Study Title:	A comprehensive comparison of the sensitivity of common exercise outcome measures for Chronic Obstructive Pulmonary Disease (COPD)	
Ethics Ref:	REC Reference - 12/WM/0306	
Date and Version No:	V8, 20th September 2016	
Chief Investigator	Professor Sally Singh	UHL, UK
Co-Lead Investigator	Professor Mike Morgan	UHL, UK
	Professor Michael Polkey	RBHFT, UK
Investigators	Theresa Harvey-Dunstan	UHL, UK
	Dr Ruth Tal-Singer	GSK, USA
	Dr William Man	RBHFT, UK
	Alan Hamilton	BI, UK
	On behalf of the COPD MAP WP4	
Other Protocol Contributors	Matthew Allinder	GSK, USA
	Ronnan Roubenoff	Novartis, USA
	Matthew Heasley	GSK, UK
	Nicholas Locantore	GSK, USA
	Matthew Richardson	Leicester BRU, UK
Sponsor	University Hospital Leicester,	UHL, UK

Protocol Signatures

I give my approval for the attached protocol.

Chief Investigator

Name: Professor Sally Singh

Signature: _____

Date: _____

Site Signatures

I have read the attached protocol and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the research without the prior written consent of the Sponsor.

Site Principal Investigator

Name: Professor Sally Singh

Signature: _____

Date: _____

Abbreviations

6MWT	6 minute walk test
ASIS	Anterior Superior Iliac Spine
ATS	American Thoracic Society
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
CPET	Cardio Pulmonary Exercise Test
CWR	Constant Work Rate
ERS	European Respiratory Society
ESWT	Endurance Shuttle Walk Test
ISWT	Incremental Shuttle Walking Test
LAMA	Long acting muscarinic antagonist
LTOT	Long Term Oxygen Therapy
MRC	Medical Research Council
MVC	Maximum Voluntary Contraction
PROactive	Electronic Diary for Physical Activity
QMVC	Quadriceps Maximum Voluntary Contraction
RPE	Rate of Perceived Exertion Score
SAMA	Short acting muscarinic antagonist
SPPB	Short Physical Performance Battery
Tlim	Constant workload cycle endurance time to limitation

TABLE OF CONTENTS

SYNOPSIS:

Study Title	A comprehensive comparison of the sensitivity of common exercise outcome measures for Chronic Obstructive Pulmonary Disease (COPD)
Sponsor Reference	UHL 111456
Study Design	Open label comparison of two proven interventions in COPD to assess responsiveness of exercise tests
Study Participants	Adult COPD subjects
Planned Sample Size	Phase 1, n=60 (to allow for drop out & interim analysis after the last visit of patient #50) Phase 2, further 79 (allowing for a 25% drop out) Total recruitment of 139 subjects
Follow-up duration	Six weeks
Planned Study Period	17 Months – Phase 1 (March 2013 – December 2014) 24 Months – Phase 2 (December 2015 – November 2017)
Aims	To assess the responsiveness of a range of exercise tests in relation to six minute walk
Outcome measures	ISWT, ESWT, 6MWT, endurance cycle, incremental cycle, SPPB, PROactive, Accelerometery.

Aim

By conducting a comprehensive comparison of exercise tests commonly employed to assess functional capacity in subjects with COPD we aim to secure a wider understanding of the relative properties (stability and sensitivity) of the these tests to guide clinical trial outcome selection. The study will produce data which are sufficiently robust to provide information for the regulatory bodies regarding the assessment of activity limitation in COPD for future clinical trials.

Hypothesis

The 6MWT is the least sensitive test that can be employed in the assessment to response to treatment of either pulmonary rehabilitation or bronchodilator therapy.

Background

Exercise outcomes are required to capture outcomes relevant to subjects missed by spirometry

Traditional measures of airflow obstruction such as FEV_1 offer an inadequate reflection of the impact of COPD and are not influenced by otherwise effective therapy, particularly pulmonary rehabilitation (1, 2). Conversely exercise tests are used to assess activity limitation (disability) and are capable of improvement after various therapies, including bronchodilators (3). Several exercise tests have been described for this purpose. The existing tests vary in the required physical environment (laboratory vs. field), exercise platform (cycling vs. walking) or protocol (maximal vs. endurance, paced vs. self-paced). There has been no comprehensive comparison of the relative reproducibility and sensitivity of these tests when performed concurrently.

Existing tests span a range of complexity

Laboratory tests of cardio-pulmonary function may be seen as the gold standard but are costly in terms of equipment and staff expertise. Field-based exercise tests have been developed as an alternative to laboratory testing. The most common field tests are the six minute walking test (6MWT) and the incremental shuttle walking test (ISWT). Both field-based exercise tests are reproducible, accessible and inexpensive, and are increasingly being used as an outcome measure for a number of interventions including pulmonary rehabilitation, lung volume reduction surgery and bronchodilator therapy (2, 4, 5). Six minute walk in particular is an accepted outcome for the FDA for pulmonary hypertension and pulmonary fibrosis. However the literature is inconsistent, numerous studies have investigated the impact of bronchodilators (LABA, LAMA and combinations), anabolic agents, and anti-inflammatories (e.g. PDE4s Roflumilast and Cilomilast, anti-TNF, and neutrophil elastase inhibitor) on exercise capacity, using a variety of interventions and a number of different outcome measures to assess the benefit. It remains unclear whether the inconsistent literature relates to the choice of test, the choice of intervention or the study population.

PROactive

PROactive is a €14m joint public private partnership between academia funded by the EU IMI and a pharma consortium. The PRO tool combines a newly developed PRO together with physical activity monitoring. The PRO steering board has determined that the responsiveness of the PRO tool in comparison with other exercise outcomes requires further data.

The interrelationship between tests remains undefined

There are several reports describing the individual properties of tests (6-10) and the use of two tests simultaneously before and after an intervention (3, 11), and one recent study has compared the baseline properties of the two walking tests to CPET (12). With this exception there is however, no data regarding the overall comparison of the broad range tests covering their reproducibility and sensitivity to a standard intervention. A review (13) of the exercise tests in the context of bronchodilators assessment has recently been described. All the studies were small scale and used an inconsistent approach to the outcome measures employed. It is most likely that a combination of outcome measures may need to be employed depending upon the nature of the intervention, reflecting the impact of disease upon lung function, disability and participation.

In order to perform a comparative assessment of exercise outcome the investigators appreciate that it is necessary to have an effective intervention. Pulmonary rehabilitation has been shown to favourably impact a range of exercise interventions (1, 2, 14-16). Likewise for long acting muscarinic anagonist therapy (LAMA) there have been a number of small scale studies which have included physical performance as an outcome (17-22). Taken together this work suggests that a walking test may be more sensitive than a cycle test to detect the impact of a LAMA, suggesting that this will also be an effective stimulus to change exercise performance.

Method

Subjects (approximately, to allow for withdrawals) will be recruited from clinics, trial registers and pulmonary rehabilitation (PR) waiting lists along with subjects identified from primary care COPD registers and poster response from displays at GP practices and hospitals. Subjects will be randomised to one of 3 groups (control:PR:LAMA) in a 1:2:2: allocation for phase 1 and a 1:1:4 for phase 2 of the trial. The aim will not be to evaluate the interventions but simply to produce a range of change in performance so that the changes in the exercise tests employed can be evaluated. The five most commonly reported exercise tests, strength testing and the Short Physical Performance Battery will be examined at baseline and after 6 weeks of the intervention or control period. The outcome measures will be conducted by blinded assessors. A planned analysis will be conducted after the 50th patient's last visit to confirm that commitment of the full resource and the 'opening' of other sites will deliver the desired data.

Eligible participants

The subjects will have a confirmed diagnosis of COPD and have GOLD stage 2-4 disease, and MRC grade dyspnoea2 or greater. Participants will be restricted to 40-85 years, so that they align with the 'classic' COPD patient. Since the aim is to compare different exercise outcomes, participants will not be stratified by exercise performance at baseline. However review of two sites (Leicester and RBHT) entrants to pulmonary rehabilitation programs suggests, based on ISWT data, that ~80% of participants will have an 6MWT <350m[1].

Exclusion criteria

Participants will be excluded from the trial if they have co-morbidities that limit the ability to walk/cycle, for example musculo-skeletal, arthritic, or neurological disorders. Common COPD co-morbidities such as controlled hypertension or heart failure will not be excluded, but will be documented. Since rehabilitation

[1] For example of 173 consecutive subjects in a currently submitted MS from Harefield the 75th centile for ISWT was 283m.

is one of the interventions, subjects who have participated in rehabilitation over the last 12 months will also be excluded, simply because they may not then gain additional benefit. Participants using LTOT therapy will also be excluded as will those requiring oxygen therapy during the course of an exercise test (i.e. desaturation documented below 85%)

Because of the lack of robust pilot data (*vide infra)* an interim analysis will be conducted once 50 subjects have completed all post intervention follow-up visits. or after recruitment of the 60th patient. One centre (Leicester) will generate phase 1 data for the sample size re-estimation prior to transition to Phase 2 (page 14). Adjustments to hypothesis will be informed from interim analysis data.

Subjects will be approached from waiting lists, clinics, rehabilitation services or departmental research databases. A patient information sheet will be given and potential participants will have at least 24 hours to consider taking part in the study. Subjects will be recruited and randomised, using a computerised randomisation service, to one of three arms as described below. Current medication will be maintained except if necessary LAMA will be withdrawn 2 weeks prior to baseline measurements and replaced with SAMA in the group randomised to the pharmaceutical bronchodilator arm. For those participants not on a LAMA upon recruitment, but with an FEV_1 less than 50% predicted a LAMA will routinely be prescribed. This is in accordance with the updated NICE COPD guidelines[2] (recommendation U7).

Exercise tests selected are shown below:-

1. Laboratory

- Maximal incremental symptom-limited cycle ergometer cardio-pulmonary exercise test
- Endurance cycle exercise test: Constant work load (85% maximum peak workload achieved during maximal CPET) at a target of rpm 60.

Subjects will perform a maximal symptom-limited incremental exercise test on an electrically-braked cycle ergometer (ramp protocol, increments 10Watts/minute) and an endurance cycle test conducted at 85% of peak workload. Ventilation and gas exchange measurements will be made throughout the exercise tests using a breath-by-breath computerised system[3]. Initial, end-exercise, 3 minutes recovery and during loaded testing (every 2 minutes), the Borg breathlessness Score, RPE Score will be recorded along with reason for termination.. The same variables will be collected pre and post intervention/control periods and iso-time data with respect to peak performance measures on the initial assessment will be reported on post intervention measurements. All inhalers will be withheld for 6 hours prior to measurements. Other medications will remain unchanged. The variables reported from these laboratory based tests will be those conventionally reported and will include peak workload (watts), peak oxygen uptake (ml/min/kg) and ventilation (l/min). For the endurance test, exercise time will be an additional important outcome (secs). Prior to, upon completion and 3 minutes into recovery of laboratory testing, measures of HR, percutaneous oxygen saturation and BP will be recorded. Patient's safety and termination of testing will be conducted in accordance with ATS/ACCP (23).

2. Field based

Prior to and upon completion of the field based tests, measures of breathlessness, perceived exertion (Borg scores), HR, BP, and percutaneous oxygen saturation will be recorded. In addition the reason for termination (leg fatigue, SOB or combination) will be reported.

[2] http://publications.nice.org.uk/chronic-obstructive-pulmonary-disease-cg101

[3] Glenfield uses a Medisoft ergocard gas analyser and Expair Software.

- 6 MWT – this will be conducted along a 30 or 50m corridor according to the ATS guidelines (24). Encouragement will be standardised and a practice walk completed. Conventionally the output from the 6MWT is expressed in metres. We will record the number and duration of any breaks in walking taken by the patient. A total of 3 tests will be required (1 at visit 1 and 2 at visit 2) in order to test repeatability following familiarisation, before intervention.
- ISWT – this will be conducted along a 10m course as described (7). One practice walk is considered necessary. The data reported will be distance completed expressed in metres. A total of 3 tests will be required (1at visit 1 and 2 at visit 2) in order to test repeatability following familiarisation, before intervention.
- ESWT (endurance shuttle walking test at 85% peak performance on the ISWT). This will be conducted after completion of the ISWT to establish the correct speed of walking. 16 speeds of walking are available and the speed selected will be the one most closely corresponding to that calculated. One practice walk will be conducted as advised in the original paper describing the test (6). The data reported will be time elapsed and the speed of walking (i.e. level of the ESWT) distance completed expressed in metres will also be recorded.
- Short Physical Performance Battery – this test has recently been described in a COPD population prior to commencing a course of pulmonary rehabilitation (25). It has an established track record in the assessment of the frail elderly. It is a multi-modal test, assessing balance, the ability to rise from a chair and 4m gait speed. The results of the three components gives an overall score, but we will also be able to examine the properties of the individual tasks (26).
- Two validated physical activity monitors will be used to measure levels of activity via accelerometery. These are small, light-weight devices that sit on the upper arm (SenseWear Pro or mini Armband) and the waist (GT3X Actigraph).
- PROactive electronic diaries (a short 9 question physical activity questionnaire) are for completion between the time frames of 2nd September 2013 and 31st march 2015. After this time existing data will be sent to the PROactive team and funding for this part of the study support will be complete. No PROactive diaries will be issued as of April 1st 2015. As of this protocol and for the remainder of the second phase of the study, participants will asked to complete the short in-clinic paper version of the PROactive questionnaire.

3 Non-exercise based assessments

- *Lower limb strength* – isometric strength, as maximal voluntary contraction force (MVC) of the dominant quadriceps muscle using methods previously described and outlined in an SOP through WP4 (27, 28) The same standard verbal script sheet will be used by both operators at all time points for instructing the patient on the technique and procedure[4].
- Health status measures
    - The CAT questionnaire – This is a short 8 item questionnaire designed to assess the impact of the disease upon the individual. It is simple to complete and will take participants approximately 2 minutes to answer the questions, and is responsive to PR (29).
    - Chronic Respiratory Disease –Self Reported- This standardised and established questionnaire has 4 domains, dyspnoea, fatigue, mastery (feeling of control over disease) and emotion (30, 31). The dyspnoea component will be the primary outcome, but the study will be powered to detect important changes in mastery. This study will be powered using data from our pilot data. A MCID of 0.5 has been established by the original authors for each domain (32). It has been frequently and successfully employed in both primary and secondary care studies (particularly rehabilitation and medication management) with no ceiling effect in milder subjects.

[4] Glenfield use PowerLab software (ADInstruments, New Zealand)

- St George's Respiratory Questionnaire (SGRQ) – This established, disease specific health related quality of life questionnaire has been validated and standardised internationally as a sensitive measure of impaired health in COPD (33, 34). Three domains are constructed from a 50 item self-administered questionnaire; these are symptoms (eight items), activity (16 items) and impacts (26 items). Domain scores are calculated using algorithms with subscale scores and total scores documented from 0 (no impairment) to 100 (maximal impairment). An MCID of 4 units has been suggested as an acceptable response to intervention in COPD (35).

Protocol (see also Figure 1)
It should be noted the purpose of the study is to test the outcome measures and not the intervention. The use of, two interventions will allow the investigators to understand performance of the test in the two different scenarios over two differing timescales.

Test Interventions- There would be 2 test interventions – long-acting muscarinic antagonist bronchodilator therapy (LAMA) and standard pulmonary rehabilitation. These would be offered in two parallel groups over six weeks. In addition there will be a control group assessed over a comparable time period. Those subjects randomised to the bronchodilator and control groups will receive rehabilitation on a clinical basis after the study (figure 1). All assessments will be performed by an assessor blinded to treatment allocation.

Intervention 1
Six week bronchodilator therapy (LAMA; Tiotropium). It is likely that a significant number of subjects recruited for this trial will have already been prescribed Tiotropium in line with NICE guidelines, and these subjects, if randomised to this arm, will be required to withdraw from this for a period for a two week washout. Tiotropium will be replaced by the prescription of a short-acting muscarinic antagonist bronchodilator therapy (SAMA) for this two week washout. These subjects will then recommence inhaled Tiotropium following baseline testing at visits two anf three.
For subjects recruited but prescribed a LAMA combination inhaler the prescription will be amended to reflect the above washout though replacing any inhaled long-acting $beta_2$ adrenergic receptor agonists or corticosteroids with the recommended alternative along with the above described SAMA and for the duration of the washout phase. Following this two week period, baseline measures will be conducted as described above. This will afford the opportunity to observe the possible detrimental effect of withdrawing Tiotropium. After reassessment of six weeks of regular bronchodilator therapy with Tiotropium (plus replacement alternatives) all outcome measures will be repeated. If subjects have not previously been prescribed a LAMA they will continue with any current prescribed inhaler therapy and if randomised to LAMA will commence the 'LAMA' arm of the trial after visit 3. Inhaler technique will be assessed and confirmed to be acceptable. Any changes in prescription will be notified to the subjects General Practitioner/Respiratory physician where future care provision will be assessed.

Intervention 2
Six week supervised course of pulmonary rehabilitation. Participating centres will have access to existing established rehabilitation programmes. The rehabilitation programmes across the sites will follow recommended practice as defined in the ATS/ERS guidelines (36). The programme will extend over 6 weeks, twice a week. Each session will be 2 hours long, one hour allocated to exercise training, and the second hour is educational. The exercise regime will be a combination of aerobic and resistance training. The aerobic exercise will conform to the ATS/ERS guidelines (36). The Intensity will be at least 60% (ideally 80%) of the speed or peak workload achieved during the maximal walking and cycling exercise tests; the target duration will be 30 minutes, 5 times a week. This of course requires a home exercise programme that mirrors the training programme at the rehabilitation programme; this will be monitored with a home training diary.

Intervention 3 (control group/usual care)

This is a usual care control group, individuals will continue with their usual medication. At the end of the six weeks the six exercise tests will be conducted in random order. Since the aim is to evaluate the relative effect of change on different outcome measures only 1/4th of the subjects recruited will be randomised to control therapy as a usual care group .

Testing procedure

The exercise tests will be presented in random order acknowledging the inter relationship between the tests for example an incremental test needing to be completed prior to an endurance test; however for each individual patient subsequent post intervention testing will be done in the same order as pre intervention testing at visits 2 and 3[5]. The exercise tests will be conducted by a blinded assessor, blinded to the prior exercise performance and the intervention. The assessors will be experienced in conducting CPET and laboratory based exercise tests, the same assessors will conduct all the tests at each site. The time of day will be recorded and repeat visits will be arranged at a similar time (am or pm). Ambient temperature (controlled by air conditioning), pressure (via the Meterological office website), date and season will be recorded in the data set.

For each exercise test conducted in the laboratory an online gas analysis system will be employed. This will not be possible for field based exercise tests. The following baseline variables will be collected for all tests, not necessarily all on every occasion but where appropriate documented at every visit.

1. Baseline spirometry (lung volumes and diffusing capacity of the lung for carbon monoxide (DLCO) to be done at entry only)
2. Height/weight (BMI)/leg length(ASIS to Medial Malleolus)
3. Fat free mass index by bio-electrical impedance[6]
4. Resting Heart rate
5. Resting fingertip oxygen Saturation
6. MRC dyspnoea score
7. Resting Borg breathlessness & RPE Scale

At the start and end of each exercise test, as well as all performance measures we will record-

1. Saturation
2. Heart rate
3. Blood pressure
4. Borg breathlessness & leg exertion
5. Reason for termination
6. For the 6MWT we will record the number and time of stops.

At baseline and after 6 weeks the exercise tests will be conducted over 4 visits following a day of familiarisation.

Visit 1 (1 day visit or split over 2 consecutive days) – Familiarisation

Consent and Eligibility confirmation

[5] So as a secondary aim possibly generating insights into order effects

[6] Glenfield use Bodystat® 1500.

Subjects will be given the opportunity to attend the initial consent and eligibility screening (including spirometry) prior to committing to a whole or half day of testing.

1. Informed consent secured
2. Spirometry (gas transfer and full lung function test)
3. Individuals will be randomised to one of three groups as described in figure 1.
4. Baseline questionnaires
5. Apply physical activity monitors
6. Isometric muscle strength (QMVC)
7. Exercise testing will be completed in random order. There will be a minimum of 30 minutes rest between each test, in addition two activity monitors will be given to the individual, to be worn for 14 days (24 hours a day). These will also be worn during exercise testing for visits 1, 2, 3, 4 and 5 to gauge intensity and energy expenditure.
    - Maximal cardiopulmonary cycle test & Endurance cycle test
    - 6 MWT (practice)
    - ISWT (practice) & ESWT (practice)
    - SPPB

Visit 2 (two weeks later, after activity monitor data collection period) – Baseline

Exercise tests will be presented in random order. There will be at least 30 minutes rest between each test.

a. Maximal incremental cardiopulmonary cycle test
b. 6 MWT (performed twice with a 30 min rest in-between)
c. ISWT (performed twice with a 30 min rest in-between)
d. Strength testing (QMVC)

Visit 3 (next day)

Three exercise tests will be conducted in random order. There will be at least 30 minutes rest between each test.

e. ESWT (85% peak performance)
f. Cycle endurance test (85% peak performance)
g. SPPB

Retesting after completion of the 6 week intervention (visits 4 and 5), will comprise the following measures presented in the same order as baseline (visits 2 and 3). These tests will be completed by a blinded assessor, blind to the intervention and previous results. Two activity monitors will be given, to be worn during visits 4 & 5 and for a further 7 days (24 hours a day).

1. ISWT
2. 6MWT
3. ESWT, at same level as baseline
4. Maximal incremental cycle test
5. Endurance cycle test, at same workload level and RPM as baseline
6. SPPB
7. Strength testing (QMVC)
8. Health Questionnaires

At the completion of the interventions a global rating scale of change will be reported for each exercise test. This will allow the description of the MID using anchor and distribution based methods. The global rating scale will identify two levels of change (a little improvement and a greater level of improvement). The scale employed will be one recently described by Pepin et al (37) describing the MCID for the ESWT.

Power calculation

In order to calculate a sample size a literature search was conducted using the search terms Tiotropium and six minute walk (and variants e.g. 6MWT) to identify studies giving an estimate of the likely benefit of the drug. Results found are shown in Table 1.

Table 1: Properties of trials investigating Tiotropium with the 6MWT.

n	**Blinded Assessor**	**Baseline 6MWT *(mean (SD))***	**Tiotropium 6MWT *(mean (SD))***	**Reference**	**notes**
30	n	344 (105)	363 (98)	Fernandes 2010 (38)	Additional use of LABA
38	y	490 (67)	+6 (19)	Oga 2000 (12)	Additional use of Oxitropium
41	n	403 (20)	429 (17)	Fujimoto (39)	-
38	n	222 (5)	+13.5 (2)	Um(40)	-
44	y	415 (75)	429 (70)	Okudan(21)	Single dose (after 120 minutes)

Based on these data Dr Winston Banya (Statistician to the Royal Brompton hospital Biomedical Research Unit) estimated the following sample sizes for achieving an increase in 25m in 6MW with 80% power and p=0.05.

Reference	**Tio 6MWT (SD of Change From BL)**	**Estimated Sample size**
Fernandes 2010	100 *	128
Oga 2000	19	7
Fujimoto	20 *	7
Um 2007	2	1
Okudan 2006	75 *	73

For this study we considered, first, that it was important not to have a falsely low sample size and second that most of our subjects would be receiving a LABA. We therefore selected the figure generated by Fernandes paper, of 128 subjects per group but reduced the size of the whole group by 2:2:1 allocation giving a total sample size of 320. The calculation has been reviewed by statisticians from both GSK and Novartis who suggested an interim analysis because of the large range of potential values obtained.

Data entry will be managed by the Leicestershire CTU and held on a secure database. At a pre-agreed time the data will be released to the investigating team, this will be upon completion of the initial baseline measures to explore the stability of the measures and final data release upon completion of the intervention arms of the study. There will is a planned interim data analysis during the intervention phase, after the LV of patient #50. The analysis plan will be pre-defined as described below. There will be a pre-planned sub group analysis on participants with a baseline 6MWT test performance of less than 350m.

Pilot study.

Over the first twelve months a pilot (feasibility) study will be conducted at a single centre (Leicester). Sixty subjects will be recruited allowing for a drop out of 10 and analysis of 50 subjects completing the intervention period & attending all visits; subjects will be randomised and followed up after randomisation to either intervention. The procedure will be as outlined above.

The analysis of this pilot data will be supported by statisticians from Novartis. Preliminary data will be used to confirm the initial power calculations.

For the pilot study web based randomisation, data entry and monitoring will be managed by the Leicester Clinical Trials Unit. The database will be developed to support the multi-centre trial.

Sample Size re-estimation following Pilot Study & Interim Analysis

Upon collection and analysis of interim data, the ESWT was chosen as the exercise measure to recalculate sample size requirements for phase 2. This measure showed high repeatability at initial visits and sensitivity to change within treatment relative to a suggested MCID of 45-85 seconds*. Interim results for ESWT reported a change from baseline of 59 seconds (SD=163 seconds) for the LAMA arm.

**Fotheringham, I., Meakin, G., Punekar, Y. S., Riley, J. H., Cockle, S. M., & Singh, S. J. (2015). Comparison of laboratory- and field-based exercise tests for COPD: a systematic review. International Journal of Chronic Obstructive Pulmonary Disease, 10, 625–643. doi:10.2147/COPD.S70518*

Based on the interim results, approximately 90 evaluable subjects in the LAMA arm are required to provide >80% power to detect a 50sec change from baseline, assuming a standard deviation of 160sec and a one-sample, two-sided t-test at a significance level of 0.05. To account for a potential 25% dropout rate in Phase 2, 120 subjects will be randomized to the LAMA treatment arm.

The table below shows the number of evaluable subjects needed from the LAMA arm in Phase II to detect a 50 second change from baseline at either 80% or 90% power, given different estimates of standard deviation.

Table 3. One-sample t-test power to detect 50sec change from baseline

N needed	**SD = 130**	**SD = 140**	**SD = 150**	**SD = 160**	**SD = 170**
Power =80%	56	64	73	83	93
Power =90%	73	85	97	110	124

As changes from baseline are not expected in a control arm, and pulmonary rehabilitation has demonstrated effects in all exercise measures in the interim analysis, these arms will serve mainly to provide additional study sensitivity data. Thus, the randomization allocation will change from 2:2:1 to 4:1:1 to make sufficient within-group comparisons. 30 subjects will be randomized to receive pulmonary rehabilitation and 30 subjects will be randomized as controls in order to provide 22 additional evaluable subjects, plus 8 more to account for a potential 25% dropout rate, in each arm. In total, 180 subjects will be randomized to Phase 2.

2. Sample size re-estimation

The revised power calculation is aligned with the actual data from the interim analysis. This new calculation is based on a mean change in the ESWT of 60±160 seconds (as per interim analysis) with 80% power and alpha of 5%. A total of 58 subjects are required in the LAMA group and allowing for 25% attrition, a total of 78 recruited subjects are required in the LAMA (table 4). As stated above there is no specific target allocation for placebo or PR in phase 2. We propose to maintain the control arm to provide a negative control to the LAMA arm and reduce the study bias, and allow us to maintain blinding.

Table 4: One-sample t-test power to detect 60sec change from baseline

N needed	SD = 130	SD = 140	SD = 160
Power =80%	39	45	58

Randomisation allocation recruitment at Glenfield hospital, Leicester, can be seen in Table 5 (April 2015 – September 2016).

Table 5: Randomisation allocation over time

Allocation and Ratio	Control	PR	LAMA
1.2.2 (actual)	16	32	32
1.1.4 (actual)	2	2	10
Current allocated totals	18	34	42
Number required for LAMA (ESWT response of 60±160 sec with 80% power and alpha of 5	-	-	78 recruited 58 completed
New allocation for recruiting n=78 in LAMA (1:0:4)	9	0	36
Total recruited to trial	27	34	78

To ensure rigor is maintained a randomisation allocation of 1:0:4 would recruit a further 9 subjects to the control group and a further 36 into the LAMA group.

Analysis Plan

All exercise test data will be analysed on a per protocol basis. All data will be assessed for normality and analysed using appropriate parametric or non-parametric statistics. Significance will be set at $p<0.05$ and differences will be expressed as mean and standard deviations (SD) or 95% confidence intervals.

Data will be presented as mean (SD) or median (IQR). Comparison of values obtained within the treatment(s) and the control groups will be made using a paired t test or the Wilcoxon signed rank test. All tests will be 2 tailed. Additional analysis will be done to determine the sensitivity and specificity of the other measures to detect the change in MCID. Similarly the sensitivity and specificity of the failure to detect change in the placebo will also be determined.

Reproducibility study – The baseline data will examine the test-re test reproducibility of each of the tests employed, including measures of strength. The primary variable for each test will be the conventional measure of performance. Data will be compared in two ways, firstly the intra-class correlation (ICC) will be reported and secondly limits of agreement using Bland & Altman techniques (41). The Bland & Altman plot will allow us to check the data for stability across a range of performance.

Sensitivity study - Comparison between the exercise test outcome measures will be made at two separate time points, baseline and 6 weeks. The primary measure for each test will be the variable that is most commonly reported e.g. distance /time/peak oxygen consumption. We will assume that an MCID of 25m is meaningful for 6MWT (15), and assess the ability of other tests to predict this change. Attention will be paid to both floor and ceiling effects.

Data accumulated from individuals offered rehabilitation upon completion of either the control or LAMA arm will be analysed after the main trial has been completed. This data will allow a repeat measures analysis comparing the relative effect of two interventions upon the exercise tests. This is a secondary planned analysis.

Opportunities for sub studies

a) MCID - This study would afford the opportunity to test this assumption and identify an MCID for the exercise tests employed in this study. We will report the MCID in one of two ways, we will employ an anchor based approach and report a statistically general distribution based approach. In addition by relating observed changes in exercise performance to the CRQ we will aim to generate a further MCID for the exercise tests, since it has recently been suggested that an MCID may differ depending on the context and nature of the intervention (37).

Practical Considerations & timescale to do (plus Gant chart)

Three sites should be adequate to recruit the required number of subjects. We estimate that it would take 36 months to complete this study, the pilot study will be conducted over the first year with a recruitment target of n=50. After this pilot phase recruitment will be extended to 3 sites.

Pilot study
Allow 3 months to gain necessary recruitment approval, advertise and recruit staff. To confirm whether MHRA approval required. Completion of ethics submission.

Months 1- 3	Finalise ethics approval/set up database & randomisation system with Leicester & staff training as required.
Month 3-24	Recruit 50 subjects to study – completion of baseline measures
Month 24-30	Completion of data collection and preliminary analysis
Month 24-30	Change ethics for multi-centre study
Month 30-33	Recruitment in place for other sites (2/3)

Study extension (planned recruitment – 180 participants – 90 per site). Recruitment will continue seamlessly at the Leicester site but allow for 21 months recruitment from the end of the pilot data).

Months 14- 1630-34	Commence baseline assessments
Months 33-50	Commence interventions & continue with baseline assessments
Months –39-50	Complete post intervention assessments
Months 50+	Baseline data analysis – reproducibility data (to negotiate release with CTU)
Months 54+	Intervention data analysis
Months 54+	Preparation of report & dissemination of results

Steering group meetings will be held at the beginning of the study, every 3 months and upon completion of the study. There will be planned meetings to discuss the data analysis and report writing. It is likely that these meetings will coincide with WP4 meetings. The steering group will comprise SS, MP, MM, PC, WM and members from the pharmaceutical companies (TBC)

Data Management - Data will be managed by the Leicester CTEU

Once analysed this data will be immediately available to the partners in WP4 and PROactive. The dissemination will take two clear routes. Firstly a report will be prepared with partners in WP4 to present to the regulatory authorities (FDA). Secondly, there will be a number of conference presentations and papers submitted to peer review journals.

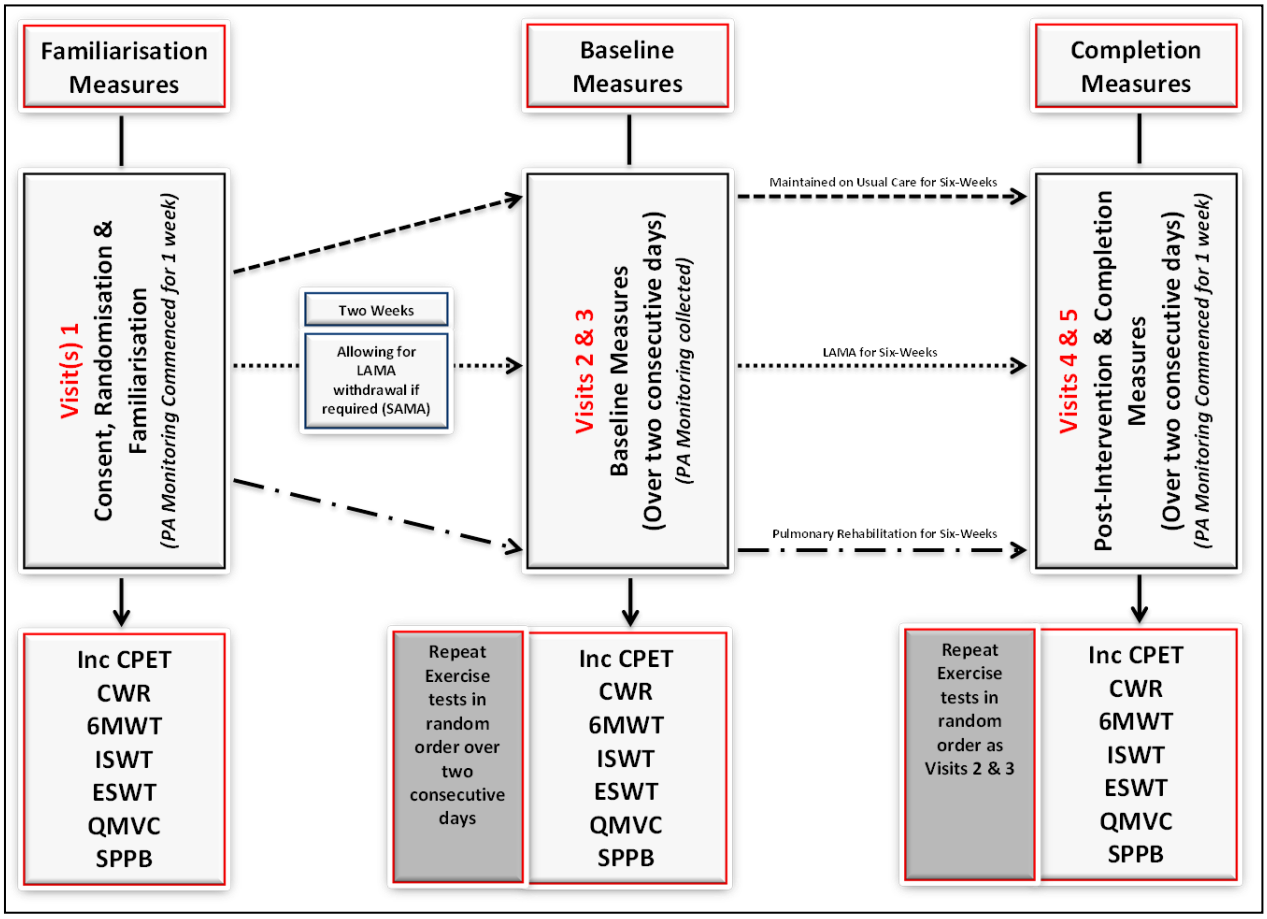
GCP

All study staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this study. This training should be updated every 2 years or in accordance with your Trust's policy.

Protocol Compliance and breach of GCP

The investigator must not implement any deviation from the protocol without formal written agreement from the Sponsor and Chief Investigator. If this necessitates a subsequent protocol amendment, or halt to the study, this should be submitted to the REC & R&D Department for review and approval if appropriate. Potential/suspected serious breach of GCP must be reported immediately to the Sponsor.

Figure 1: ExOS Visit Schedule



Serious Adverse Event (SAE) Reporting

Any Serious Adverse Events (SAE's) will be reported through the sponsors (UHL NHS Trust Research and Development) robust pathway and SOP for SAE reporting for non-Investigation Medicinal Products (Non-IMP). This MUST be reported within 24hours of the research team being aware of the event on the appropriate Non-IMP paperwork (SAE Report Form B). The initial report may be submitted without a PI signature, but must be followed up with a signed copy within 7 days.

Once a signed initial report is received a follow up or final report will be submitted within 28 days. If the participant is still an inpatient or there is an unavoidable delay in the provision of further information, the sponsor R&D office will be informed.

Trial funders will be copied into any SAE reporting though confidential correspondence with the Trial and sponsor R&I teams, and will conform to GCP standards at all times. A separate SAE form will be completed and sent on to Boehringer Ingelheim (BI). This will be the standard BI SAE form required for BI supported trials.

Schedule of Visits

Investigation	**Visit 1** **Day 0 or 0&1**	**Visit 2** **Day 14**	**Visit 3** **Day 15**	**Visit 4 & 5 (over 2 days)** **Day 57**
Informed Consent	X			
Lung Function	X			
CPET (Maximal incremental)	X	X		X
CWR (Endurance)	X		X	X
6MWT	X	X X		X
ISWT	X	X X		X
ESWT	X		X	X
SPPB	X		X	X
QMVC	X	X		X
Health Questionnaires Physical Activity Monitoring	X X	 X	 X	X X
PROactive tool	X (ISSUED 02.09.2013 - 31.3.2015 ONLY)	PAPER CLINIC VERSION AS OF V7 APPROVAL	X	X (ISSUED 02.09.2013 - 31.3.2015 ONLY) PAPER CLINIC VERSION AS OF V7 APPROVAL
Randomisation	X			

References

1. McGavin CR, Gupta SP, Lloyd EL, McHardy GJ. Physical rehabilitation for the chronic bronchitic: results of a controlled trial of exercises in the home. Thorax. 1977;32(3):307-11.
2. Troosters T, Gosselink R, Decramer M. Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. Am J Med. 2000;109(3):207-12.
3. Pepin V, Saey D, Whittom F, LeBlanc P, Maltais F. Walking versus cycling: sensitivity to bronchodilation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005;172(12):1517-22.

4. Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, Ries A, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med. 2003;348(21):2059-73.
5. Sewell L, Singh SJ, Williams JE, Collier R, Morgan MD. How long should outpatient pulmonary rehabilitation be? A randomised controlled trial of 4 weeks versus 7 weeks. Thorax. 2006;61(9):767-71.
6. Revill SM, Morgan MD, Singh SJ, Williams J, Hardman AE. The endurance shuttle walk: a new field test for the assessment of endurance capacity in chronic obstructive pulmonary disease. Thorax. 1999;54(3):213-22.
7. Singh SJ, Morgan MD, Scott S, Walters D, Hardman AE. Development of a shuttle walking test of disability in patients with chronic airways obstruction. Thorax. 1992;47(12):1019-24.
8. Cote CG, Casanova C, Marin JM, Lopez MV, Pinto-Plata V, de Oca MM, et al. Validation and comparison of reference equations for the 6-min walk distance test. Eur Respir J. 2008;31(3):571-8.
9. Cote CG, Pinto-Plata V, Kasprzyk K, Dordelly LJ, Celli BR. The 6-min walk distance, peak oxygen uptake, and mortality in COPD. Chest. 2007;132(6):1778-85.
10. Casanova C, Cote CG, Marin JM, de Torres JP, Aguirre-Jaime A, Mendez R, et al. The 6-min walking distance: long-term follow up in patients with COPD. Eur Respir J. 2007;29(3):535-40.
11. Pepin V, Brodeur J, Lacasse Y, Milot J, Leblanc P, Whittom F, et al. Six-minute walking versus shuttle walking: responsiveness to bronchodilation in chronic obstructive pulmonary disease. Thorax. 2007;62(4):291-8.
12. Oga T, Nishimura K, Tsukino M, Hajiro T, Ikeda A, Izumi T. The effects of oxitropium bromide on exercise performance in patients with stable chronic obstructive pulmonary disease. A comparison of three different exercise tests. Am J Respir Crit Care Med. 2000;161(6):1897-901.
13. Aguilaniu B. Impact of bronchodilator therapy on exercise tolerance in COPD. Int J Chron Obstruct Pulmon Dis. 2010;5:57-71.
14. Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K, et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. Lancet. 2000;355:362-8.
15. Puhan MA, Chandra D, Mosenifar Z, Ries A, Make B, Hansel NN, et al. The minimal important difference of exercise tests in severe COPD. Eur Respir J. 2011;37(4):784-90.
16. Puhan MA, Mador MJ, Held U, Goldstein R, Guyatt GH, Schunemann HJ. Interpretation of treatment changes in 6-minute walk distance in patientswith COPD. Eur Respir J. 2008;32(3):637-43.
17. Bedard ME, Brouillard C, Pepin V, Provencher S, Milot J, Lacasse Y, et al. Tiotropium improves walking endurance in chronic obstructive pulmonary disease. Eur Respir J.
18. Casaburi R, Kukafka D, Cooper CB, Witek TJ, Jr., Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. Chest. 2005;127(3):809-17.
19. Maltais F, Hamilton A, Marciniuk D, Hernandez P, Sciurba FC, Richter K, et al. Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD. Chest. 2005;128(3):1168-78.
20. O'Donnell DE, Fluge T, Gerken F, Hamilton A, Webb K, Aguilaniu B, et al. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. Eur Respir J. 2004;23(6):832-40.
21. Okudan N, Gok M, Gokbel H, Suerdem M. Single dose of tiotropium improves the 6-minute walk distance in chronic obstructive pulmonary disease. Lung. 2006;184(4):201-4.
22. Verkindre C, Bart F, Aguilaniu B, Fortin F, Guerin JC, Le Merre C, et al. The effect of tiotropium on hyperinflation and exercise capacity in chronic obstructive pulmonary disease. Respiration. 2006;73(4):420-7.
23 ATS/ACCP Statement on Cardiopulmonary Exercise Testing. Am J Respir Crit Care Med. 2003;167:211–277.
24. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111-7.
25. M S Patel, A L Clark, K A Ingram, R P Fowler, A V Donaldson, S S Kon, M I Polkey, W D Man. Effect of pulmonary rehabilitation on the Short Physical performance battery (SPPB) in COPD. Thorax. 2010;65(Suppl 4):A35

26. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 1994;49(2):M85-94.
27. Edwards RHT, Young A, Hosking GP, Jones DA. Human skeletal muscle function: description of tests and normal values. Clin Sci. 1977;52:283-90.
28. Seymour JM, Spruit MA, Hopkinson NS, Natanek SA, Man WD, Jackson A, et al. The prevalence of quadriceps weakness in COPD and the relationship with disease severity. Eur Respir J. 2010;36(1):81-8.
29. Dodd JW, Hogg L, Nolan J, Jefford H, Grant A, Lord VM, et al. The COPD assessment test (CAT): response to pulmonary rehabilitation. A multicentre, prospective study. Thorax. 2011;66(5):425-9.
30. Williams JE, Singh SJ, Sewell L, Guyatt GH, Morgan MD. Development of a self-reported Chronic Respiratory Questionnaire (CRQ-SR). Thorax 2001 Dec;56(12):954-9.
31. Williams JE, Singh SJ, Sewell L, Morgan MD. Health status measurement: sensitivity of the self-reported Chronic Respiratory Questionnaire (CRQ-SR) in pulmonary rehabilitation. Thorax 2003 Jun;58(6):515-8.
32. Schünemann HJ, Puhan M, Goldstein R, Jaeschke R, Guyatt GH. Measurement properties and interpretability of the Chronic Respiratory Disease Questionnaire (CRQ). COPD 2005;2:81–89.
33. Jones PW, Quirck FH, Baveystock CM. The St George's Respiratory Questionnaire. Respiratory Medicine (1991);85 (Supplement B), 25-31.
34. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis 1992;145:1321–1327.
35. Jones PW. St. George's Respiratory Questionnaire: MCID. COPD 2005;2:75–79.
36. Nici L, Donner C, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. Am J Respir Crit Care Med. 2006;173(12):1390-413.
37. Pepin V, Laviolette L, Brouillard C, Sewell L, Singh SJ, Revill SM, et al. Significance of changes in endurance shuttle walking performance. Thorax. 2011;66(2):115-20.
38. Fernandes FL, Pavezi VA, Dias SA, Jr., Pinto RM, Stelmach R, Cukier A. [Short-term effect of tiotropium in COPD patients being treated with a beta2 agonist]. J Bras Pneumol.36(2):181-9.
39. Fujimoto K, Kitaguchi Y, Kanda S, Urushihata K, Hanaoka M, Kubo K. Comparison of efficacy of long-acting bronchodilators in emphysema dominant and emphysema nondominant chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2011;6:219-27.
40. Um SW, Yoo CG, Kim YW, Han SK, Shim YS. The combination of tiotropium and budesonide in the treatment of chronic obstructive pulmonary disease. J Korean Med Sci. 2007;22(5):839-45.
41. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986;1(8476):307-10.