The Trajectory of Change in Physical Activity Following Pulmonary Rehabilitation

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Protocol & SAP

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Background and rationale

Physical activity in COPD patients is reduced, (1) and this inactivity is associated with poor outcome, including increased health care utilization and mortality. (2-5) Bronchodilators, considered a first line therapy of COPD, have documented effectiveness in physiologic function, symptom relief, and exercise capacity enhancement, but apparently do not consistently increase in physical activity. Even pulmonary rehabilitation exercise training, with remarkable effectiveness in increasing exercise capacity, does not consistently increase physical activity.(6, 7) There are probably multiple reasons behind this apparent lack of efficacy, but two important ones are a poor signal-to-noise ratio in accelerometers (used to measure activity) and real problems translating increases in physiologic function (such as increased FEV1 or six minute walk distance) into increases in physical activity. Both of the above are major areas of interest that need to be addressed to improve our care of COPD.

This study will follow physical activity following pulmonary rehabilitation longitudinally over 48 weeks. We will use a state-of-the-art accelerometer, the DynaPort (https://www.mcroberts.nl/products/movemonitor), to analyze minutes walking per day

as the primary outcome, rather than vector magnitude units (VMU) or estimated steps per day. The DynaPort device was rated favorably by PROactive COPD (http://www.proactivecopd.com) which tested accelerometers. Additionally, there is too much variability in VMU, and estimated steps per day in slow moving COPD patients are inaccurate. Minutes per day of walking activity appears to be a more useful outcome. Walking activity from the DynaPort has been demonstrated to be very responsive to exercise training in lung transplant patients. (8) Finally, more information is needed to determine the factors that influence the translation of exercise capacity gains realized in the rehabilitation center into increased physical activity in the home and community settings. One editorial commented that it takes 3 months to train the muscles and 6 months to train the brain.(9) We will explore potential factors influencing this important outcome, including baseline activity levels, demographic variables, changes in exercise capacity, psychological variables, and self-efficacy scores. Finally, we will evaluate the rate of change (trajectory) in physical activity over approximately six months after the pulmonary rehabilitation intervention. There are limited data suggesting it takes time for the translation of increased exercise capacity into increased physical activity to occur. (10) If our study corroborates these findings, it would potentially influence our therapeutic approach to the physically inactive COPD patient.

Design:

This will be predominately a hypothesis-generating study. Its general design is that of a longitudinal study (without a control group) evaluating directly-measured physical activity in COPD patients who had participated in pulmonary rehabilitation. Activity measurements will be at baseline (before exercise training is started), and at approximately 12, 24, 36, and 48 weeks (+/- 3 weeks at each time period) following pulmonary rehabilitation. There will be no direct change, per protocol, in the patient's pharmacological treatment for COPD (controller or rescue inhaler medication) or other medical problems; this treatment will be directed by the patient's health care provider.

Three distinct types of analysis will be performed:

1. Evaluation of changes in physical activity before and after pulmonary rehabilitation

2. Predictors of baseline physical activity
3. Predictors of *change* in physical activity following pulmonary rehabilitation.

This will be an intent-to-treat analysis, providing patients complete 50% or more of the pulmonary rehabilitation sessions. Those dropping out with less than 50% attendance will be dropped from the study.

Dealing with Exacerbations: It is anticipated that patients will have COPD exacerbations over the course of the study. Since exacerbations themselves affect physical activity, activity testing will be postponed for 2 weeks following the clinical end of the exacerbation. We have determined that physical activity returns to close to baseline by two weeks after the exacerbation (Ehsan et al, A Longitudinal Study Evaluating the Effect of Exacerbations on Physical Activity in Patients with Chronic Obstructive Pulmonary Disease. Annals of American Thoracic Society 2013; 10(6):559-64). If two exacerbations occur within the same time block, testing for that period will not be performed, and the last observation will be carried forward. If a patient is hospitalized for an exacerbation, that patient will be dropped from the study.

Comment: We will not be altering the pharmacological management of the patient; this study will focus only on the pulmonary rehabilitation component and specifically how it affects physical activity. It is currently almost impossible to carry out a randomized, controlled trial of pulmonary rehabilitation, since the intervention is considered a gold standard of therapy. The within-group analysis without a control group would be feasible and would not raise ethical issues. While this approach (without a control group) limits the strength of conclusions, the primary intent of this analysis is to explore the rate of change in physical activity with pulmonary rehabilitation (realizing that it probably takes longer to improve than exercise capacity) and predictors of response to the intervention.

Hypotheses to be tested:

Changes in activity following pulmonary rehabiliation

1. Compared with baseline, COPD patients participating in outpatient pulmonary rehabilitation will show an increase in directly-measured physical activity

(minutes per day of walking activity from the DynaPort) at the 12 ± 3 week assessment. (primary hypothesis)

2. Compared with baseline, COPD patients participating in outpatient pulmonary rehabilitation will show increases in upright activity, activity intensity, steps per day, minutes with METs > 2 (from the DynaPort) after 24 ± 3, 36 ± 3 and 48 ± 3 weeks

3. Exploratory: We will analyze the trajectory of physical activity over the 48 weeks after initiating pulmonary rehabilitation.

Predictors of baseline physical activity

4. Exploratory: We will analyze predictors of baseline physical activity. Baseline variables tested will include age, gender, body mass index (BMI), six minute walk distance, FEV1, self-efficacy (using the PRAISE questionnaire), motivation for exercise (using the BREQ-2 instrument, questionnaire), MRC dyspnea, health status (using the self-administered Chronic Respiratory Disease (CRQ) questionnaire, anxiety and depression (HADS questionnaire, appendix), sleep efficiency and awakenings (from DynaPort output), functional performance using the Timed Up and Go (TUG) test.

Predictors of *change* in physical activity

5. Exploratory: We will be able to identify responders versus non-responders with respect to: 1) the change in activity at 12 weeks, and 2) the trajectory (over 48 weeks) in these activity measurements; this will include the slopes of change in physical activity. We will then relate baseline variables to responder status. We cannot a priori determine a threshold for physical activity responder status; this will have to be done a posteriori when data are available. We anticipate from the post-lung transplant study the responder threshold will be an increase in 10 minutes walking time per day. Predictor variables are listed above.

Study patients:

Inclusion criteria:

1. Adults (≥ 40 years) with a primary clinical diagnosis of COPD
2. A post-bronchodilator FEV1/FVC < 0.70 from spirometry performed within the preceding 12 months (no specific FEV1 percent-predicted requirement, although we anticipate the FEV1 will average around 45% of predicted, based on previous studies of pulmonary rehabilitation)
3. The patient was referred to pulmonary rehabilitation
4. The patient is clinically-stable: no exacerbation in preceding 4 weeks
5. Modified Medical Research Council (mMRC) dyspnea rating of at least 2 out of 5.

Exclusion criteria

1. Disease severity or co-morbidity that would make the patient be at-risk for participation this study
2. A significant movement disorder, such as hemiplegia, etc.
3. Inability to read and comprehend the questionnaires, which will be in English
4. A history of poor wound healing or chronic skin conditions that might predispose to local problems from wearing the DynaPort. (The DynaPort can be worn outside a thin garment, such as a tee shirt, and is relatively thin, without protruding parts. However, since the device may be worn overnight, and there is a remote risk of pressure problems, this exclusion criterion was added).

Comments: It is commonly accepted by pulmonary rehabilitation centers that symptoms and functional status limitation are important for referral, not simply FEV1 values. The PI investigators at the various centers will make the clinical decisions as to whether a patient referred to that center has a principal diagnosis of COPD, is clinically stable (basing this decision on recent exacerbation history), and does not have co-morbidity or disease severity or a movement disorder that would make him/her inappropriate for the study. This is the standard procedure of most rehabilitation centers.

Sample size estimates

Sample size estimates are based on Langer et al. Am J Transpl 2012 and using http://www.biomath.info/power/ttest.htm. Patients following lung transplantation were randomized to exercise training or standard care. Walking activity (min/day) from baseline to 12 weeks increased from 36 ± 16 to 56 ± 24 in the treatment group. Assuming a treatment difference, in minutes, of 18 and a SD of 20 and a within-group analysis, an n of ~ 12 would have a power of 0.80 to show this difference. We expect our improvement in walking time with rehabilitation in COPD patients will be less robust. Assuming an increase in activity (minutes per day of walking) of 10 minutes would require an n of 34 to give a power of 0.80, but an improvement of 8 minutes would require 52 patients. Forty evaluable patients appears to be a reasonable number.

Number of subjects: Our goal will be to recruit 40 patients with evaluable data at 12 weeks. Assuming 10 dropouts during rehabilitation, we would need to recruit 50.

Study period: Recruitment over the 6 sites will be over 10 months (~ 40 weeks). Since study follow-up is for 48 weeks per patient, the study will last approximately 84 weeks from first patient in to last patient out.

Activity measurement: We will use the DynaPort MoveMonitor to assess: sedentary activity, upright activity, walking activity, activity intensity, and steps per day. Activity will be measured for 7 consecutive days, 3 days (12 hours per day) minimum. Patients will be asked to wear the devices 24 hours per day, if possible.

Protocol synopsis:

1. Patients with COPD entering pulmonary rehabilitation at the study sites will be recruited. Each center will be under its own IRB authority.
2. Rehabilitation will be given per usual pulmonary rehabilitation center protocol; there will be no specific changes in COPD medications, including long acting bronchodilators, short-acting bronchodilators, or inhaled corticosteroids. As is typical with pulmonary rehabilitation, these medications will be managed by the patient's health care provider.

3. Standardized, written post-rehabilitation home exercise recommendations will be given to all patients during rehabilitation and upon completion of the program.
4. Baseline testing:
    a. Collect information on demographics, baseline testing (see below), list co-morbidities
    b. First measurement of physical activity (before starting pulmonary rehabilitation exercise training), within 6 weeks of beginning pulmonary rehabilitation
    c. Outcomes testing
5. Weeks from study entry: 12, 24, 36, 48:
    a. Timing: ± 3 weeks, except for the 12 week visit, which will be after the end of formal pulmonary rehabilitation, and therefore may occur outside of this 3-week window (rationale: to avoid measuring physical activity during pulmonary rehabilitation days)
    b. Evaluate for adverse events, list concurrent medications.
    c. Evaluation for Serious Adverse Events: Evaluation for serious adverse events (SAE) will be made at each study visit if the patient is taking a Boehringer Ingelheim drug. If an SAE is identified on a visit, regardless of causal relationship, it will be reported to Boehringer Ingelheim using the Serious Adverse Event Report (SAE) in Non Interventional Studies (NIS) template within 24 hours or the next business day. The following will be the plan of action for SAE assessment and planning:
        i. Definitions of adverse events
            a. An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical

product. The event does not necessarily have to have a causal relationship with this treatment.

b. A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

2. Patients may be hospitalised for administrative or social reasons during the study (e.g. days on which infusion takes place, long distance from home to site,). These and other hospitalisations planned at the beginning of the study do not need to be reported as a SAE in case they have been reported at screening visit in the source data and have been performed as planned.

ii. The intensity of the AE should be judged based on the following:

- Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated
- Moderate: Enough discomfort to cause interference with usual activity
- Severe: Incapacitating or causing inability to work or to perform usual activities

Causal relationship of adverse event: Medical judgment should be used to determine the relationship, considering all relevant factors, including

pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms.

iii. Yes: There is a reasonable causal relationship between the investigational product administered and the AE.

iv. No: There is no reasonable causal relationship between the investigational product administered and the AE.

Worsening of the underlying disease or other pre-existing conditions: Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the (e)CRF.

Changes in vital signs, ECG, physical examination, and laboratory test results: Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the (e)CRF , if they are judged clinically relevant by the investigator.

Responsibilities for SAE reporting: The Investigators shall report (i.e., from signing the informed consent onwards through the trial defined follow-up period) all SAEs and non-serious AEs which are relevant for a reported SAE by fax or other secure method using BI SAE Form to the BI Unique Entry Point in accordance with timeline specified below.

v. Within five (5) calendar days upon receipt of initial and follow-up SAEs containing at least one fatal or immediately life-threatening event;

vi. Within ten (10) calendar days upon receipt of any other initial and follow-up SAEs.

vii. BIPI Unique Entry Point:

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road Ridgefield, CT
Fax: 1-203-837-4329
E-mail: PV_global_casemanagement@boehringer-ingelheim.com

For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the BI marketed drug. The investigator will determine the expectedness of the BI marketed drug to the AEs as defined in the Listed or BI Drug Information e.g. Investigator's Brochure, Summary of Product Characteristics (SmPC) or Product Information (PI).

d. Physical activity measurements, each over 7 days

e. Outcomes testing

f. Scripted exercise at home directions (except 48 week visit)

6. Comments: Three to 5 days of activity testing is considered adequate to capture a particular patient's activity profile (ERS Statement on Physical Activity, submitted for publication). We will accept a minimum of three days of activity measurement for each assessment. Twelve hours per 24 hour day of activity assessment will be considered a day's measurement. Although we will ask patients to wear the devices day and night, we anticipate many will not wear them at night because of inconvenience. Therefore, a requirement of 12 of a potential 16 hours (75% wear-time) appears reasonable. The DynaPort device has an algorithm that determines wear time. If a missing observation occurs over the course of the 48-week study (such as from technical problems, two or more exacerbations in that time block, etc.), we will carry the last observation forward into that missing spot.

Safety considerations: Pulmonary rehabilitation will be performed per usual protocol by centers with considerable experience in providing this intervention. The DynaPort device is registered with the FDA:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfrl/rl.cfm?rid=145003
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfrl/rl.cfm?lid=386697&lpcd=IKK

We do not believe this has any significant risk associated with it. Outcomes assessments are standard and will be performed in the pulmonary rehabilitation area by trained personnel.

Table: Measurements during study

Week	Visit	Measurements
0	Baseline, Pre-Rehab	Age, gender, BMI, concurrent medications, six minute walk distance, FEV1 (may use historical information if within 1 year), self-efficacy (using the PRAISE questionnaire), motivation for exercise (using the BREQ-2 instrument), MRC dyspnea, CRQ health status, anxiety and depression (HADS questionnaire), sleep efficiency and awakenings (from DynaPort output), functional performance (Timed up and Go test, TUG), activity assessments from DynaPort
12 ± 3 (when patient has completed rehab)	Post-Rehab	Concurrent medications, six minute walk distance, self-efficacy (PRAISE questionnaire), motivation for exercise (BREQ-2 instrument), MRC dyspnea, CRQ health status, anxiety and depression (HADS), sleep efficiency and awakenings (DynaPort output), TUG, activity assessments from DynaPort, Scripted exercise at home directions
24 ± 3	Short-term Follow-up	Concurrent medications, six minute walk distance, self-efficacy (PRAISE questionnaire), motivation for exercise (BREQ-2 instrument), MRC dyspnea, CRQ health status, anxiety and depression (HADS), sleep efficiency and awakenings (DynaPort output), TUG, activity assessments from DynaPort, Scripted exercise at home directions
36 ± 3	Intermediate Follow-up	Concurrent medications, six minute walk distance, self-efficacy (PRAISE questionnaire), motivation for exercise (BREQ-2 instrument), MRC dyspnea, CRQ health status, anxiety and depression (HADS), sleep efficiency and awakenings (DynaPort output), TUG, activity assessment from DynaPort, Scripted exercise at home directions
48 ± 3	Late follow-up	Concurrent medications, six minute walk distance, self-efficacy (PRAISE questionnaire), motivation for exercise (BREQ-2 instrument), MRC dyspnea, CRQ health status, anxiety and depression (HADS), sleep efficiency and awakenings (DynaPort output), TUG, activity assessment from DynaPort

Comment: We fully anticipate the difficulties we will have in getting our study patients to return at the proper follow-up dates. To help in this regard, we have incorporated a 6 week window (± 3 weeks) at each time measurement. Even this may not be adequate: if an exacerbation intervenes, the test date will have to be postponed. Further, if patients cannot come in for that particular measurement (for instance, they may be away on vacation), we will allow the off-protocol data entry at the investigator's discretion, and note it as a protocol violation. Time points will have error-bars depicting the range of times patients came in for testing.

Data analysis

The primary variable to be assessed will be changes in daily walking activity (in minutes) from baseline to week 12. The statistical approach for this will be a repeated measures analysis of variance using SAS. Covariates may be added, if necessary. We anticipate day of week variation (Sundays have less activity) and seasonal variation (less activity in winter). This will be handled by including these variables as covariates in the analysis. We will also analyze the 24 36 and 48 week endpoints compared to baseline this way. Trajectory changes will be first analyzed by graphs relating activity (in minutes) at each data collection time. We will also analyzed slopes of activity, it possible. Responder non-responder analyses will be performed using logistic analysis with demographics and baseline disease characteristics as potential predictor variables.

Factors Affecting Study Duration:

1. Each patient will be followed for approximately 48 weeks from the beginning of pulmonary rehabilitation until the last testing day.

2. St. Francis Hospital will be the first to seek IRB approval and begin patient recruitment. We anticipate IRB approval by approximately mid-February 2015 and first patient entry shortly after that date. Each study site will be required to obtain local IRB approval; we anticipate final approval in all 6 centers within 4 months of study initiation at St. Francis Hospital. If St. Francis secures IRB approval and begins recruiting by February 15, 2015, the last site will begin recruiting by approximately June 15, 2015.

3. Each site will be expected to recruit 8-9 patients over 10 months. However, we anticipate total recruitment will be somewhat shorter than 10 months. Recruitment will be competitive, so patient numbers will probably not be identical across centers. However, we will require four study patients, minimum, per center.

4. Assuming that the last patient will be enrolled by October 15, 2015 (4 months after the last center has secured IRB approval), we should have a data lock and analysis by 48 weeks after that date.

References

1. Pitta F, Troosters T, Spruit MA, Probst VS, Decramer M, Gosselink R. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;171:972-977.
2. Pitta F, Troosters T, Probst VS, Spruit MA, Decramer M, Gosselink R. Physical activity and hospitalization for exacerbation of copd. *Chest* 2006;129:536-544.
3. Garcia-Aymerich J, Farrero E, Felez MA, Izquierdo J, Marrades RM, Anto JM, Estudi del Factors de Risc d'Aguditzacio de la Mi. Risk factors of readmission to hospital for a copd exacerbation: A prospective study. *Thorax* 2003;58:100-105.
4. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Anto JM. Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: A population based cohort study. *Thorax* 2006;61:772-778.
5. Garcia-Rio F, Rojo B, Casitas R, Lores V, Madero R, Romero D, Galera R, Villasante C. Prognostic value of the objective measurement of daily physical activity in copd patients. *Chest* 2012.
6. Ng LW, Mackney J, Jenkins S, Hill K. Does exercise training change physical activity in people with copd? A systematic review and meta-analysis. *Chronic respiratory disease* 2011.
7. Casaburi R. Activity promotion: A paradigm shift for chronic obstructive pulmonary disease therapeutics. *Proceedings of the American Thoracic Society* 2011;8:334-337.
8. Langer D, Burtin C, Schepers L, Ivanova A, Verleden G, Decramer M, Troosters T, Gosselink R. Exercise training after lung transplantation improves participation in daily activity: A randomized controlled trial. *Am J Transplant* 2012;12:1584-1592.
9. Polkey MI, Rabe KF. Chicken or egg: Physical activity in copd revisited. *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology* 2009;33:227-229.
10. Pitta F, Troosters T, Probst VS, Langer D, Decramer M, Gosselink R. Are patients with copd more active after pulmonary rehabilitation? *Chest* 2008;134:273-280.