow flexion and extension using free weights	As per supervised for upper limb exercises Lower limb strengthening exercise such as sit to stand and step ups

Table 2. A comparison of the characteristics between completers and non-completers of the trial at three months

	Completers (n = 30)	Non-completers (n =31)
Age (yrs)†	58 (11)	50 (15)
Female, n (%)	18 (60%)	20 (65%)
BMI (kg/m ²)	32 (5)	33 (8)
MRC, median (IQ)	2 (2)	2 (2-3)
FEV ₁ (L/min)	1.7 (0.7)	2.2 (0.7)*
FEV ₁ %predicted	65 (18)%	73 (19)%
FEV ₁ /FVC†	66 (10)	72 (12)
Atopic, n (%)	20 (67%)	22 (71%)
ICS (mcg)†	1683 (291)	1445 (316) *
Oral prednisolone, n (%)	17 (57%)	17 (55%)
ACQ	1.9 (0.8)	2.1 (1.0)
CRQ Dyspnoea	3.3 (1.3)	3.3 (1.6)
CRQ Fatigue	4.0 (1.4)	3.5 (1.4)
CRQ Emotional Function	5.4 (1.3)	4.4 (1.4)
CRQ Mastery	5.1 (1.4)	5.4 (3.0)
Total AQLQ	20.0 (4.3)	18.6 (5.5)
AQLQ Symptom	5.1 (1.1)	4.7 (1.4)
AQLQ Activity Limitation	5.0 (1.2)	4.8 (1.3)
AQLQ Emotional Function	5.0 (1.4)	4.4 (1.6)
AQLQ Environmental Stimuli	4.8 (1.3)	4.7 (1.8)
HADS Anxiety	5.4 (4.1)	7.8 (5.5)
HADS Depression	4.2 (2.6)	5.5 (3.8)
ITM VO _{2pk} (ml/kg/min)	22.6 (5.5)	23.0 (5.9)
ICE VO _{2pk} (ml/kg/min)	17.4 (5.0)	18.9 (5.0)
ISWT Distance (m)	425 (157)	493 (153)
QMVC (Newton)	106 (48)	113 (38)
FeNO (ppb)†	28 (18 to 38)	29 (16 to 44)
Sputum Eosinophil (%)	-0.10 (1.0)	0.13 (1.0)

Data presented as mean (SD) unless †: median (IQR), *: $p < 0.05$ between groups, ACQ: Asthma Control Questionnaire, CRQ: Chronic Respiratory Questionnaire, AQLQ: Asthma Quality of Life Questionnaire, HADS: Hospital anxiety and Depression Scale, ITM: incremental treadmill test, ICE: incremental cycle-ergometer test, VO_{2pk} : peak oxygen uptake, ISWT: Incremental Shuttle Walk Test, QMVC: quadriceps maximal voluntary contraction, FeNO: fractional exhaled nitric oxide

Table 3. Percentage of secondary outcome measures completed

	Completion rate at baseline	Completion rate at 12 weeks
ITM	100%	97%
ICE	96%	80%
ISWT	98%	100%
QMVC	100%	97%
ACQ	98%	100%
AQLQ	98%	100%
CRQ	98%	100%
HADS	98%	100%
Sputum Sample	82%	70%
FeNO	98%	93%
Spirometry	100%	97%
DEXA Scan	100%	90%

Data presented as percentage of patients who completed the test, ITM: incremental treadmill test, ICE: incremental cycle-ergometer test, ISWT: Incremental Shuttle Walk Test, QMVC: quadriceps maximal voluntary contraction, ACQ: Asthma Control Questionnaire, AQLQ: Asthma Quality of Life Questionnaire, CRQ: Chronic Respiratory Questionnaire, HADS: Hospital Anxiety and Depression Scale, FeNO: fractional exhaled nitric oxide, DEXA: dual energy x-ray absorptiometry

572 **Table 4. A comparison of the secondary outcome measures between Asthma-Tailored Pulmonary**
 573 **Rehabilitation and Usual Care at 12 weeks**

	AT-PR		Usual Care		AT-PR vs. UC
	Before	After	Before	After	Change
ITM VO_{2pk} (ml/kg/min)	22.5 (6.2)	23.2 (7.6)	22.9 (3.9)	22.3 (2.4)	1.4 (-1.1 to 3.8)
EIB on ITM					NA
Mild	7 (33%)	8 (38%)	1 (12.5%)	3 (37.5%)	
Moderate	2 (10%)	3 (14%)	1 (12.5%)	1 (12.5%)	
Severe	2 (10%)	0 (0%)	0 (0%)	0 (0%)	
ICE VO_{2pk} (ml/kg/min)	17.5 (6.0)	18.8 (6.9)	16.9 (4.3)	16.1 (2.8)	2.0 (-0.3 to 4.2)
EIB on ICE					NA
Mild	3 (17%)	5 (28%)	0 (0%)	1 (17%)	
Moderate	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
ISWT Distance (m)	418 (172)	450 (199)	443 (121)	403 (104)	74 (25 to 124)
QMVC	103 (53)	116 (64)	113 (35)	110 (28)	22 (4 to 41)
Sputum Eosinophil (%)	-0.46 (1.01)	0.26 (1.07)	0.30 (0.49)	-0.01 (0.18)	NA
FeNO † (ppb)	28.5 (13.5 to 37.0)	25.0 (19.0 to 35.0)	28.5 (18.5 to 53.3)	37.5 (21.3 to 51.8)	NA
ACQ	2.1 (0.8)	1.9 (0.8)	1.5 (0.9)	1.9 (1.0)	-0.4 (-0.9 to 0.1)
CRQ-D	3.1 (1.2)	4.1 (1.3)	3.7 (1.5)	3.6 (1.1)	0.9 (0 to 1.8)
CRQ-F	3.7 (1.8)	4.7 (1.2)	4.7 (1.7)	4.4 (1.6)	0.9 (-0.1 to 1.8)
CRQ-EF*	5.1 (1.4)	5.4 (1.1)	6.1 (0.7)	6.1 (0.8)	-0.1 (-0.6 to 0.5)
CRQ-M*	4.7 (1.3)	5.4 (1.1)	6.1 (1.0)	6.0 (0.8)	0.2 (-0.5 to 0.9)
AQLQ*	19.0	19.7	22.2	21.7	-0.2

	(4.5)	(4.0)	(3.0)	(2.6)	(-2.7 to 2.3)
AQLQ-S	4.9 (1.2)	5.1 (1.1)	5.6 (0.9)	5.6 (0.9)	-0.1 (-0.7 to 0.6)
AQLQ-AL	4.8 (1.3)	5.0 (1.1)	5.3 (0.8)	5.1 (0.9)	0.2 (-0.5 to 0.8)
AQLQ-EF*	4.6 (1.4)	4.9 (1.2)	6.0 (0.8)	5.7 (1.1)	0.1 (-0.7 to 0.9)
AQLQ-ES	4.6 (1.4)	4.6 (1.5)	5.3 (1.1)	5.2 (0.7)	-0.2 (-1.2 to 0.8)
HADS-A*	6.3 (4.4)	5.1 (3.7)	3.2 (2.5)	2.4 (2.8)	0.4 (-1.3 to 2.1)
HADS-D*	4.8 (2.7)	3.5 (2.8)	2.8 (1.6)	2.4 (1.0)	-0.3 (-1.9 to 1.3)
EQ-5D VAS Score	68.0 (14.2)	73.4 (13.2)	82.8 (16.4)	72.8 (26.1)	15.4 (1.7 to 29.1)
EQ-5D Index Score	0.85 (0.14)	0.85 (0.13)	0.94 (0.10)	0.88 (0.14)	0.05 (-0.05 to 0.15)

Data presented as mean (SD) for before and after intervention except for †: median (IQR), data presented as mean difference (95% CI) for changes between groups, *: significant difference at baseline between groups ($p < 0.05$), AT-PR: asthma tailored pulmonary rehabilitation, UC: usual care, ITM: maximal incremental treadmill test, VO_{2pk} : peak oxygen uptake, ICE: maximal incremental cycle-ergometer test, ISWT: incremental shuttle walk test distance, EIB: exercise induced bronchoconstriction, ACQ: Asthma Control Questionnaire, ACQ-6: Asthma Control Questionnaire without the question on lung function test, CRQ: Chronic Respiratory Questionnaire, D: dyspnoea, F: Fatigue, EF: emotional function, M: mastery, AQLQ: Asthma Quality of Life Questionnaire, S: symptom, AL: activity limitation, ES: environmental stimuli, HADS-A: anxiety domain of Hospital Anxiety and Depression scale, HADS-D: depression domain of HADS, VAS: visual analogue scale, VO_{2pk} presented in ml/kg/min, ISWT distance presented in m, QMVC presented in newton, FeNO presented in ppb. Comparisons for FeNO and Sputum eosinophils not provided due to small numbers in usual care.

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Table 5. A description of the secondary outcome measures at baseline and nine months for the Asthma-Tailored Pulmonary Rehabilitation and Usual Care groups

	AT-PR Group (n=17)		UC Group (n=6)	
	Before	Follow-up	Before	Follow-up
ITM VO _{2pk} (ml/kg/min)	22.5 (6.2)	24.1(10.4)	22.9 (3.9)	20.3 (3.3)
ICE VO _{2pk} (ml/kg/min)	17.5 (6.0)	20.6 (8.9)	16.9 (4.3)	16.9 (4.2)
ISWT Distance (m)	418 (172)	412 (245)	443 (121)	421 (76)
QMVC (N)	103 (53)	113 (66)	113 (35)	103 (21)
ACQ	2.1 (0.8)	2.0 (0.7)	1.5 (0.9)	2.0 (0.7)
CRQ-D	3.1 (1.2)	3.7 (1.2)	3.7 (1.5)	3.9 (1.6)
CRQ-F	3.7 (1.1)	3.7 (1.1)	4.7 (1.7)	4.5 (1.5)
CRQ-EF	5.1 (1.4)	5.0 (1.1)	6.1 (0.7)	5.6 (1.4)
CRQ-M	4.7 (1.3)	5.2 (1.1)	6.1 (1.0)	5.9 (1.1)
AQLQ-S	4.9 (1.2)	5.0 (1.1)	5.6 (0.9)	5.3 (1.3)
AQLQ-AL	4.8 (1.3)	4.3 (1.2)	5.3 (0.8)	5.4 (0.9)
AQLQ-EF	4.6 (1.4)	4.7 (1.2)	6.0 (0.8)	6.1 (1.1)
AQLQ-ES	4.6 (1.4)	4.2 (1.5)	5.3 (1.1)	5.5 (0.8)
HADS-A	6.3 (4.4)	6.6 (3.7)	3.2 (2.5)	3.6 (2.9)
HADS-D	4.8 (2.7)	5.4 (3.3)	2.8 (1.6)	3.1 (2.8)
EQ-5D VAS Score	69.8 (14.0)	70.2 (13.1)	79.4 (21.1)	75.8 (13.6)
EQ-5D Index Score	0.85 (0.14)	0.79 (0.13)	0.92 (0.12)	0.88 (0.14)

Data presented as mean (SD), AT-PR: asthma tailored pulmonary rehabilitation, UC: usual care, ITM: maximal incremental treadmill test, VO_{2pk}: peak oxygen uptake, ICE: maximal incremental cycle-ergometer test, ISWT: incremental shuttle walk test distance, ACQ: Asthma Control Questionnaire, ACQ-6: Asthma Control Questionnaire without the question on lung function test, CRQ: Chronic Respiratory Questionnaire, D: dyspnoea, F: Fatigue, EF: emotional function, M: mastery, AQLQ: Asthma Quality of Life Questionnaire, S: symptom, AL: activity limitation, ES: environmental stimuli, HADS-A: anxiety domain of Hospital Anxiety and Depression scale, HADS-D: depression domain of HADS, VO_{2pk} presented in ml/kg/min, ISWT distance presented in m, QMVC presented in newton, FeNO presented in ppb

Figure 1. Study design

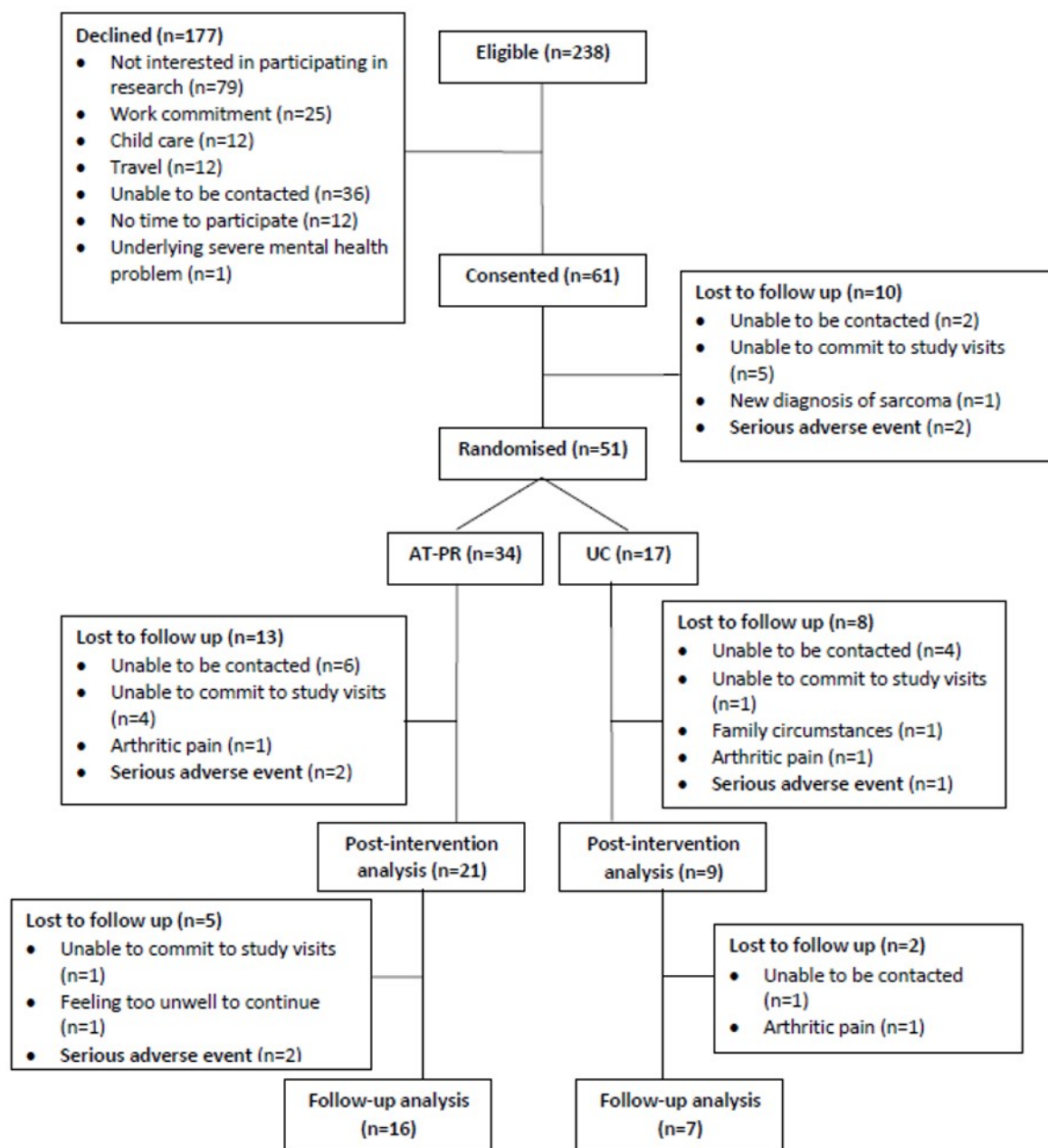
*: tests performed on visit one, †: tests performed on visit two, ‡: tests performed on visit three, ¥: if patients were unable to provide spontaneous sputum sample they had sputum induction on visit two, FeNO: fractional exhaled nitric oxide, ITM: maximal incremental treadmill test, ICE: maximal incremental cycle ergometer test, ISWT: incremental shuttle walk test, DEXA: dual energy x-ray absorptiometry, ESWT: endurance shuttle walk test

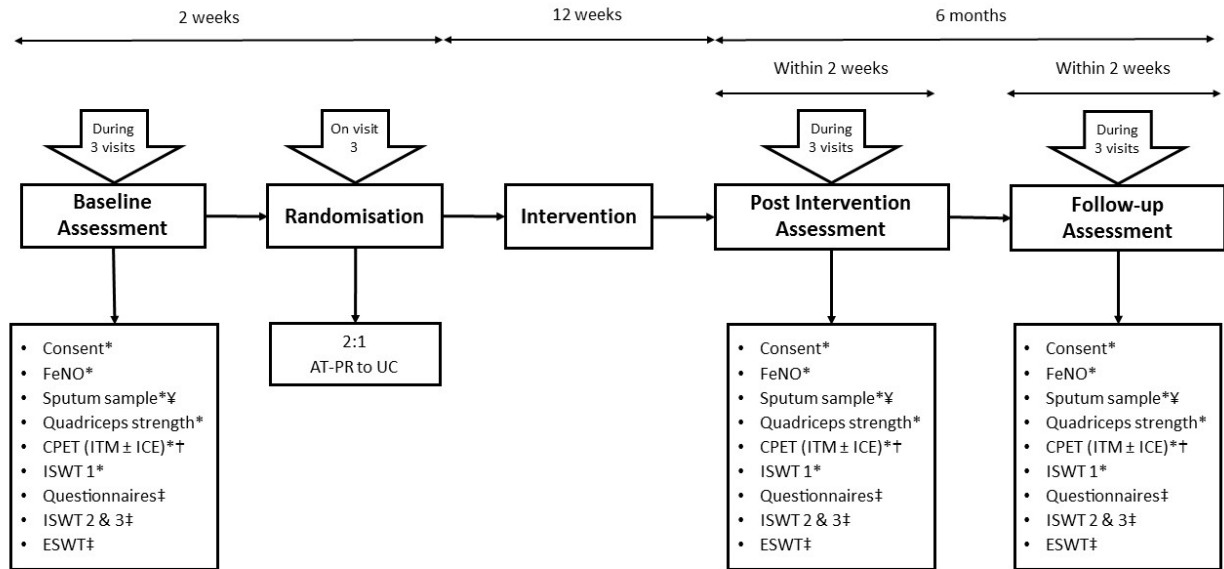
Figure 2. Topics included within 12 interactive sessions delivered by healthcare professionals

Figure 3. Consort Study Flow Diagram

n: number, AT-PR: asthma-tailored pulmonary rehabilitation, UC: usual care.

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- Medication management
- Inhaler technique
- Managing breathlessness
- Managing anxiety
- Managing exacerbations
- Asthma control and self-management
- Identifying and managing aggravating factors
- Specific disease education
- Exercise
- Nutrition
- Healthy lifestyle including smoking cessation
- Sputum clearance
- Signposting to support including other organisations

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