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EFFECTIVENESS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)
MANAGEMENT PROGRAM AT THE UNIVERSITY OF LOUISVILLE

By

Malhar Anantbhai Jhaveri

M.B.B.S., Sardar Patel University, March 2005

M.P.H., University of Kentucky, May 2009

A Dissertation

Submitted to the Faculty of the

School of Public Health and Information Sciences of the University of Louisville

in Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy

Department of Epidemiology

University of Louisville

Louisville, Kentucky

May 2014

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EFFECTIVENESS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)
MANAGEMENT PROGRAM AT THE UNIVERSITY OF LOUISVILLE

By

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April 18th 2014

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FGFECVQP "

I dedicate this dissertation to my parents

Mr. Anantbhai C Jhaveri and Mrs. Sulataben A Jhaveri, who has always been source of
my inspiration and hard work.

CEMP QY NGFI GO GP VU

I would like to gratefully and sincerely thank Dr. Frank Groves for his guidance, understanding, patience, and most importantly, his mentorship during my graduate studies at the University of Louisville. His mentorship was paramount in providing a well-rounded experience consistent with my long-term career goals. He encouraged me to not only grow as an epidemiologist but also as an instructor and an independent thinker. I would also like to thank Dr. Rodney Folz for his assistance and guidance in getting my graduate career started on the right foot and providing me with the foundation for becoming an independent researcher. I would specially thank him for allowing me to use his data for my dissertation. I would also like to thank my dissertation committee members: Drs. Richard Baumgartner, Guy Brock, and Susan Muldoon, who gave me their valuable time whenever I needed and advise me during the time of doctoral program. I would also like to thank the entire team of researchers at the University of Louisville COPD management program team who were actively involved in the program.

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EFFECTIVENESS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)
MANAGEMENT PROGRAM AT THE UNIVERSITY OF LOUISVILLE

Malhar A Jhaveri

April 18th 2014

Background: Chronic obstructive pulmonary disease (COPD) is a progressive disease of the respiratory system characterized by airflow limitation that is not completely reversible and is associated with systemic effects especially of the cardiovascular system. COPD is frequently complicated by acute exacerbations that contribute to physical impairment and increased health care use. As COPD is a chronic lung disease with significant systemic manifestations, it is important to have chronic disease management programs specifically targeting individuals with COPD designed to improve their overall quality of life, reduce the burden of disease and decrease the impact of COPD on daily life. Chronic disease management encompasses a multidisciplinary approach designed to enhance the quality and cost-effectiveness of health care for chronic conditions and has been defined as “an approach to patient care that emphasizes coordinated, comprehensive care along the continuum of disease and across health care delivery systems”. The purpose of this present study is to evaluate the effectiveness of a chronic obstructive

pulmonary disease management program implemented at the University of Louisville in 2011.

Methods: We conducted a retrospective observational cohort study of COPD subjects using clinical data from medical records and cost data from a claims dataset. Respiratory health was assessed by pulmonary function testing, St. George Respiratory questionnaire, COPD Assessment Test (CAT), 6 minute walk test (6MWT), Modified Medical Research Council (mMRC) dyspnea scale, and BODE index. General measures include Duke Profile for assessing overall health and Patient Health Questionnaire (PHQ-9) for assessing depression. At baseline, chi-square test for categorical variable and t-test for continuous variable was used to check for any difference between the two groups. To check for any longitudinal significant change in quality of life measures like SGRQ, CAT score, mMRC scale, BODE index, six minute walk distance and PFT measures from baseline paired t-test was performed. For each subject, the baseline probability of participation in the disease management program was calculated by the propensity score method using logistic regression analysis. Multiple linear regression analysis was performed to assess the rate of deterioration of various clinical parameters like FEV₁ and FVC between two groups. Cost analysis was done by comparing the cost related to COPD among subjects in DMP group versus those under usual care. These costs includes total COPD cost, and also sub-categories of cost like office visit cost, in-patient hospitalization (IPH) cost, out-patient hospitalization (OPH) cost, pharmacy cost, cost related to home care and laboratory cost.

Results: A total of 52 subjects were enrolled in the disease management program between February 1st 2011 and December 31st 2013: 37 in 2011, 11 in 2012 and 4 in

2013. The usual care group consists of 662 subjects diagnosed with COPD. There is a significant difference in average age of subjects between the two groups (54.2 in DMP versus 58.3 in usual care; P value 0.0094). Subjects who suffered from asthma, rhinitis and arthritis were significantly more likely to enroll in the disease management program. At baseline, the average PHQ9 was 6.3 which improved at the end of 12 months (mean = 4) and at 24 months (mean = 3.1). At baseline, the average duke score was 64.1 which were improved at the end of 12 months (mean = 71.6) and 24 months (mean = 68.3). At baseline average SGRQ score was 37.1 which were improved at the end of 12 months (mean = 28.4, P = 0.02) and 24 months from (mean = 30.2, P = 0.21). We found that not only did those subjects enrolled in the COPD program decrease their rate of loss of lung function, but remarkably showed a significant improvement in FEV₁ from baseline to 12 months (mean difference: 140 ml, P value = 0.0046) and from baseline to 24 months (mean difference: 30 ml, P value 0.55). Average cost per person per year among subjects in DMP group in first year is \$3693, which decreased to \$3608.8 in second year and to \$2934 in third year. Pharmacy cost contributes majority of total COPD cost followed by office cost and out-patient hospitalization. There is a significant decline in cost related to all major diseases like arthritis, hypertension, hyperlipidemia, diabetes, and osteoporosis after enrollment of COPD subjects into disease management program comparing to cost before enrollment into program. Average cost per person per year for in-patient hospitalization is significantly high for subjects in usual care (\$5578.7) versus subjects in DMP group (\$250.9).

Conclusion: The University of Louisville COPD disease management program appears to be effective in improving lung health and reducing airflow limitations among COPD

subjects as evidence by significant improvement in objective measures like FEV₁.

Program is also effective in reducing the impact of COPD on daily activities as evident

by significant improvement in subjective measures for health related quality of life like St

George Respiratory Questionnaire, COPD assessment test, PHQ9 and Duke Profile.

Notwithstanding subjects in DMP had higher COPD related cost, they had significantly

low in-patient hospitalization cost and also significant reduction in cost associated with

major co-morbidities after enrollment in the disease management program.

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Chronic obstructive pulmonary disease (COPD) is a progressive disease of the respiratory system characterized by airflow limitation that is not completely reversible and is associated with systemic effects especially of the cardiovascular system^{1,2}. COPD is frequently complicated by acute exacerbations that contribute to physical impairment and increased health care use². The COPD GOLD (Global Initiative for Obstructive Lung Disease) stage directly correlates with both severity and frequency of acute exacerbations³. COPD is a major public health burden whose current prevalence is estimated to be approximately 8-10% in adults aged 40 years or more in developed countries like the USA. However, in developing countries, the prevalence varies widely and is difficult to estimate because of different definitions used to identify cases of COPD⁴. Regardless of the burden that COPD places on health care systems and the availability of recommendations for its management¹, COPD remains a condition that is all too often sub-optimally managed. As COPD is a chronic lung disease with significant systemic manifestations, it is important to have chronic disease management programs specifically targeting individuals with COPD designed to improve their overall quality of life, reduce the burden of disease and decrease the impact of COPD on daily life. The University of Louisville implemented a chronic disease management program (DMP) for COPD in 2011. We evaluate here the clinical and cost effectiveness of the DMP for individuals with COPD at the University of Louisville.

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Definition of COPD

COPD is a disease characterized by the combination of two conditions: chronic bronchitis and pulmonary emphysema^{5,6}. Chronic bronchitis is best characterized as chronic inflammation of the bronchial airways and is defined clinically “as cough with sputum production every day for at least three months in a year for two or more consecutive years”^{7,8}. Pulmonary emphysema, on the other hand, is defined pathologically as “a dilation of alveoli distal to the terminal bronchioles along with destruction of the lining of the air sacs”⁶. There are many ways of defining COPD but the widely accepted definitions of COPD are from the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the Global Initiative for chronic Obstructive Lung Disease (GOLD).

According to the ATS definition⁹ COPD is “a disease state characterized by the presence of airflow limitation due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible”. As per ERS, COPD is defined as¹⁰ “reduced maximum expiratory flow and slow forced emptying of the lungs, which is slowly progressive and mostly irreversible to present medical treatment”. GOLD defines COPD as¹¹ “a disease state characterized by airflow limitation that is not fully reversible and the airway limitation is gradually progressive”. More recently ATS/ERS jointly defined COPD as

“a preventable and treatable disease state characterized by airflow limitation that is not fully reversible” and is the most common definition being used now¹. COPD is classified into four stages based on FEV₁/FVC ratio and % predicted FEV₁. In all four stages FEV₁/FVC ratio is <0.7 and severity is further classified based on % predicted FEV₁. In Stage 1 (mild) % predicted FEV₁ is ≥ 80 , Stage-II (moderate) it is 50-79, Stage III (severe) it is 30-49 and Stage IV (very severe) it is ≤ 30 ¹¹. The prevalence of COPD varies depending on the type of definition and national surveys used to estimate the prevalence of COPD¹².

Spirometry

Spirometry is a routinely performed pulmonary function test¹³ and, as the name suggests, is a measurement of the amount of air you breathe. This includes measurements of both the volume and rate of air that can be inhaled and exhaled as a function of time. Both ATS¹⁴ and ERS¹⁵ publish guidelines for performing and interpreting pulmonary function tests in respiratory diseases like COPD and Asthma. Based on spirometry testing results, patient can be classified further into an obstructive or restrictive pattern of pulmonary disease (See Table 1).

Important spirometry measurements of the pulmonary function test¹⁶ are forced vital capacity (FVC), forced expiratory volume (FEV), peak expiratory flow (PEF), maximum voluntary ventilation (MVV), total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV)¹⁶. FVC is the maximum volume of air exhaled forcefully following a maximal inspiratory effort. FEV is the volume of air

exhaled with force in one breath. The volume of air exhaled measured after 1 second is called the FEV_1 . FEV_1 is one of the important spirometry measures in COPD subjects. PEF measures how quickly one can exhale and is the highest airflow rate measured during the FVC procedure. MVV is the greatest amount of air that one can breathe in and out during a one minute interval. TLC is the amount of air contained in the lungs after a full inspiration. FRC is the amount of air in lungs at the end of a normal exhaled breath. Residual volume is the amount of air remained in lungs after full expiration.

The primary pulmonary function parameters that distinguish obstructive versus restrictive lung disease are FEV_1 , FVC and the ratio of FEV_1 to FVC expressed as a percentage (FEV_1/FVC %). Table 1 summarizes the different findings of pulmonary function tests in individuals who are normal and those with obstructive lung disease and restrictive lung disease¹⁷. The rates of decline of FEV_1 with age in different ethnic groups are shown in Appendix 1 and 2.

Table 1 Pulmonary Function test findings in different lung disease

	Normal Lung	Obstructive Lung disease	Restrictive Lung disease
% predicted FEV_1	Normal (80-120%)	Low	Low
% predicted FVC	Normal (80-120%)	Low or normal	Low
FEV_1/FVC	Normal (> 0.70 of predicted ratio)	Low	Normal

Spirometry measurements in NHANES

National Health and Nutritional Examination Survey (NHANES) is a series of complex surveys started in 1960 to assess the health and nutritional status of adults and children in USA¹⁸. The survey includes history, personal interview and physical exam of the participant. Spirometry was done in NHANES with a primary focus to assess the burden of respiratory diseases, like asthma and COPD, among the US general population and also to calculate estimated prevalence of COPD. NHANES III data was used to calculate reference standards for spirometry¹⁹. NHANES III was a stratified multistage probability sample of the U.S. population and the survey was conducted nationally by the National Center for Health Statistics (NCHS) from 1988 to 1994²⁰. Hankinson (1999)¹⁹ conducted a detailed analysis of NHANES III spirometry data to generate reference equations for describing pulmonary function in three major ethnic groups namely Caucasians, African-Americans and Mexican-Americans. Comparing FEV₁ against age for different ethnic groups (See Appendix 1) it can be seen that both Mexican-Americans and African-Americans, irrespective of gender, have lower FEV₁ values than do Caucasians for all age groups¹⁹. Whereas comparing FEV₁ against height, only African-Americans had lower FEV₁ values while Caucasians and Mexican-Americans had similar values¹⁹. Along with absolute FEV₁ and FVC values, % predicted values are calculated by comparing the values of similar age, gender and body composition. NHANES III standards are routinely used in clinical practice to diagnose and monitor the severity of COPD²¹.

The rate of decline of FEV₁ by age is directly related to the severity of airway inflammation¹³. Several studies have sought to model the association of FEV₁ decline with COPD mortality²², recurrent exacerbations², and COPD prognosis². COPD patients with frequent exacerbations have faster decline in FEV₁ (-40 ml/year) versus those with infrequent exacerbations (-32ml/year)².

The Spirometry Longitudinal data Analysis (SPIROLA) software designed and developed by CDC has been used to estimate the decline in slope of pulmonary function (e.g. FEV₁) and can be used to compare to a normal decline in people of the same age, gender and height²³. SPIROLA software uses the NHANES III standard developed by Hankinson et. al. in 1999 to calculate the slope and compare it to normal individuals. This software is being widely used in workplace settings to monitor FEV₁ and FVC longitudinally over time among occupational workers²⁴. Longitudinal monitoring in the work place settings is very important for the identification of individuals who are at high risk of developing COPD based on their excessive loss of lung function²⁴. SPIROLA will be useful in this setting by allowing for the implementation of proper treatment or prevention strategies for high risk workers that may delay or reduce the loss of lung function. SPIROLA can perform individual or group evaluation of longitudinal changes in pulmonary function. At the individual level it can monitor FEV₁ change over time in relation to the limit of longitudinal decline (LLD). It can be downloaded free from Center for Disease Control and Prevention (CDC) website²³.

Pathophysiology of COPD

COPD is a disease characterized by airflow limitation which is poorly reversible. The basic pathogenesis occurring in COPD patients involves damage to lung tissue due to chronic inflammation aggravated by smoking and other toxins²⁵. The detailed pathophysiology of COPD has been discussed in many articles²⁵⁻²⁸. Exposure to airway irritants causes accumulation of inflammatory cells, including neutrophils, lymphocytes and macrophages and initiates the release of various inflammatory mediators such as tumor necrosis factor, C - reactive protein, and interleukins resulting in structural damage to lung parenchyma¹⁴. A detailed role of chronic inflammation was studied by Denterer et. al. with the aim to test the hypothesis that chronic inflammation in COPD is due to defective anti-inflammatory mechanism(s). This study concluded that in patients with stable COPD, there is a significantly higher level of leukocyte counts, C-reactive protein (CRP), and lipopolysaccharide binding protein (LBP). They showed that effective COPD treatment significantly reduces levels of CRP and LBP in comparison to baseline levels²⁸.

Apart from inflammation, other pathological factors involved in COPD include increased levels of proteases²⁷, decreased levels of anti-proteases and oxidative stress. The above pathogenic mechanisms leads to a series of physiological abnormalities in COPD including airflow obstruction due to mucosal hyper-secretion and mucosal edema, airway hyperresponsiveness, hyperinflation of lung, dysfunction of cilia, loss of elasticity of lung due to proteolysis by elastase, and abnormalities in gas exchange due to destruction of alveoli²⁶.

Natural history of COPD

As discussed in the above definitions, COPD is a chronic progressive disease with airway limitation not completely reversible. The most important parameter that measures airflow limitation is FEV_1 . Hence the natural history of the disease strongly correlates with the level of FEV_1 from birth. Appendix 2 displays the normal decline of FEV_1 by age (Curve D) alongside impaired lung growth (Curve A), early decline (Curve B) and rapid decline (Curve C)²⁹. Subject A has impaired lung growth with a lower plateau phase but the rate of decline in FEV_1 is normal. Subject B has normal lung growth (i.e. normal plateau) and a rapid decline in initial years but the rate of decline is normal thereafter. Subject C has a normal plateau and normal decline in initial years but the rate of decline accelerates thereafter. Most published literature uses FEV_1 to study the natural history of disease²⁹⁻³¹; but if someone starts smoking very early they could just skip the plateau phase and proceed directly to rapid decline after early lung growth³². Gold. et. al. conducted a detailed study of tobacco smoke effects on adolescent boys and girls³². The study found that girls who smoke 5 or more cigarettes per day have 1.09% (95% CI: 0.7-1.47) slower growth of FEV_1 per year versus non-smokers and 0.2% slower growth among boys who smokes versus non-smokers (95% CI: -0.16 to 0.56). In a detailed review of the pathophysiology and natural history of disease by Mannino et. al.^{33,34}, the author's state that FEV_1 is not the only parameter of interest in the natural history of COPD. Since COPD is a heterogeneous disease, it should be noted that the natural history of COPD is a mixture of naturally occurring phenotypes including small airway disease, systemic inflammation, chronic mucus secretion, auto immunity and bronchial hyperresponsiveness³⁴.

Pharmacotherapy of COPD

Apart from monitoring the disease and reducing risk factors, effective management of COPD includes management of stable COPD and also exacerbations which requires proper use of drugs¹¹. The principal role of drugs in COPD treatment is to improve the symptoms, reduce frequency of exacerbations, reduce severity of disease, slow the progression of disease and improve the quality of life¹¹. The primary categories of drugs given to COPD subjects are bronchodilators and corticosteroids^{35 36}. These can be given alone or in combination therapy and either inhaled or in oral form³⁵.

I) Bronchodilators³⁶

Any medication that dilates bronchi and bronchioles, by altering the tone of airway smooth muscle, is called a bronchodilator. Bronchodilators also improve FEV₁ and other parameters like forced vital capacity and residual volume. There are three types of bronchodilators commonly given to COPD subjects. These include β adrenergic receptor agonists, anti-cholinergic agents and methylxanthines³⁶. A β_2 adrenergic receptor agonist relaxes airway smooth muscle by stimulating β_2 receptors present on respiratory airways resulting in increases in intracellular levels of cyclic adenosine monophosphate (c-AMP)³⁷. β_2 agonists are either short acting (SABA) or long acting (LABA). SABA effects last for 4-6 hours and LABA have duration of effect lasting for up to 12 hours. The most common side effects of β_2 agonist bronchodilators include tremor, tachycardia, anxiety, nervousness and headache³⁸. Anti-cholinergic drugs relax smooth muscle by blocking the action of acetylcholine on M₃ and M₂ receptors. The most common side effects of anti-cholinergic drugs include constipation, dryness of skin due to decreased

sweating, dryness of mouth, headache, and blurring of vision. The last group of bronchodilators is the methyxanthines which dilate bronchioles by acting as non-selective phosphodiesterase inhibitors. The most common drug in this category is theophylline which has been used as a bronchodilator for over 80 years. Theophylline is not commonly used nowadays due to cardiac arrhythmias and the ready availability of other bronchodilators³⁹.

II) Glucocorticosteroids

Steroids can be given either orally (OCS) or inhaled (ICS)⁴⁰. In contrast to asthma, subjects with COPD are less responsive to inhaled corticosteroids (ICS) if given alone and so ICS are given in combination with bronchodilators^{40,41}. Inhaled corticosteroids given in combination with bronchodilators reduce acute COPD exacerbations and improve overall quality of life^{42,43}. Anuzeto conducted a randomized clinical trial comparing the effect of fluticasone propionate (ICS) given in combination with salmeterol versus salmeterol alone and found that there was a significant reduction in moderate to severe acute exacerbations in the combination arm (1.1 vs. 1.50 per subject per year) along with fewer hospitalizations than in the salmeterol alone arm⁴⁴. Several other studies support the use of inhaled corticosteroids to improve outcomes and reduce exacerbations among COPD subjects^{45,46}. Common side effects of oral steroids include weight gain, mood changes, increase in blood sugar, increase in blood pressure, and osteoporosis (if used for long term). Side effects associated with inhaled steroids are few and include sore throat, hoarseness of voice³⁶.

Epidemiology of COPD

COPD is a leading cause of morbidity and mortality not only in the USA but also globally^{4,47}. Chronic Obstructive Pulmonary Disease (COPD) is a major cause of chronic morbidity and a public health problem of increasing concern in the United States^{12,48}. According to World Health Organization (WHO), the estimated prevalence of moderate to severe COPD is 65 million and COPD is the fourth leading cause of mortality (3.4 million) worldwide after ischemic heart disease (7 million), stroke (6.2 million) and lower respiratory infections (3.2 million)⁴⁹.

Prevalence of COPD

The prevalence of COPD varies depending on the definition and type of survey used to estimate its prevalence. The first national survey to estimate the prevalence of COPD was NHIS (National Health Interview Survey)⁵⁰. In that survey, COPD prevalence was estimated by adding the cases of chronic bronchitis (50.5 per 1000 persons for all age) and emphysema (6.0 per 1000 persons for all age)⁵¹. Accordingly, the NHIS survey calculated that there were approximately 12.7 million adults above 25 years of age living with COPD. Unfortunately, COPD is under diagnosed as the diagnosis is based on self-report to two questions¹². Due to this limitation, Mannino et. al. used pulmonary function test measures from the NHANES-III survey to estimate the prevalence of COPD¹². NHANES-III used a stratified, clustered design to select a representative sample of the civilian, non-institutionalized USA population from 1988 to 1994 and it included pulmonary function testing⁵². Prevalence was estimated by applying GOLD stage criteria to pulmonary function test measures from NHANES-III¹². That

study found an estimated prevalence of COPD of 23.4 million (13.9%) among people aged 25–75 years. The estimated prevalence of mild COPD (defined $FEV_1/FVC < 70\%$ and $FEV_1 \geq 80\%$ predicted) was 6.9% and moderate COPD (defined as $FEV_1/FVC < 70\%$ and FEV_1 50-80% predicted) was 6.6%¹².

The state-based Behavioral Risk factor Surveillance System (BRFSS)⁵³ was also used to estimate the prevalence of COPD nationally and statewide⁵⁴. BRFSS used only one question to assess COPD prevalence i.e. “Have you ever been diagnosed with COPD, emphysema or chronic bronchitis?” The 2011 BRFSS was the first year that provided a complete estimate of the prevalence of COPD by each state⁵⁴. According to BRFSS, 6.3% of US adults (approximately 15 million) have COPD with the highest prevalence among subjects aged between 65-75 years (12.1%)^{47,54}. Prevalence varies by state with Kentucky and Alabama having the highest prevalence of COPD ($>9\%$)⁵⁴. There has not been a significant change in prevalence of COPD from 1998 to 2009 and it remains mostly stable around 5% among all adults aged greater than 18 years for all gender⁵⁵. Age specific prevalence’s and unadjusted prevalence rates of COPD in US adults aged ≥ 25 years is shown in figure 1. Numbers used in creating Figure 1 are taken from Ford et. al. article of COPD surveillance in United States from 1999-2011 using BRFSS survey⁴⁷. From the figure, COPD rates gradually increase from age 25 to 75 years but decline thereafter due to more mortality among subjects more than 75 years of age.

Figure 1 Age specific prevalence of COPD among US adults aged ≥ 25 years (BRFSS)

A thorough review of COPD prevalence and trends in mortality in different countries were discussed by Rycroft et al.⁵⁶. According to that review, there is a significant variation in the prevalence of COPD worldwide; mainly due to type of definitions and classification used to diagnose COPD along with type of survey used to estimate the prevalence. The prevalence is high among men aged ≥ 75 years with decrease in mortality among men in several countries like Australia, while increasing or stabilizing among women in countries like USA.

COPD is projected to be the third leading cause of death for both males and females by 2030⁵⁷. In USA According to preliminary reports of deaths from vital statistics by Hoyert et al.⁵⁸, COPD is the third leading cause of death with approximately 150,000 total deaths contributed to COPD following that of heart disease and cancer.

The prevalence of COPD is increasing and will continue to climb as our population grows. In the report on COPD surveillance published by Mannino et. al., in the year 2000 alone COPD accounted for 8 million physician office and hospital outpatient visits, 1.5 million emergency department visits, 726,000 hospitalizations, and 119,000 deaths¹².

Overall there has been a decline in COPD mortality in many countries, but in a few countries including the US, Australia and France, the mortality rate has increased in women and decreased in men⁵⁶. In the US, there has been a huge increase in the COPD death rate in females that has occurred over the last 20 years: i.e. a rise from 20.1 per 100,000 in 1980 to 56.7 per 100,000 in 2000 for females versus 73.0 per 100,000 in 1980 to 82.6 per 100,000 in 2000¹².

In summary, COPD is a disease of major public health concern and measures must be taken to decrease the rate and improve the quality of life of subjects living with COPD. This project reviews the effectiveness of implementing a COPD disease management program (DMP).

Risk factors for COPD

The most important risk factor for COPD is smoking as documented by numerous epidemiological studies, summarized in Table 2. Although smoking is the most important risk factor for COPD⁵⁹⁻⁶², not all smokers will develop COPD which implies involvement of other factors including genetic predisposition⁶³, socioeconomic status⁶⁴, exposure to occupational dust and chemicals⁶⁵, and outdoor air pollution⁶⁶. An interaction between genetic and environmental risk factors increases the risk for COPD.

The most common genetic factor associated with COPD is the deficiency of α_1 antitrypsin^{67,68}. Subjects with α_1 -antitrypsin deficiency have reduced levels of circulating proteinase inhibitor which protect the lungs against proteolytic attack which results in the occurrence of emphysema⁶⁸.

Table 2 Epidemiological studies of Smoking and COPD

Study	Type of Study	Location	Smoking status	Risk measure	Estimate
Lokke et. al., 2006 ⁶⁰	25 years of cohort, (Copenhagen city heart study)	Copenhagen, Denmark	Never	Incidence rate	39/401 (9.7%)
			Ever		196/806 (24.3%)
Mastrangelo et. al., 2003 ⁶¹	Case control study	Padova, Italy	Never (15 cases, 99 controls)	Odds Ratio	1
			Former (31 cases, 96 controls)		2.13 (1.08-4.2)
			Current (76 cases, 86 controls)		5.83 (3.12-10.9)
Jordan, et. al., 2011 ⁵⁹	Cross sectional study (Health survey of England, HSE)	England	Never	Odds Ratio	1
			Ex-smokers		1.50 (1.30 to 1.72)
			Current		3.94 (3.43 to 4.52)
Higgins, et. al., 1993 ⁶²	Cross sectional study (Cardiovascular Health study, CHS)	USA	Never	Prevalence (%)	7.3
			Former		18.5
			Current		45.1

Several genome wide association studies (GWAS)⁶⁹⁻⁷² and candidate gene studies^{71,73} had been completed in last few years to begin to identify genes associated with COPD and also to understand the pharmacogenetics⁷⁴ of COPD. Pillai et. al. conducted a GWAS in a homogenous case-control cohort from Bergen, Norway (823 COPD cases and 810 smoking controls) and evaluated the top 100 single nucleotide polymorphisms (SNPs) in the family-based International COPD Genetics Network (ICGN) study. Further evaluation of polymorphisms was done among subjects from US National Emphysema Treatment Trial (NETT) cohort, Normative Aging Study (NAS)

cohort and Boston Early-Onset COPD population cohort⁶⁹. From that study researchers found two polymorphisms in the α -nicotinic acetylcholine receptor 3/5 locus on chromosome 15 that showed definite evidence of association with COPD.

Economic burden of COPD

COPD also imposes a major economic burden in the USA and globally^{75,76}. According to the American Lung Association, in the year 2010, COPD cost approximately \$50 billion which included \$30 billion in direct health care costs and \$20 billion in indirect costs⁷⁷. The direct medical cost for COPD has almost doubled since 1996 when they were \$14.5 billion⁷⁸. Direct costs refer to expenditures related to diagnosis, treatment and prevention of disease directly related to COPD, including office visits for COPD, investigations related to COPD, medical management costs and hospitalization costs related to COPD exacerbation⁷⁹. Indirect costs are related to morbidity and mortality caused by COPD⁷⁹. Indirect costs are associated with output losses (loss of work time and productivity) and family costs as a result of COPD consequences^{79,80}. Many studies have estimated direct and indirect costs of COPD in the USA and globally^{75,80-82}. Ward et. al. conducted a retrospective study using a public-payer perspective to estimate direct medical costs of COPD in the USA and these authors found that approximately out of \$6.6 billion, \$2.3 billion was due to the cost of long-term oxygen therapy, \$1.9 billion was associated with in-hospitalizations usage while the remaining cost were attributable to outpatient visits and medications for COPD⁸¹.

A more recent retrospective study using a managed care claims database to estimate the direct cost of COPD was done by Dalal et. al⁸² in 2010. The study includes 37,089 COPD patients divided into five cohorts i.e. outpatient, urgent outpatient, emergency department, standard inpatient admission, and intensive care unit (ICU). Mean standard annual COPD-related health care costs (2008 US\$) increased across the cohorts (P value 0.001), ranging from \$2003 for the outpatient cohort to \$43,461 for the ICU cohort. Average cost, combining patients from all cohorts, was \$3943 which included \$2731 in medical costs and \$1211 in pharmacy cost⁸². Akazawa et. al. also conducted a similar type of retrospective administrative claims data analysis⁸³ and concluded that COPD patients in the U.S. had significantly more healthcare utilization and higher costs in the year prior to COPD diagnosis than matched control subjects. Teo et. al.⁷⁵ conducted a study to estimate direct medical costs of COPD in two public health clusters in Singapore from 2005 to 2009 and study found that average cost of COPD was \$9.9 million per year with hospitalization contributing to approximately 73% of total cost.

According to study by Simoni et. al., among Medicare beneficiaries residing in long term facilities, twelve-month COPD-related and all-cause direct expenditures per beneficiary were US \$7391 and \$48,183⁸⁴. The Center for Medicare and Medicaid services reported that approximately 12 percent of Medicare beneficiaries aged 65 years and above have COPD⁸⁵. Blanchette et. al. reported that the respiratory-related costs accounted for 22 percent of total all-cause health care costs for among Medicare beneficiaries with COPD⁸⁶. In summary COPD is major contribution to the overall

economic burden of healthcare costs in USA and globally with in-patient hospitalization contributing a major portion of all COPD related costs.

Chronic Disease Management

Definition of chronic disease management

Many definitions of chronic disease management have been proposed since this innovative approach was introduced in the USA⁸⁷⁻⁹¹. Epstein and colleagues⁸⁸ defined disease management as “ the use of an explicit systematic population-based approach to identify person at risk, intervene with specific programs of care and measure clinical outcome”. More recently Faxon et. al.⁹¹ in 2004 defined disease management as “ a multidisciplinary effort to improve the quality and cost-effectiveness of care for selected patients suffering from chronic conditions”. With several definitions in practice, the primary goal of disease management is to improve both objective and subjective quality of life of subjects with chronic disease.

In summary disease management is a multidisciplinary coordinated preventive intervention focusing on target groups with chronic diseases like diabetes, heart disease, and chronic obstructive pulmonary disease with an overall goal to improve both objective clinical outcomes and subjective quality of life.

Disease management Program (DMP)

As discussed above, the primary goal of any disease management program is to improve overall quality of life for subjects living with chronic conditions and to reduce total health care costs. Several studies have evaluated the effect of disease management programs on clinical outcomes among subjects with heart failure, diabetes, and chronic obstructive pulmonary disease. McAlister et. al. conducted a systemic review of 11 randomized clinical trials of DMP in heart failure and found significant reductions in follow up hospitalizations (RR 0.87, with 95% CI: 0.79 to 0.96) for DMP enrollees with even greater reductions in recurrent hospitalization if the DMP trial includes follow up by a multidisciplinary specialized team rather than limited follow up by telephone. These findings were supported by a recent retrospective study conducted in Spain, which found that heart failure subjects who had exposure to a DMP had a lower risk of death and readmission due to heart failure⁹². Apart from heart failure subjects, DMPs are also effective in diabetes patients. Sidorov et. al. evaluated a Health management organization (HMO) sponsored DMP for Diabetes and this study found a significant improvement in quality of life and reduction in cost for those enrolled in the program⁹³.

Our present study will focus on the effectiveness of the COPD management program by comparing several clinical outcomes and claims related costs for those enrolled in the DMP versus for those receiving usual care.

COPD management program

As discussed previously, COPD is a serious public health problem with major extrapulmonary manifestations of disease leading to chronic morbidity and resulting in the fourth leading cause of mortality in USA. COPD also imposes a major economic burden not only in the USA but globally with total expenditures estimated to be upwards of \$50 billion, including both direct and indirect cost⁷⁷. Since COPD is a chronic disease with multiple co-morbidities, a multidisciplinary approach to disease management is recommended in order to improve quality of life and reduce health care utilization related to COPD exacerbations⁹⁴⁻⁹⁶. Several studies have been published in the last 10 years regarding the role of disease management program in COPD but the results are inconsistent and inconclusive. Most of the studies evaluated clinical outcomes and self-reported quality measures (like St George Respiratory Questionnaire, COPD assessment test) with few studies evaluating cost effectiveness of the program.

Components of COPD disease management programs include self-management, patient centered education, case management, home-based pulmonary rehabilitation and an action plan for identification and treatment of exacerbation⁹⁷⁻⁹⁹. Some studies evaluated the effect of one component, like self-education, or combined more than one component in an integrated approach to study different clinical outcomes with the goal of improving quality of life on COPD subjects⁹⁷. Another approach, called the Proactive Integrated care (PIC) approach, is a combination of disease specific education and self-management principles along with simple remote monitoring platform and was used by Koff et. al.⁹⁹ and Linderman et. al.⁹⁸. Fan et. al. used a Comprehensive Care Management Program (CCMP) including four individual COPD education sessions, one

group session, an action plan for exacerbations, and scheduled proactive telephone calls for case management¹⁰⁰. A detailed review of self-management education was done by Effing et. al.¹⁰¹. The review includes results from 14 different trials and reported a significant reduction in hospital admission among self-management group versus usual care and also significant reduction in SGRQ score and BORG dyspnea score for those who enrolled into self-management program.

A recent multi-center randomized clinical trial was completed by Fan et. al.¹⁰⁰ that included COPD patients from 20 Veteran Affairs hospital with the objective to determine the efficacy of CCMP in reducing COPD hospitalization. The trial was stopped prematurely due to excess mortality in the intervention group (28 deaths) versus the comparison group (10 death) with hazard ratio of 3 (95% CI: 1.46 to 6.17; $P = 0.003$). At the time of termination, the 1-year cumulative incidence of COPD-related hospitalization was 27% in intervention group versus 24% in the usual care group (hazard ratio, 1.13 [95% CI, 0.70 to 1.80]; $P = 0.62$)¹⁰⁰. A similar study by Mehring et. al. evaluated retrospectively the effect of a German Disease management program on COPD⁹⁶. This study found significant reductions in prescription of theophylline and oral corticosteroids along with an increased utilization of patient education, smoking cessation and a reduction in the occurrence of exacerbations⁹⁶ and study conclude that the German DMP for COPD was effective in enhancing the quality of care but was not able to prevent increase in emergency admissions for stable COPD cohort.

Moullec et. al. used a combination of patient centered education and case management as an integrated care approach to evaluate its effectiveness and found significant reductions in COPD related hospitalization (OR: 0.44; 95% CI: 0.23-0.85)

compared to usual care⁹⁷. In the proactive integrated care approach by Linderman et. al., there was a significant improvement in SGRQ score (from 50.8 to 39.2), BODE index (4.3 to 2.9), mMRC (from 2.0 to 1.7) and six minute walk distance (from 265.1 to 319.4) after the implementation of proactive integrated care approach among COPD patients.

Respiratory measures in COPD

As discussed above spirometry is the most important pulmonary function test not only to diagnose COPD but also to assess the prognosis of COPD patient. Apart from spirometry, other measures routinely performed among COPD patients includes six minute walk test (6 MWT), COPD assessment test (CAT), St George respiratory questionnaire (SGRQ) and BODE index.

Six Minute Walk Test (6 MWT)

The 6MWT is an important measure of daily living among COPD subjects¹⁰², and simply measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. Functional and exercise capacity is determined by the integrated response of multiple systems, including the pulmonary, cardiovascular, hematopoietic, skeletal and metabolic¹⁰². The 6MWT does not provide specific information on the function of each organ and system involved in the exercise mechanism; instead, it serves as a surrogate estimate of the collective mechanism¹⁰².

In clinical practice, the 6MWT is used for measuring the response to medical interventions for patients with moderate to severe heart or lung disease¹⁰². Solway et al.

(2001) performed a qualitative review of measurement properties of the shuttle walk test and 6MWT and concluded that exercise performed was similar to a symptom-limited, maximal, incremental treadmill test¹⁰³. The shuttle walk test is more difficult to administer, requires more equipment, and is less reflective of activities of daily living¹⁰³. The 6MWT is easy to administer, better tolerated, and more reflective of activities of daily living. Therefore, currently, the 6MWT is the test of choice when administering a functional walk test for clinical or research purposes especially among COPD cohort¹⁰².

Hernandes et. al. investigated the reproducibility of the 6 MWT in COPD patients in a retrospective cohort study and also quantified the learning effect between two 6MWTs performed on subsequent days¹⁰⁴. The study¹⁰⁴ found that, on average, the second 6MWT increased by 27 m (or 7%), and 82% of patients showed improvement in their second 6MWT distance. Additional factors associated with improvement on the second six minute walk distance (6MWD) by >42 m are first 6MWD >350 m, Charlson index <2 and body mass index < 30 kg/m².

By conducting the 6MWT in the follow up visits of COPD subjects, it is important to understand whether change in walking distance observed over time represents a clinically important effect on subjects overall quality of life because a change in 6MWD from previous values may be significant statistically but not clinically^{105,106}. Holland et. al. conducted a prospective study to establish the minimal important difference (MID) in 6MWD in COPD subjects and authors found that a MID of 25 meter (95% CI: 20-61 meter) in COPD or a 14% change in 6MWD compared with baseline represents clinically important effect; but the % change is less sensitive (0.70) than absolute change (0.85)¹⁰⁶.

MMRC Dyspnea Scale

The modified Medical Research Council (mMRC) scale is a validated tool and most commonly used scale to assess dyspnea in subjects with chronic respiratory lung disease¹⁰⁷. See Appendix 4 for MMRC dyspnea scale. To assess health related quality of life using MMRC, a cross-sectional study of 328 COPD patients was conducted and mMRC was found to be a good and reliable indicator¹⁰⁸. Currently, GOLD supports the use of either the mMRC or CAT index to assess the severity of breathless among COPD subjects¹⁰⁹.

BODE Index

BODE index is a multidimensional staging tool first developed and validated by Celli. et. al. in 2004 to assess the pulmonary and systemic manifestation among subjects with COPD¹¹⁰. The BODE index consists of four components: BMI [B], Obstruction [O] as measured by FEV₁, Dyspnea [D] severity as measured by Modified Medical Research Council (MMRC) Dyspnea scale, and exercise [E] capacity as measured by distance covered in 6 MWT¹¹⁰. Before the development of the BODE index, the only variable that could predict mortality among COPD patients was FEV₁¹¹¹. As COPD is a systemic disease and FEV₁ will explain only the respiratory component of COPD, it is important to include measures that also reflect systemic components and exercise capacity along with spirometric measures which predicts all-cause mortality, CODP specific mortality and hospitalization due to COPD¹¹².

Development and validation of BODE Index¹¹⁰

Celli. et. al. used several variables to predict mortality among 207 COPD patients. These variables includes age, gender, smoking, FEV₁, FVC, 6 MWT, BMI, degree of dyspnea measures using MMRC dyspnea scale, functional residual capacity, inspiratory capacity, hematocrit, and albumin level¹¹⁰. By evaluating the association of each of these explanatory variables to predict one year mortality using stepwise logistic regression method, researchers found only four variables (BMI, FEV₁, dyspnea severity and 6 MWD) that had a strongest association to predict mortality. The BODE index was then created using those 4 variables. The BODE index can be calculated by summing a score assigned to each component as outlined in the table below. For all-cause mortality, the HR was 1.34 (1.26 to 1.42; $p < 0.001$) and for respiratory death it was 1.62 (1.48 to 1.77) for every one point increase in BODE index. The C statistic of BODE index to evaluate the ability of the index to predict death was 0.74 versus 0.65 for FEV₁ alone (0.74 v 0.65). The BODE index will range from 0-10, with higher scores indicating a high risk of mortality (See Appendix 5 for complete scoring of BODE index).

Since the development of BODE index in 2004, many studies had been done among COPD subjects to predict mortality¹¹³, to predict hospitalization¹¹⁴, and to compare BODE with GOLD criteria to assess anxiety and depressive symptoms¹¹⁵. Study by Cote et. al. used BODE index to compare the outcome among COPD patients who received pulmonary rehabilitation (PR) versus those without PR and the study found that at the end of 1 year the BODE index improved by 19% among patients in PR group and worsened by 4% among patients in no PR group¹¹⁶. Ong et. al.¹¹⁴ conducted a study

to predict hospitalization for COPD and found that the BODE index is a significant better predictor for hospitalization than FEV₁.

St George Respiratory questionnaire

St George Respiratory questionnaire (SGRQ) is the metric to measure the health related quality of life of subjects with respiratory problems like COPD and Asthma^{117,118}.

SGRQ was first developed and validated by Paul Jones from St George University London¹¹⁹. See Appendix 6 for the detailed SGRQ questionnaire. The original SGRQ consisted of 76 items categorized into three sections¹¹⁹

1. Symptoms related items: consists of item related to cough, wheeze, breathlessness and its severity
2. Activity related items: consists of questions related to activity that is affected by breathlessness
3. Impact related items: consists of items related to the impact (either social or psychological) due to breathlessness

Interpretation of scores:

A score can be calculated individually for each section (i.e. symptom score, activity score, and impact score) as well as a total score^{119,120}. Factors taken into consideration for calculating score include age, gender, weight, disease duration, current and worst pulmonary function test measures¹¹⁹. The SGRQ score ranges from 0 to 100; with higher scores indicating more severe disease and causing more limitations in daily living of COPD subjects^{119,120}. A study by Ferrer et. al. relating to the interpretation of

the quality of life scores from SGRQ, found that the strongest association of SGRQ total scores is % predicted FEV₁ along with smoking, age, gender and education which independently associated with the SGRQ total score¹²¹. The current American version of the SGRQ consists of 50 items classified into the same three categories¹²².

As full version of SGRQ is lengthy and more generalized. Meguro et. al. developed a shorter and improved version of SGRQ designed specifically for COPD patients called the SGRQ-C¹²³. This study was conducted with the aim of identifying items that are weak, have low response rate, redundant and fit poorly with other items using the Rausch reduction technique. A total of 10 weaker items were identified and removed without altering the performance of the instrument¹²³. One item that was removed due to low response rate was employment because most of subjects were retired. The SGRQ-C has been developed using COPD data only, so it is valid for subjects with COPD¹²³. In conclusion SGRQ-C is short, reliable, valid, and contains most of the items from original SGRQ and the principal differences from the original SGRQ are smaller number of items (reduction from 50 to 40 items).

Several studies had been published to identify and interpret the threshold for clinical significant change in SGRQ in COPD patients¹²⁴⁻¹²⁶. Based on a study by Jones et. al. 2002, an improvement of mean score of 4.3 is considered an effective treatment and mean score of 8.1 is considered very effective treatment¹²⁴.

COPD Assessment Test (CAT)

COPD assessment test is a short, simple questionnaire to measure the quality of life and monitor the health status of person's living with COPD.^{127,128} It's a simple questionnaire that is useful to patients and also to clinicians to assess the severity of COPD. Because of the length of several other questionnaires [like SGRQ, COPD clinical questionnaire, chronic respiratory questionnaire (CRQ)] to measure health related quality of life in COPD subjects; there is a need to create a short and easy questionnaire for COPD subjects. This led to the development of COPD assessment test (CAT) by Dr. PW Jones in 2009¹²⁷. See Appendix 7 for detailed CAT questionnaire.

Development of CAT and Interpretation of CAT score¹²⁷: Initially the CAT consisted of 21 questions but following a structured approach to item reduction, the final CAT consists of 8 questions assessing cough, phlegm, chest tightness, breathlessness, activities, confidence, sleep and energy. An item reduction process was used to create a tool which is bias free from demographic factors such as sex, country, language spoken and the instrument which has a good reliable measurement property. Countries studied for the development of CAT includes USA (n=229), Spain (n=369), The Netherlands (n=109), Germany (n=431), France (n=294), Belgium (n= 71). By studying in 6 different countries for testing internal consistency, the CAT score provides a reliable measure of COPD severity independent of the language spoken. The CAT scores range from 0-40 with the higher scores indicating more severe impact of COPD on daily life. A reduction in the CAT score by 2 points is considered a minimal clinically important difference (MCID)¹²⁹.

Since the development of the CAT score, many studies had been published to discuss the properties of CAT score¹³⁰, responsiveness of CAT following acute exacerbation and pulmonary rehabilitation in COPD subjects¹²⁸. The CAT score is a good reliable tool to measure the severity of COPD GOLD stage (Stage I: 16.2 ± 8.8 , Stage II: 16.3 ± 7.9 , Stage III: 19.3 ± 8.2 , Stage IV: 22.3 ± 8.7) and has a strong correlation with SGRQ ($r = 0.8$, p value < 0.0001) suggesting that the patient's response to the eight item CAT were valid¹³⁰.

Fractional Exhaled Nitric Oxide

FENO testing is a simple noninvasive test that will measure the amount of nitric oxide in exhaled air¹³¹. It is a marker for eosinophilic inflammation in respiratory diseases like COPD and asthma¹³². ATS published guidelines on the measurement of FENO and how to interpret the level of FENO in COPD and Asthma¹³¹. FENO is measured in parts per billion (ppb) and based on its value can be categorized into three levels: low (<25 ppb), medium (25-50 ppb) and high (>50 ppb). The primary role of FENO in COPD patients is to measure the level of inflammation that will predict the response to inhaled steroids. Several studies strongly support the association of eosinophilic inflammation, as measured by high FENO, with the response to inhaled steroid treatment¹³³⁻¹³⁵. In a case control study by Ziekowski, a higher baseline FENO level in COPD subjects was directly related to significant improvements in FEV₁ after treatment of inhaled steroids.

General health measures

Duke Profile

The Duke profile is a self-report instrument widely used to measure and assess overall health as an outcome in medical interventions and health promotion programs like chronic disease management programs¹³⁶. The Duke health profile is the shorter version of the original 67 item Duke UNC health profile¹³⁶. The current version consists of 17 items with respective questions responses to a 3 point Likert scale and can be completed in 5-8 minutes¹³⁶. See the Appendix 8 for Duke Health profile questionnaire. From the 17 items, 6 summary scores are calculated for health function and include physical health, mental health, social health, general health, perceived health, self-esteem; while 4 summary scores for health dysfunction includes anxiety, depression, pain and disability¹³⁶. Duke health profile is available in many languages and several studies had been published worldwide using this profile to measure quality of life among subjects¹³⁷ including COPD subjects¹³⁸.

PHQ-9

PHQ-9 is an instrument to screen and diagnose depression^{139,140}. It is also used clinically to monitor and measure the severity of depression in different clinical conditions like prenatal depression¹⁴¹, depression in HIV patients¹⁴² and also in COPD patients¹⁴³. It consists of 9 questions with a total score ranging from 0 to 27 as each item is scored from 0 (not at all) to 3 (nearly every day). (See Appendix 9 for detailed PHQ9 questionnaire). Scores from 5-9 is mild depression, 10-14 is moderate depression, 15-19 is moderately severe depression and >20 is severe depression¹⁴⁰. Diagnostic validity of

PHQ 9 has been shown in several studies conducted in different countries like Japan¹⁴⁴, China¹⁴⁵, and in USA¹⁴⁰. Minimal clinical important difference for PHQ9 measured on a scale from 0-27 is 5 which represent true change rather than a measurement error¹⁴⁶.

Sleepiness Scale

As COPD is strongly associated with sleep disorders like obstructive sleep apnea^{147,148} it is important to assess sleep hygiene among COPD patients. Most commonly used measure for sleep disorders are Epworth sleepiness scale¹⁴⁹ and Berlin questionnaire¹⁵⁰. Epworth sleepiness scale was first invented by Johns et. al. in year 1991 as a new method of measuring daytime sleepiness¹⁴⁹. It's a valid, reliable measure to quantify daytime sleepiness in different countries and it's a valuable tool for clinical practice and multicenter research^{151,152}. The Berlin questionnaire consists of three categories of questionnaire related to risk of having sleep apnea and depending on their response to questionnaire subject can classified as high risk (if 2 or more categories where the score is positive) or low risk (if 1 or no categories where the score is positive)¹⁵⁰. See Appendix 10 for a detailed Berlin Questionnaire and scoring and Appendix 11 for Epworth sleepiness scale.

Table 3 summarizes the range score and minimal clinical important difference for all the important parameters (both general and respiratory) measured in COPD subjects to assess the impact of COPD on individual subjects life and to assess general health of the subject.

Table 3 Summary of Respiratory and General Measures in COPD

Measure	Score Range	Interpretation of Score	Minimal Clinical Important Difference (MCID)
Respiratory measures			
SGRQ	0-100	Higher scores indicates more limitation	4.3 units ¹²⁴
MMRC Dyspnea	0-5	Lower value indicates less severe dyspnea	
6 MWD	Continuous measure	Lower distance walked indicates more impact of COPD in patients life	25 meter ¹⁰⁶
BODE index	0-10	Higher score indicates high risk of mortality	
COPD Assessment Test	0-40	Higher scores denote a more severe impact of COPD on a patient's life	2 units ¹²⁹
General measures			
PHQ9	0-27	Mild (5-9) Moderate (10-14) Moderately severe (15-19) Severe (>20)	5 units ¹⁴⁶
Duke profile	0-100	For health measures high score means good health	

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Disease management, a multidisciplinary approach proposed to enhance the quality and cost-effectiveness of health care for chronic conditions⁹¹ has been defined as “an approach to patient care that emphasizes coordinated, comprehensive care along the continuum of disease and across health care delivery systems”. The purpose of the present study is to evaluate the effectiveness of the COPD disease management program implemented at the University of Louisville in year 2011. We conducted a retrospective comparative effectiveness research study of pulmonary clinic patients with Chronic Obstructive Pulmonary Disease (COPD) that compares clinical outcomes of those enrolled in the disease management program to those under usual care. Primary outcomes included pulmonary function test (PFT) results, six minute walk distance, quality of life measures and cost related to COPD. The disease management program was intended to improve the quality of life of persons living with COPD by reducing the number of exacerbations and in-patient hospitalizations, improving overall respiratory health and reducing the burden of disease and mortality.

The disease management program, per se, is an innovative approach to improve the quality of life and overall health of persons living with COPD. This study will be the first application of comparative effectiveness research to COPD subjects using the

propensity score (PS) method to evaluate the effectiveness of a COPD disease management program by comparing important clinical outcomes between DMP group and usual care group. Propensity score matching is a common method used in comparative effectiveness research and in pharmacoepidemiology¹⁵³. The PS estimates each patient's probability of enrollment in the intervention group rather than usual care. Propensity score is a probability ranging from 0 to 1. Subjects with a low propensity score will have a lower probability of enrolling in the disease management program. Similarly, a higher score suggests a higher probability of enrolling in the disease management program. The propensity score can be used as a matching variable or as a covariate in regression analyses; we opted for the latter approach.

Goals

The overall goal of the disease management program is to delay the progression of COPD, enhance quality of life, improve clinical outcomes, and also to reduce health care utilizations and overall health care costs.

Specific Aims

Specifically, the following aims were proposed to assess and evaluate the effectiveness of the disease management program. Aim 1 will evaluate the clinical effectiveness of the program and Aim 2 will focus on evaluating cost effectiveness of the program.

Aim 1

- a) To test for differences in key clinical parameters, such as the pulmonary function test and six minute walk distance, between COPD subjects enrolled in disease management program and those who are in usual care.
- b) To compare longitudinal changes in respiratory and general measures among subjects in disease management program.

Aim 2

To test for differences in cost between the DMP group and the usual care group

Hypothesis

Primary Hypothesis 1

Research Hypothesis (H_{1a}): Subjects participating in the disease management program will experience better clinical outcomes compared to patients receiving usual care.

Null Hypothesis (H_{0a}): Implementation of disease management program will not improve clinical outcomes among COPD subjects comparing to COPD subjects under usual care.

Research Hypothesis (H_{1b}): Subjects participating in the disease management program will improve their clinical outcomes longitudinally from baseline.

Null Hypothesis (H_{0b}): Implementation of disease management program will not improve clinical outcomes among COPD subjects longitudinally from baseline.

Primary Hypothesis 2

Research Hypothesis (H_2): Health care costs for subjects enrolled in the disease management program will be lower than for subjects receiving usual care.

Null Hypothesis (H_0): Implementation of disease management program will not lower cost for COPD subjects than for subjects receiving usual care.

Methods

We conducted a retrospective observational cohort study of COPD subjects using clinical data from medical records and cost data from a claims dataset.

The COPD subjects were obtained from three data sources:

- i. From Administrative claims dataset: Male and female University of Louisville health plan members who are beneficiaries of United health care during the time frame from January 1st 2009 through December 31st 2013 (five years).
- ii. From Pulmonary Function Test dataset: Male and female subjects who had physician diagnosed COPD and had pulmonary function testing done at the University of Louisville hospital and/or clinics.
- iii. From Disease management dataset: Male and female subjects diagnosed with COPD and are under University of Louisville Disease Management Program (DMP). See Appendix 3 for a detailed description of University of Louisville DMP for COPD.

Inclusion criteria for the study included physician diagnosed COPD while exclusion criteria include pregnant women and non-ambulatory subjects. The study

subjects were divided into two groups based on their enrollment into the disease management program. Group A included COPD subjects in the disease management program (DMP group). Group B included COPD subjects in the usual care (Usual Care group), including those subjects who have health care claims for COPD (from claims data) or whose physicians diagnosed COPD and are cared for at the University of Louisville clinics.

Sources of Data

Data was collected primarily from two sources:

i. Clinical charts

Data from the clinic charts were retrieved electronically through Allscripts[™] electronic medical record system. These data included demographics, co-morbidities, pulmonary function test parameters, six minute walk distance, general measures and sleepiness scales.

ii. Claims data

Navigator MD Design 180 was used to retrieve claims data. Navigator MD is a data analytic company which focuses on processing administrative claims data through its product named Design 180. Design 180 is flexible and easy to use database software that can query claims data for specific medical conditions like COPD¹⁵⁴. Subjects who had claims for COPD were retrieved from the data set first. Costs related to COPD and other major co-morbidities like asthma, heart disease, hypertension, diabetes mellitus, arthritis, rhinitis, depression were extracted from the dataset in the Microsoft Excel format. Costs for those who enrolled in the disease management program were collected

as COPD related costs in the first, second and third years of the program. Costs of COPD subjects in usual care were collected from January 1st 2009 to December 31st 2013.

Person-years for each subject were calculated from the effective and termination date of the health coverage plan. Costs were calculated as average cost per person per year.

Costs related to COPD were further classified into in-patient hospitalization cost, out-patient hospitalization cost, office cost, laboratory cost and home cost. Home service costs included those associated with oxygen concentrator, nebulizer, and continuous positive airway pressure device.

Statistical methods

Predictors (independent or explanatory variables)

The key variable in analysis was group membership: Group A (Disease management group) or Group B (Usual care group). Other covariates were age, gender, race, time of measurement of respiratory and general measures, co morbidities (diabetes, heart disease, hyperlipidemia, hypertension, depression, asthma, rhinitis, osteoporosis, obstructive sleep apnea). Time variable was categorized as 0 (baseline), 6 months, 12 months, and 18 months with the increment of 6 months from baseline. For DMP group, 0 months means at the time of enrollment into disease management program and for usual care group first pulmonary function test measure available from PFT dataset was considered as 0 month and follow-up longitudinal values were rounded up to nearest 6 months, 12 months, etc. The propensity score was used as a covariate in regression analysis.

For each subject, the baseline probability of participation in the disease management program was calculated by the propensity score method using logistic regression analysis. Variables included in logistic regression analysis included baseline age, gender, race, co-morbidities like asthma, rhinitis, diabetes, heart disease, hyperlipidemia, sleep disorders, arthritis, hypertension and osteoporosis.

At baseline, chi-square test for categorical variable and t-test for continuous variable was used to check for any difference between the two groups. For comparison between two groups (DMP group versus Usual care group), Odds Ratio (OR) was used as a risk measure along with 95% CI and associated P value. P value < 0.05 was considered statistically significant.

Outcome (dependent variables)

Absolute and predicted FEV₁, FVC, quality of life measures (Duke, PHQ9 questionnaire), respiratory measures (6MWD, CAT score, BODE index, mMRC scale), cost related to COPD (from claims data).

To compare longitudinal changes in quality of life measures like SGRQ, CAT score, mMRC scale, BODE index, six minute walk distance and PFT measures in DMP group paired t-test were performed to check for any significant difference in respiratory and general measures from baseline. Longitudinal values of absolute FEV₁ (ml) and absolute FVC (ml) were displayed by using CDC Spirola software. Multiple linear regression analysis was performed to assess the rate of deterioration of various clinical parameters like FEV₁ and FVC between two groups. Regression models were also

adjusted for propensity score. Regression coefficient and P value intervals will be reported for comparing clinical outcomes between two groups.

Regression model for clinical outcomes:

$$Y_{ij} = \alpha + \beta_0 X_{1i} + b_{0i} + (b_{1i} + \beta_1) X_{2ij} + \beta_2 X_{1i} X_{2ij} + \epsilon_{ij};$$

$$b_{0i} \sim N(0, \sigma_{b_{0i}}^2); b_{1i} \sim N(0, \sigma_{b_{1i}}^2); \epsilon_{ij} \sim N(0, \sigma^2)$$

Where “Y” is the dependent or response variable (for e.g. absolute or predicted FEV₁, absolute or predicted FVC); “X₁” is an independent indicator variable for DMP group (1) or usual care group (0); ‘i’ is the subject; ‘j’ is time; X₂ is the time in months (0, 6, 12, 24); $\alpha + \beta_0$ and $\beta_1 + \beta_2$ are intercepts and slopes for DMP group respectively; b_{0i} is the random deviation of the ith subject from the overall or population’ intercept (β_0); b_{1i} is the random deviation of the ith subject from the population slope (β_1), β_1 is the estimate slope for variable X₁; Y_{ij} is the outcome variable value (for e.g. FEV₁) of subject ‘i’ at time ‘j’.

Cost analysis was done by comparing the cost related to COPD among subjects in DMP group versus those under usual care. These costs included total COPD cost, and also sub-categories of cost like office visit cost, in-patient hospitalization (IPH) cost, out-patient hospitalization (OPH) cost, pharmacy cost, cost related to home care and laboratory cost. Regression analysis will be performed for cost related to COPD. All the analysis will be done using SAS 9.3 Statistical software.

Linear regression model for cost

$$Y_i = \alpha + \beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3i} + \epsilon_i;$$

Where Y_i is the total cost related to COPD from 2009-2013; $X_1 = 1$ if less than one year in program, else 0; $X_2 = 1$ if one to two years in program, else 0; $X_3 = 1$ if more than three year in program, else 0; $\beta_1, \beta_2, \beta_3$ are regression coefficients respectively for X_1, X_2 and X_3

Sample size calculation

Sample size was calculated based on difference in 6MWT between two disease management group and usual care group. If the mean difference in 6MWT distance between the two group is 7.5 with standard deviation of 17.5 in the both groups, the sample size needed to detect a difference with alpha level of 0.05, and power of 80% will be 48 (for intervention group) and 144 (for usual care group) based on t-test and allocation ratio of 3:1 usual care versus DMP group. In this study, we have a total of 52 subjects in the intervention group and 662 subjects in usual care group.

Descriptive statistics and baseline characteristics of the study subjects

A total of 52 subjects were enrolled into disease management program between February 1st 2011 and December 31st 2013: 37 in 2011, 11 in 2012 and 4 in 2013. The usual care group consists of 662 subjects diagnosed with COPD from the University of Louisville Pulmonary function test database or subjects who had claims related to COPD from the Navigator MD claims database. Table 4 describes the baseline demographic characteristics of both the groups. There is a significant difference in average age of subjects between the two groups (54.2 in DMP versus 58.3 in usual care; P value 0.0094). 41% of subjects in usual care group are current smokers and only 28.8 % in DMP group but the difference is not statistically significant (P = 0.07). Both groups have approximately same number of white subjects (P value 0.77).

Table 4 Baseline characteristics of study subjects

	All subjects	DMP Group	Usual Care Group	DMP vs. UC group
N	714	52	662	<u>P value</u>
Baseline Age	58.1 ± 11.1	54.2 ± 7.4	58.3 ± 11.2	0.0094
Male gender	334	27, 51.9	307, 46.3	0.44
Race				
White	367	40, 76.9	327, 75.1	0.77
AA	117	11, 21.1	106, 24.3	
Smokers				
Current	177	15, 28.8	162, 40.7	0.07
Former	247	31, 59.6	216, 54.2	0.23
Never	26	6, 11.5	20, 5.0	

Additional data at baseline on sleep and FENO were collected from subjects enrolled in the disease management program. Mean $\pm$ SD for baseline FENO level is 23.8 ± 15.3 and Epworth sleepiness scale is 7.5 ± 4.5 . Total of 31 (59.6%) subjects had high baseline Berlin score in DMP group. Based on COPD GOLD stage at the time of enrollment, 29 subjects have stage 1 COPD, 16 subjects have stage 2, 6 subjects have stage 3 and only 1 subject has Stage 4.

Comorbidities

Table 5 describes the prevalence of comorbidities in both groups. The DMP group has a high prevalence of asthma, rhinitis, hyperlipidemia, osteoporosis and obstructive sleep apnea. Table 5 also presents unadjusted relative risks for comparing different morbidities between two groups. The diagnosis of asthma is a labelled diagnosis based on their pre bronchodilators pulmonary function test and high prevalence among DMP group is likely due to increased screening for asthma at the time of enrollment in the disease management program. There is no significant difference in the prevalence of depression and heart disease between two groups. These comorbidities were used in the multiple logistic regression models to calculate propensity score.

Table 5 Prevalence of Co-morbidities among the study subjects

	All subjects (N=714)		DMP Group (N=52)		Usual Care Group (N=662)		Relative Risk	P value
	n	%	n	%	n	%		
Asthma	149	22.1	28	53.8	121	17.9	2.77	<0.0001
Rhinitis	220	34.1	35	67.3	195	31.3	2.14	<0.0001
Arthritis	238	35.3	26	50.0	212	64.1	1.46	0.02
Depression	141	20.1	16	30.7	125	20.0	1.53	0.06
Heart Disease	314	46.5	25	48.0	289	46.3	1.03	0.8
Hypertension	396,	58.7	37	71.1	359	57.7	1.23	0.058
Hyperlipidemia	270,	40.1	31	59.6	239	38.4	1.55	0.002
Diabetes	160	23.7	18	34.6	142	22.8	1.51	0.055
Osteoporosis	138	20.5	19	36.5	119	19.2	1.90	0.002
Obstructive Sleep Apnea	116	26.2	26	50.0	90	23.0	2.17	<0.0001

Propensity score calculation

Table 6 Logistics regression model for propensity score calculation

	Odds Ratio	P value
Age	0.91	<0.001
Male Gender	1.99	0.07
Asthma	4.76	<0.0001
Rhinitis	3.46	0.0006
Arthritis	2.58	0.01
Heart Disease	1.18	0.66
Hypertension	0.96	0.92
Hyperlipidemia	2.03	0.06
Diabetes	0.97	0.94
Depression	1.09	0.82
Osteoporosis	0.91	0.82

As discussed above, propensity is the probability of being enrolled in the disease management program after controlling for important variables. Multiple logistic regression method was used to calculate the probability of each subject being enrolled in the disease management program rather than usual care. Subjects who suffered from

asthma, rhinitis and arthritis were significantly more likely to enroll in the disease management program (Table 6).

Figure 2 Distribution of Propensity score in DMP group and Usual care group

Distribution of probability for both groups is shown in figure 2. Average propensity score in disease management group were 0.34 versus 0.14 in usual care group. From the figure 2 there is an overlap in the distribution of propensity score between disease management group and usual care group. The propensity score has been

incorporated as a covariate in multiple regression analysis when comparing primary outcomes like FEV₁, FVC, and cost related to COPD.

Clinical effectiveness of the program

The clinical effectiveness of the program was assessed by both general measures and respiratory measures. General measures like PHQ9 (for assessing depression) and Duke Profile (for assessing general health) were used among COPD subjects in the DMP group. Respiratory measures like pulmonary function test, SGRQ, CAT score, BODE index, 6MWT and MMRC dyspnea scale were used to assess the severity of disease and impact of COPD on individual's daily activities. Six minute walk distance and pulmonary function test (absolute and % predicted values of FEV₁ and FVC) were primary outcomes used to compare two groups and also to compare longitudinal changes within each group from their baseline values.

Longitudinal changes of General Measures in DMP group

Table 7 represents the longitudinal changes of PHQ9 and Duke Profile among subjects in DMP group.

Table 7 Longitudinal changes of general measures in DMP group

	0 month	12 month	24 month
PHQ9 (n, Mean $\pm$ SD)	19 6.3 $\pm$ 5.4	30 4.0 $\pm$ 4.4	13 3.1 $\pm$ 2.1*
DUKE (n, Mean $\pm$ SD)	52, 64.1 $\pm$ 17.4	30 71.6 $\pm$ 16.7*	19 70.8 $\pm$ 18.7*
	* represents statistically significant from baseline		

PHQ9

PHQ9 is a measure for depression; lower values indicate fewer depressive symptoms. At baseline, the average PHQ9 was 6.3 which improved at the end of 12 months (mean = 4) and at 24 months (mean = 3.1). Figure 3 depicts longitudinal changes in PHQ9 (mean $\pm$ SE) every six months from baseline to 30 months. There is a gradual decline in PHQ9 from baseline to 30 months except for a surge from 12 to 18 months. PHQ9 was implemented later in the program resulting in missing baseline PHQ9 values for 33 subjects. Notwithstanding the small number of subjects, change in PHQ9 from baseline is statistically significant at 24 months and we can conclude that disease management program significantly improves depressive symptoms among COPD subjects enrolled in the disease management program.

Figure 3 Longitudinal changes in PHQ9 in DMP group

Duke Profile

Duke profile is a self-reported measure of general health status and higher scores are better. At baseline, the average duke score was 64.1 which were improved at the end of 12 months and 24 months. Figure 4 depicts longitudinal changes in duke score (mean $\pm$ SE) every six months from baseline to 30 months. There is a gradual improvement in duke score from baseline to 12 months. Notwithstanding score declined slightly at 18 and at 30 months it is still significantly high than baseline. In conclusion, the disease management program improves general quality of life of COPD subjects over baseline.

Figure 4 Longitudinal changes in Duke score in DMP group

Longitudinal changes of Respiratory Measures in DMP group

The respiratory measures followed longitudinally among subjects in DMP group include St George Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT), mMRC dyspnea scale, BODE index along with pulmonary functions test and Six Minute Walk Distance (6MWD). Table 8 summarizes longitudinal changes of SGRQ, CAT score and mMRC dyspnea scale among subjects in DMP group at baseline, 12 months and 24 months.

Table 8 Longitudinal changes of Respiratory measures in DMP group

	0 month	12 month	24 month
SGRQ (n, Mean $\pm$ SD)	52, 37.1 $\pm$ 17.1	29, 28.4 $\pm$ 16.1*	11, 30.2 $\pm$ 16.1
CAT score (n, Mean $\pm$ SD)	14, 18.4 $\pm$ 6.7	22, 12.2 $\pm$ 5.9 *	18, 14.2 $\pm$ 7.7
mMRC (n, Mean $\pm$ SD)	50, 0.56 $\pm$ 0.7	32, 0.46 $\pm$ 0.6	21, 0.95 $\pm$ 0.8
	* represents statistically significant from baseline		

St George Respiratory Questionnaire (SGRQ)

SGRQ is an instrument used among obstructive lung disease subjects to measure impact on overall health, daily life, and perceived well-being. Score is ranging from 0 to 100, higher the score indicates more severe limitation. At baseline average SGRQ score was 37.1 which were improved at the end of 12 months ($P = 0.02$) and 24 months from ($P = 0.21$). Figure 5 depicts longitudinal changes in SGRQ score from baseline. There is slight deterioration in score at 24 months but it is still low from baseline. The difference in SGRQ after 12 months is not only statistically significant but also clinically significant as the minimal clinical important difference for SGRQ is 4 for effective treatment thus we can conclude that there is a significant improvement in overall health, daily life and perceived well-being of COPD subjects after enrollment in the disease management program.

Figure 5 Longitudinal changes in SGRQ score in DMP group

COPD Assessment Test (CAT)

CAT is a shorter version of SGRQ questionnaire and is designed to measure the impact of COPD on subject's life and score can be compared to assess the changes over time. Score is ranging from 0-40 with higher scores indicate more severe impact of COPD on an individual's life. Figure 6 depicts longitudinal changes in CAT score from baseline. There is significant decline in mean CAT score from baseline to 12 months ($P = 0.01$). From one year to two year score slightly deteriorates to 14.4, but remains below baseline. Based on minimal clinical important difference (MCID) value of 2 for CAT, this measure is also clinically significant at 12 and 24 months.

Figure 6 Longitudinal changes in CAT score in DMP group

Modified Medical Research Council (mMRC) Dyspnea Scale

mMRC is a subjective assessment of breathlessness in respiratory diseases like COPD and its value are ranging from 0-5. Table 9 describes longitudinal comparison of changes in scale from baseline to 1 year and 2 years. mMRC scale decreased by 0.06 at 1 year ($P = 0.57$) and increased by 0.20 units at 2 year ($P = 0.29$) but the changes are not statistically significant from baseline.

Figure 7 Longitudinal changes in mMRC scale in DMP Group

Table 9 Longitudinal comparison of mMRC Dyspnea Scale

MMRC Dyspnea scale		
	12 months vs. 0 month	24 months vs. 0 month
N	32	21
Mean difference (95% CI)	-0.06 (-0.30, 0.17)	0.20 (-0.19, 0.59)
P value	0.57	0.29

Longitudinal changes of Pulmonary Function Test in DMP Group and Usual Care Group

Pulmonary function test is most common spirometry measured among COPD subjects. Table 10 describes longitudinal changes in FEV₁ (absolute and % predicted) and FVC (absolute and % predicted) for DMP group and Usual care group. Percent predicted FEV₁ is defined FEV₁% of the patient divided by the average FEV₁% in the population for any person of similar age, sex and body composition (height)¹⁹. Out of 52 subjects, 39 subjects had measured values at 1 year and 23 subjects at 2 year in DMP group; while 94 out of 426 subjects had measured values at 1 year and 48 at 2 year in usual care group.

Table 10 Longitudinal changes in Pulmonary Function test measures in DMP and Usual care group

	0 month	12 month	24 month
DMP Group			
	N=52	N = 39	N = 23
FEV ₁ (liter)	2.16 ± 0.7	2.27 ± 0.7	2.04 ± 0.8
% Predicted FEV ₁	0.67 ± 0.2	0.72 ± 0.2	0.69 ± 0.2
FVC (liter)	3.49 ± 1.1	3.58 ± 0.9	3.30 ± 1.1
% Predicted FVC	0.83 ± 0.2	0.9 ± 0.2	0.87 ± 0.2
Usual Care Group			
	N = 426	N = 94	N = 48
FEV ₁ (liter)	1.44 ± 0.8	1.37 ± 0.6	1.21 ± 0.56
% Predicted FEV ₁	0.50 ± 0.2	0.49 ± 0.2	0.45 ± 0.18
FVC (liter)	2.78 ± 1.1	2.67 ± 1.1	2.47 ± 1.2
% Predicted FVC	0.74 ± 0.2	0.74 ± 0.2	0.69 ± 0.2
* Values are Mean ± SD			

Forced Expiratory Volume in one second (FEV₁)

Table 11 presents longitudinal comparison of changes in absolute FEV₁ at the end of 1 year, 2 year and 3 years for both the groups. From the table subjects in DMP group has significant improvement in their absolute FEV₁ (140 ml) from baseline to 12 months (P value 0.0046). There is also improvement in FEV₁ at 24 months by 30 ml and at 36 months by 60 ml but the difference is not statistically significant due to less number subjects at the end of 2 years and 3 years. FEV₁ in usual care group is monotonically declining at 12 months (-5ml), 24 months (-130 ml) and at 36 months (-130ml). So in addition to improvement in general measures, subjects in DMP group had significant improvement in FEV₁ which is also one of the predictor for mortality among COPD subjects.

Table 11 Longitudinal comparison of changes in absolute FEV₁ (ml)

Absolute FEV ₁ (ml)	12 month vs. 0 month	24 month vs. 0 month	36 month vs. 0 month
DMP Group			
N	39	23	3
Mean difference (95% CI)	140 (40-250)	30 (-90, 170)	60 (-170, 290)
P value	0.0046	0.55	0.36
Usual Care Group			
N	92	46	30
Mean difference (95% CI)	-5 (-60, 50)	-130 (-230, -30)	-130 (-260, -10)
P value	0.85	0.01	0.03

Linear regression estimates for FEV₁ as a ‘dependent variable’ while DMP group versus usual care, time of measurement of FEV₁ and propensity score as an ‘independent variable’ is shown in Table 12. Main effect model will include DMP variable, time and interaction between them (Model 1). Model 2 is an adjusted model with addition of propensity score in the regression analysis. From the results of Model 1, FEV₁ for usual care group is 1455 ml (estimate for intercept) and for DMP group is 2207.1ml (by adding estimates for intercept and DMP group). Slope for usual care group is -3.77 ml which means FEV₁ is declining by time in usual care group but in DMP group slope is 1.126 ml means there is an improvement in FEV₁ with time and its marginally significant (P=0.0536). From model 2 propensity score was found to be significantly associated with FEV₁. AIC and BIC for model 2 is less than model 1 and thus model 2 is a more fitted model. Even after adding propensity score, slope is still positive for DMP group (1.001 ml) but not statistically significant (P=0.0916).

Table 12 Estimates from Linear regression Models for examining changes in absolute FEV₁ (ml)

	Model 1			Model 2		
Fixed Effects						
	Estimates	SE	P value	Estimates	SE	P value
Intercept	1455	35.97	<0.0001	1349.6	42.74	<0.0001
DMP group	752.1	108.8	<.0001	527	121.8	<.0001
Time	-3.77	1.057	0.0005	-3.28	1.082	0.0028
Time*DMP	4.896	2.52	0.0536	4.281	2.523	0.0916
Propensity score				996.4	240.4	<0.0001
Error variance						
Intercept	516.2	36.06	<0.0001	493	36.07	<0.0001
Time	0.039	0.024	0.0542	0.043	0.025	0.0444
Residuals	39.46	4.109	<0.0001	37.93	4.058	<0.0001
Model Fitness						
AIC	1199.7			1074.3		
BIC	1216.4			1090.6		
AIC is Akaike information criterion; BIC is Bayesian information criterion, SE is Standard Error						

Forced Vital Capacity (FVC)

Table 13 represents longitudinal comparisons of changes in absolute FVC (ml) at 1 year, 2 year and 3 year in both groups. FVC is monotonically improving in DMP group at the end of 1 year, 2 years and 3 years but the changes were not significant from baseline. But in Usual care group FVC improved only at the end of 1 year, but is declining thereafter from baseline. Subjects in usual care group had mean decline of 130 ml (at 24 months) and 210 ml (at 26 months) in FVC from baseline, but FVC among subjects in DMP group monotonically improves from baseline.

Table 13 Longitudinal comparison of changes in absolute FVC (ml)

Absolute FVC (ml)	12 month vs. 0 month	24 month vs. 0 month	36 month vs. 0 month
DMP Group			
N	39	23	3
Mean difference (95% CI)	100 (-10, 210)	40 (-100, 190)	130 (-530, 780)
P value	0.06	0.53	0.49
Usual Care Group			
N	92	46	30
Mean difference (95% CI)	40 (-50, 140)	-130 (-270, 10)	-210 (-440, 10)
P value	0.39	0.07	0.06

Linear regression estimates for FVC as a dependent variable for both the models is shown in Table 14. From the table FVC for usual care group is 2795.8 ml (model 1) and for DMP group is 3519.7 ml. Here also slope for FVC is negative (-3.43 ml) for subjects in usual care group and positive for subjects in DMP group. For every one month increase in time, subjects in usual care had a decline of FVC by 3.43 ml, while subjects in disease management program actually had an improvement of 1.32 ml. Propensity score is found to be significantly associated with FVC with P value of 0.0046 (Model 2). Propensity score adjusted model fits well as evident by decrease in AIC and BIC values comparing to Model 1.

Table 14 Estimates from linear regression models for examining change in absolute
FVC (ml)

	Model 1			Model 2		
Fixed Effects						
	Estimates	SE	P value	Estimates	SE	P value
Intercept	2795.8	53.36	<0.0001	2690.5	63.85	<0.0001
DMP group	723.9	161.4	<0.0001	485.3	182	0.0084
Time	-3.43	1.624	0.0360	-2.95	1.691	0.0825
Time*DMP	4.754	3.834	0.2167	4.306	3.864	0.2668
Propensity score				1034.5	36.02	0.0046
Error variance						
Intercept	1134.8	79.1	<0.0001	1100.3	80.05	<0.0001
Slope	0.1	0.045	0.0133	0.117	0.048	0.0076
Residual	87.54	8.313	<0.0001	81.61	8.065	<0.0001
Model Fitness						
AIC	1874.0			1707.3		
BIC	1890.7			1723.5		

Figure 8 Longitudinal FEV₁ and FVC changes in DMP Group and Usual Care Group (by SPIROLA software)

Figure 8 is displaying longitudinal FEV₁ and FVC in both the groups from 2009 to 2013 created through CDC SPIROLA software. Visually from the figure, there is a significant improvement in FEV₁ among COPD subjects in disease management program from 2011 to 2012 and slight decline in FEV₁ in third year but it is still high from baseline values of 2011. But the values of FEV₁ are monotonically declining from 2011 to 2012 in usual care group.

Six minute Walk Distance (6MWD)

Table 15 and Table 16 presents longitudinal changes and comparison to baseline in six minute walk distance in meter at 0 month, 12 months and 24 months for both the group. In DMP group 52 subjects have baseline 6MWD, 32 subjects have values at 12 months and 21 subjects have values at 24 months. There is a monotonic decline in six minute walk distance in DMP group from baseline to 2 years but after doing a paired t-test analysis at 12 months and 24 months comparing values to baseline, difference is not statistically significant. In usual care group distance declined slightly at 12 months but improved at 24 months, but doing a paired t-test analysis subjects in usual care group declined by 24.8 meter at 1 year and by 13.5 meter at 2 year but again the difference is not statistically significant.

Table 15 Longitudinal changes in 6 MWD (meter) in DMP and Usual care group

	0 month	12 month	24 month
	DMP Group		
	N=52	N = 32	N = 21
6 MWD (meter)	435.2 ± 99.1	432.3 ± 117.2	408.2 ± 134.5
% predicted 6MWD	83.1 ± 4.5	85.7± 15.7	82.5 ± 20.2
	Usual Care Group		
	N = 143	N = 26	N = 11
6 MWD (meter)	318.1 ± 101.4	317 ± 90.9	347.2 ± 90.3
% predicted 6MWD	65.1 ± 38.4	67.4 ± 15.8	68.5 ± 19.1

Table 16 Longitudinal comparison of changes in 6 MWD

Longitudinal comparison of changes in 6 MWD		
	12 month vs. 0 month	24 month vs. 0 month
DMP Group		
N	32	21
Mean difference (95% CI)	3 (-10.2, 16.2)	-15.2 (-39.8, 9.5)
P value	0.64	0.22
Usual Care Group		
N	26	11
Mean difference (95% CI)	-24.8 (-56.3, 6.5)	-13.5 (-40.9, 13.9)
P value	0.11	0.29

BODE Index

BODE index is a multidimensional grading system to evaluate COPD subjects. BODE index made of BMI, FEV1, mMRC dyspnea scale and six minute walk distance. Average BMI of subjects in disease management program at baseline was 36.1 ± 9.1 , at 12 months it was 37.2 ± 10.1 and at 24 months it was 37.9 ± 9.2 . Change in BMI was not statistically significant from baseline. Figure 9 display longitudinal BODE index values for subjects in disease management program from baseline to 36 months. Longitudinal comparison of changes in BODE index (mean difference and associated P value) is presented in Table 17. At baseline average BODE index was 1.5 which was improved significantly at the end of 12 months with mean difference of -0.40 and P value of 0.03 (Paired t-test). There is also decline in BODE index at 24 months (mean difference - 0.14) but it's not statistically significant from baseline as there are fewer subjects at 24 months and thereafter.

Figure 9 Longitudinal changes in BODE index in DMP Group

Table 17 Longitudinal comparison of changes in BODE index in DMP Group

Longitudinal comparison of changes in BODE index in DMP group		
	12 month vs. 0 month	24 month vs. 0 month
N	32	21
Mean difference (95% CI)	-0.40 (-0.78, -0.03)	-0.14 (-0.55, 0.27)
P value	0.03	0.48

Cost effectiveness of the program

Cost analysis will be done for cost related to COPD and also cost related to major co-morbidities like arthritis, rhinitis, hyperlipidemia, depression, diabetes, hypertension, heart disease among COPD subjects in disease management program and usual care.

Table 18 represents COPD related cost for subjects in DMP group from the time they first enrolled in the disease management program and this cost categorized into three groups (i.e. cost in first year of program, cost in second year of program and cost in third year of program). From the table average cost per person per year in first year is \$3693, which decreased to \$3608.8 in second year and to \$2934 in third year. Pharmacy cost contributes majority of total COPD cost followed by office cost and out-patient hospitalization. There are no claims for in-patient hospitalization in the third year.

All cost related to COPD for those who are in the program is presented in Table 18

Table 18 COPD related cost in DMP Group

Time in Program	First Year (N=52)	Second Year (N=39)	Third Year (N=23)
Total cost	\$3693.0	\$3608.8	\$2934.0
Office cost	\$770.3	\$338.5	\$249.1
In-patient cost	\$4.1	\$191.0	\$0
Out-patient cost	\$223.6	\$357.0	\$252.5
Home cost	\$28.3	\$14.1	\$0
Laboratory cost	\$7.0	\$8.4	\$4.2
Pharmacy cost	\$2327.0	\$2591.7	\$2360.2
	* Values are presented in average cost per person year		

Table 19 represents COPD cost for DMP group and usual care group from 2009-2013. This cost is also average cost per person per year based on the effective and termination dates into health coverage. There are total of 226 subjects in usual care group who claims for COPD. Average cost per person per year for in-patient hospitalization is significantly high for subjects in usual care (\$5578.7) versus subjects in DMP group (\$250.9). Pharmacy cost is high for subjects in DMP group. Histogram of cost is shown in Figure 10. Figure 11 graphically presents average cost per person per year for different sub-categories of COPD cost.

Comparison of COPD related cost between two groups

Table 19 Comparison of COPD related cost between two groups from 2009-2013

	DMP Group	UC Group
Total COPD cost	\$2297.9	\$1675.3
< 1 year in the program	1329.8	
1-2 years in the program	1487.9	
2-3 years in the program	2949.9	
Office cost	\$376.2	\$158.9
In-patient hospitalization (IPH) cost	\$250.9	\$5578.7
Out-patient hospitalization (OPH) cost	\$290.3	\$341.1
Home cost	\$202.7	\$480.6
Laboratory cost	\$16.1	\$53.1
Pharmacy cost	\$1694.8	\$496.0
	* Values are presented in average cost per person year	

Figure 10 Histogram of COPD related cost

Figure 11-Categories of COPD cost in DMP and Usual Care Group

Regression analysis results for COPD related cost from 2009-2013 were shown in Table 20. Exposure time is the total time contributed into program (0 represent usual care, 1 means less than one year in the program, 2 means between one to two years in the program and 3 mean between two-three years in the program). From table 20, subjects who are in program less than one year have lower COPD related cost comparing to those who are in usual care. In the adjustment model propensity score is not significantly associated with COPD cost.

Table 20 Regression model for COPD related cost

All COPD cost	Model 1		Model 2	
	Estimates	P value	Estimates	P value
Intercept	1675.3	0.0005	2183.1	0.0010
Enrollment duration*				
1 vs. 0	-345.5	0.87	-134.2	0.95
2 vs. 0	-187.4	0.93	-105.4	0.96
3 vs. 0	1274.6	0.36	1574.1	0.27
Propensity score			-2301.1	0.26
	*Enrollment duration is coded as 0, 1, 2, 3; cost is presented in average cost per person per year; Model 2 is adjusted for propensity score			

Health Care Utilizations

Table 21 summarized health care utilizations related to COPD for both the groups. Subjects in disease management program have higher claims associated with office visits, out-patient hospitalization and laboratory testing. Subjects in both group had approximately same percentage for in-patient hospitalization claims, but those in DMP group had significantly less number of average claims per subject (2.2 versus 12.2).

Table 21 Health Care Utilizations and Average number of claims

	DMP Group	Usual Care Group
	N=52	N=226
≥1 IPH, n (%)	8, 15.3	34, 15.1
Mean (SD) number of IPH Claims	2.2	12.2
≥1 OPH, n (%)	35, 67.3	112, 49.5
Mean (SD) number of OPH Claims	4.8	3.4
≥1 Office visit, n (%)	47, 90.3	160, 70.7
Mean (SD) number of office visit Claims	15.69	4.7
≥1 home service, n (%)	8, 15.3	25, 11.1
Mean (SD) number of home service Claims	3.8	8.9
≥1 laboratory, n (%)	20, 38.4	50, 22.1
Mean (SD) number of laboratory Claims	1.9	2.3

Cost associated with major co-morbidities

As discussed in the background, COPD also imposes major economic burden through cost associated with major co-morbidities. Figure 12 depicts co-morbidities among COPD subjects before and after enrollment in the disease management program. This cost was calculated as average cost per person per year. There is a significant decline in cost related to all major diseases like arthritis, hypertension, hyperlipidemia, diabetes, and osteoporosis after enrollment of COPD subjects into disease management program comparing to cost before enrollment into program.

Figure 12 Co-morbidities cost before and after enrollment into disease management group

Table 22 summarizes total healthcare cost (combining COPD related cost and associated morbidities), COPD related cost and cost related to major co-morbidities among all COPD subjects in DMP and Usual care group from 2009-2013. From table 22

subjects in disease management group had lower cost for arthritis, rhinitis, hypertension, hyperlipidemia, depression and osteoporosis.

Table 22 Co-morbidities related cost in Usual Care Group and Disease management Group from 2009-2013

	DMP Group	Usual Care Group
Total health care cost	\$18246.1	\$13164.1
COPD related cost	\$2297.9	\$1675.3
Asthma	\$1146.3	\$752.2
Arthritis	\$1221.8	\$1790.6
Rhinitis	\$120.7	\$469.89
Heart disease	\$9128.8	\$3263.6
Hypertension	\$858.0	\$1007.7
Hyperlipidemia	\$278.8	\$435.6
Diabetes	\$2399.7	\$2249.9
Depression	\$540.5	\$1007.6
Osteoporosis	\$253.6	\$511.7
	Values are presented as average cost per person per year;	

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Introduction

We have evaluated the effectiveness of the University of Louisville Disease management program for Chronic Obstructive Pulmonary disease by comparing clinical outcomes and cost with usual care. Our main findings include improvement in respiratory measures like FEV₁, FVC along with subjective measures like SGRQ. Implementing this chronic disease management program will reduce the impact of COPD on daily activities and improve overall health. Even though subjects in disease management program had higher COPD related cost, cost associated with major co-morbidities were significantly reduced for subjects in DMP group after enrollment in the program.

Clinical effectiveness of the program

There are several general and respiratory measures used to assess the clinical effectiveness of the program and also to compare with the subjects in the usual care group. PHQ9 depression scores were significantly reduced from 6.3 to 3.1 after 24 months in the program. Several studies¹⁵⁵⁻¹⁵⁷ had been done in the past to study role of depression among COPD cohort and found the COPD subjects with co-morbid depressive symptoms had significantly shorter survival (Hazard ratio: 1.93; 95%

confidence interval, 1.04-3.58), longer hospital stay (1.1 more days; $P = .02$), persistent smoking 2.30 (95% confidence interval, 1.17-4.52), increased symptom burden, and poorer physical and social functioning¹⁵⁵ and also exacerbations were more frequent among COPD subjects with depression¹⁵⁷. Likewise general health related quality of life and functional health status as measured by Duke Health profile also improved from mean baseline value of 64.1 to 70.8 after 24 months in the disease management program. Thus implementing this program will significantly reduce depressive symptoms and comorbid outcomes associated with depression like exacerbations and longer hospital stay among COPD cohort.

Among respiratory measures, ones that are significantly improves are SGRQ, CAT score and BODE index. SGRQ which is a disease specific valid instrument to measure the impact of COPD on health and daily life activities was improved from 37.1 at baseline to 28.4 at 12 months ($P = 0.02$) and 30.2 at 24 months ($P = 0.21$). Reduction of score by at least 4 point is considered to be clinically effective. These findings are similar to study conducted by Labrecque et. al. about the role of self-management education program in improving quality of life¹⁵⁸. In that study subjects who were in intervention trial (self-management education arm) had significant improvement in SGRQ score at three months (mean reduction of 5 points, $P = 0.006$) and 12 months (mean reduction of 6.7, $P < 0.001$) in contrast to increase in score by 3.7 units in control group¹⁵⁸. But in that study only self-management education component was used in the intervention group. CAT score was also improved significantly from 18.4 to 12.2 at the end of one year into program and also at the end of 2 year (Figure 6).

Apart from subjective measures, objective measures of pulmonary function were also improved significantly from baseline to 1 year and 2 year (Table 10-14). Mean FEV₁ at baseline was 2.16 liter which improved to 2.27 at the end of 1 year into program (P=0.0046). FEV₁ is a good predictor for mortality and thus implementing this program is expected to reduce the mortality among COPD subjects. Subjects in disease management program had a positive longitudinal slope for FEV₁ compared to subjects in usual care. BODE index which is a multidimensional grading system to evaluate COPD subject is a good predictor of mortality among COPD subjects. In our study BODE index declined by 0.40 units (95% CI: -0.78 to -0.03, P value 0.03) from baseline to 12 months among subjects in disease management group (Table 17). These results are in agreement with the results from study by Linderman et. al.⁹⁸ where authors studied the effect of proactive integrated care for COPD subjects and found that mean BODE index decreased by 1.1 units at the end of 12 weeks into the integrated care program. Several previous studies predicted mortality among COPD subjects by longitudinally following the BODE index¹¹². In a longitudinal cohort study of COPD subjects by Martinez et. al., researchers conclude that increase in mean BODE index by more than 1 point from baseline to 6, 12, and 24 months of follow-up was predictive of subsequent mortality. In our study even with the small number of subjects in disease management program, BODE index was significantly reduced at 12 months so implementing this program in a larger COPD cohort for a longer period of time will be expected to reduce subsequent mortality among COPD subjects. In conclusion, University of Louisville COPD Disease Management Program appears to be highly effective in improving lung health and reducing airflow limitations.

Cost effectiveness of the program

Average cost related to COPD after enrollment into program in first year was \$3693, in second year was \$3608.8 and in third year it was \$2934. Average cost per person per year in DMP group was \$2297.9 and in usual care group was \$1675.3. Although cost related to COPD was higher among disease management subjects, there was significant improvement in health related quality of life of COPD subjects. The in-patient hospitalization cost was lower and most costs among subjects in disease management group were attributable to pharmaceutical expenses related to COPD (Figure 11). This suggests that subjects in the disease management program were more adherent to their medicines and will enhance their healthy life expectancy as compared to those receiving usual care. Disease management program participants also had more claims associated with office visits. These findings are in agreement with the results by Chuang et. al. who studied the effect of patient-centric chronic obstructive pulmonary disease program among 141 COPD patients and found primary care physician visit were significantly higher among subjects in the intervention group¹⁵⁹. Patient-centric approach consists of initial face to face assessment by nurse, supplementation of education material and action plan and call from nurse staff to the subjects once every week. The reason for more office visits is because subjects in disease management program have more planned office visits as a protocol for disease management program, but this is expected to improve overall quality of life and reduce the impact of COPD on daily activities and reduce in-patient hospitalization. In a recent randomized control trial study of disease management program at different VA centers by Dewan et. al, authors found that average

cost per person for subjects in intervention group is \$593 less than those in usual care group¹⁶⁰.

Despite the higher cost related to COPD among subjects in the disease management program, costs associated with major co-morbidities were subsequently reduced after enrollment into disease management program (Figure 12). Cost associated with heart disease and diabetes was significantly lower after enrollment into the disease management program. Average cost per person per year for heart decreased from \$3969 before the enrollment to \$1543 after the enrollment and for diabetes it decreased from \$3101 to \$972. Subjects in the disease management program had significant lower cost for hypertension, hyperlipidemia, depression and osteoporosis comparing to subjects in usual care. According to American Lung Association, indirect cost contributes approximately \$20 billion among COPD subjects⁷⁷, so implementing the disease management program is expected to significantly reduce the economic burden associated with COPD.

Strengths

This study contributes to the growing literature on the effectiveness of disease management programs in chronic diseases like COPD. We demonstrated improvement in absolute FEV₁; previous studies showed that decreasing level of FEV₁ is one significant predictor of mortality among COPD cohort¹⁶¹. Implementing this chronic disease management program is expected to reduce the impact of COPD on daily activities and reduce the mortality from COPD.

Limitations

There are several limitations of this study. Certain limitations are associated with any retrospective record review, such as bias associated with different follow-up time for each group and lack of complete information on certain measures among subjects in the usual care group. Secondly, the sample size in disease management group was small; nevertheless, we were able to detect a significant difference in FEV₁ at 12 months. Third, enrollment of subjects into the disease management program was not randomized and so there was no comparison group who had detailed and complete information on subjects in the same calendar time comparing to subjects in disease management program. Fourth, there are always limitations associated with using administrative claims data. The main pitfall of the claims data is that it can only identify services received for which a bill was submitted. So if the charges were delayed or not submitted at all, there is always a chance of missing data from administrative claims database. Also claims data do not provide sufficiently detailed clinical history to allow researchers to classify subjects based on severity of COPD. Fifth, use of propensity score as a covariate in the regression analysis is not the best method we use as there are other methods like matching based on propensity score is an appropriate approach to control for baseline differences. Finally, we were not able to identify which component of this disease management program works as all the subjects in the program received the full spectrum of interventions. More evidence will be needed by conducting large randomized controlled trial with a long term follow up of at least 5 years.

Future recommendations

Future implementation of this program at a larger scale can be recommended among COPD cohort and it can be randomized. Randomization of subjects with few components of program in one group versus other components in second group will help researchers to understand exactly which component of disease management program works. It may also prove worthwhile to explore a more comprehensive program for the simultaneous management of multiple chronic diseases (e.g. diabetes mellitus, congestive heart failure or hypertension).

Conclusion

The University of Louisville COPD disease management program appears to be highly effective in improving lung health and reducing airflow limitations among COPD subjects as evidenced by significant improvement in objective measures like FEV₁. Program is also effective in reducing the impact of COPD on daily activities as evidenced by significant improvement in subjective measures for health related quality of life like St George Respiratory Questionnaire, COPD assessment test, PHQ9 and Duke Profile. Notwithstanding subjects in DMP had higher COPD related cost, they had significantly low in-patient hospitalization cost and also significant reduction in cost associated with major co-morbidities after enrollment in the University of Louisville COPD disease management program.

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CRRGP F KZ "

Crr gpf kz "3<P J CP GU"Ur kqo gw { "tghgtgpegu"i tcr j u"

Crr gpf k'4<P cwtch'F genpg"qh'HGX3"d{'Ci g'"

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Program Highlights:

- Case Manager / Respiratory Therapist will serve as care manager to enrollees and liaison to physician and nurse practitioners.
- Case Manager is embedded and working closely with physicians and mid-level health care providers.
- Primary care physicians will be advised of program and provided clinical updates of enrollees.
- High amount of personal touch and face-to-face time with program participants.

Program Components:

I. COPD Screening:

- Potential enrollees will be targeted and recruited into the program as outlined above.

II. Participant requirements:

- The program will be explained and the potential enrollee will be required to sign a participation agreement documenting their intention to participate fully in the program.

III.a Each enrollee will have an initial Comprehensive Evaluation and Assessment, which will include:

Performed at Healthcare Outpatient Center by ULP

- Comprehensive Office visit
- 6 Minute Walk Test
- Pulmonary Function Testing, complete, with and without bronchodilator
- Fractional exhaled nitric oxide

- Overnight oximetry
- ECG
- Alpha-1 anti-trypsin level (we use a HIPAA certified laboratory that provides this service at no charge)
- Questionnaires (PHQ9, St. George Respiratory Questionnaire, Epworth Sleepiness Score, Duke Profile)

Performed at HealthCare Outpatient Center by ULH

- Chest X-Ray (if not done within the past 12 months)
- Sputum Analysis (if enrollee fits into category of chronic bronchitis with sputum production)

III.b Follow-up Visits

- Follow-up visits and testing is based on disease risk stratification. In general, those with mild COPD, as determined by GOLD stages 1-2, are followed less often and less intensely. Those with more severe COPD, as determined by GOLD stages 3-4, are followed more closely. See below.

COPD GOLD STAGES 1 or 2

- 6 month follow-up clinic visits
- Spirometry
- Review Action Plan
- Questionnaire (PHQ9, Duke Profile, Respiratory Health)

COPD GOLD STAGE 3 or 4

- 3 month follow-up clinic visits

- Spirometry
- Review Action Plan
- 6 minute walk test (every 6 months)
- Questionnaire (PHQ9, Duke Profile, Respiratory Health)

IV. Support Group Education Classes

- All participants will be required to participate in a group education session which covers a variety of topics including COPD causes and prevention, nutrition, exercise, healthy life style, bone health, proper medication use, tobacco cessation and self-management of their disease. These classes are held monthly and are run by our certified respiratory therapists with support from our pulmonologists and nurse specialists.
- Additionally, individualized education and training is provided by the clinic respiratory therapists and these concepts are reinforced with most every participant / health care encounter.

MODIFIED MEDICAL RESEARCH COUNCIL DYSPNEA SCALE

ID NUMBER:	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
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FORM CODE: MRC
VERSION: 1.0 10/26/10

Visit Number	<input type="text"/>	<input type="text"/>
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SEQ #	<input type="text"/>	<input type="text"/>	<input type="text"/>
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0a) Form Date //

0b) Initials

Instructions: This form should be completed during the participant's visit. Choose the one best response.

Please choose the one best response to describe your shortness of breath.

Grade

- 0 "I only get breathless with strenuous exercise"
- 1 "I get short of breath when hurrying on the level or walking up a slight hill"
- 2 "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level"
- 3 "I stop for breath after walking about 100 yards or after a few minutes on the level"
- 4 "I am too breathless to leave the house" or "I am breathless when dressing"

1. Grade

Cr r gpf kz'7<DQF G"Kf gz"

Variable	Points on BODE index			
	0	1	2	3
BMI	>21	≤21		
FEV ₁	≥65	50-64	36-49	≤35
MMRC dyspnea scale	0-1	2	3	4
Distance walked in 6 minutes	≥350	250-349	150-249	≤149

Source: Celli. et. al. 2004 NEJM pg1005-1012

The St. George's Respiratory Questionnaire

This questionnaire is designed to help us learn more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you the most problems, rather than what the doctors and nurses think your problems are.

Please read the questions carefully and ask the study nurse if you do not understand anything. Answer the questions as honestly as possible. There are no right or wrong answers; only the answer that best applies to you. Do not spend too much time deciding about your answers.

Part 1

Describe how often your lung/respiratory problems have affected you over **the last 4 weeks**. Please place a mark in one box for each question.

	almost every day	several days a week	a few days a month	only with lung/ respirator y infections	not at all
1. Over the last 4 weeks, I have coughed:					
2. Over the last 4 weeks, I have brought up phlegm (sputum):					
3. Over the last 4 weeks, I have had shortness of breath:					
4. Over the last 4 weeks, I have had episodes of wheezing:					

5. During the **last 4 weeks**, how many severe or very unpleasant episodes of lung/respiratory problems have you had? Mark one answer only.

- ☐ more than 3 episodes
☐ 3 episodes
☐ 2 episodes
☐ 1 episode
☐ no episodes

6. How long did the worst episode of lung/respiratory problem last? Mark one answer only.

Go to question 7 if you didn't have a severe episode.

- ☐ a week or more
- ☐ 3 or more days
- ☐ 1 or 2 days
- ☐ less than a day

7. Over the last 4 weeks, in an average week, how many good days (with few lung/respiratory problems) have you had? Mark one answer only.

- ☐ None
- ☐ 1 or 2
- ☐ 3 or 4
- ☐ nearly every day
- ☐ every day

8. If you wheeze, is it worse in the morning? If you don't wheeze, go to Part 2.

- ☐ No
- ☐ Yes

Part 2

Section 1:

How would you describe your lung/respiratory condition? Mark one answer only.

- ☐ The most important problem I have
- ☐ Causes me a lot of problems
- ☐ Causes me a few problems
- ☐ Causes me no problem

St. George's Respiratory Questionnaire. Reproduced and used with permission from PW Jones. U.S. version adapted and modified with permission by Judith Barr, Sc.D., Northeastern Univ., Boston, MA.

If you have ever held a job, please mark one of these answers:

- _____ My lung/respiratory problem made me stop my job.
_____ My lung/respiratory problem interferes with my job or made me
change my job.
_____ My lung/respiratory problem does not affect my job.

Section 2: These are questions about what activities usually make you feel short of breath. Mark either True or False as it applies to you **now**.

	True	False
Sitting or lying still		
Washing yourself or dressing		
Walking in the house		
Walking outside on level ground		
Walking up a flight of stairs		
Walking up hills		
Playing sports or active games (baseball, tennis, etc.)		

Section 3: These are more questions about your cough and shortness of breath. Mark either True or False as it applies to you **now**.

	True	False
Coughing hurts.		
Coughing makes me tired.		
I am short of breath when I talk.		
I am short of breath when I bend over.		
My coughing or breathing disturbs my sleep.		
I become exhausted easily.		

Section 4: These are questions about other effects that your lung/respiratory problem may have on you. Mark either True or False as it applies to you **now**.

	True	False
My coughing or breathing is embarrassing in public.		
My lung/respiratory problem is a nuisance to my family, friends or neighbors.		
I panic or get afraid when I cannot catch my breath.		
I feel that I am not in control of my lung/respiratory problem.		
I do not expect my lung/respiratory problem to get any better.		
I have become frail or an invalid because of my lung/respiratory problem.		
Exercise is not safe for me.		
Everything seems too much of an effort.		

Section 5: These are questions about your lung/respiratory medication, including oxygen, inhalers and pills. If you are not receiving medication, go to Section 6. Mark either True or False as it applies to you **now**.

	True	False
My lung/respiratory medication does not help me very much.		
I get embarrassed using my lung/respiratory medication in public.		
I have unpleasant side effects from my lung/respiratory medication.		
My lung/respiratory medication interferes with my life a lot.		

St. George's Respiratory Questionnaire. Reproduced and used with permission from PW Jones. U.S. version adapted and modified with permission by Judith Barr, Sc.D., Northeastern Univ., Boston, MA.

Section 6: These are questions about how your activities might be affected by your breathing problem. For each item, answer True if one or more parts applies to you because of your breathing problem. Otherwise answer False.

	True	False
I take a long time to get washed or dressed.		
I cannot take a bath or shower, or I take a long time to do it.		
I walk slower than other people my age, or I stop to rest.		
Jobs such as household chores take a long time, or I have to stop to rest.		
If I walk up one flight of stairs, I have to go slowly or stop.		
If I hurry or walk fast, I have to stop or slow down.		
My breathing problem makes it difficult to do things such as walking up hills, carrying things up stairs, light gardening such as weeding, dancing, playing golf or light sports such as horseshoes.		
My breathing problem makes it difficult to do things such as carrying heavy loads, digging in the garden or shoveling snow, jogging or walking briskly, playing tennis or swimming.		
My breathing problem makes it difficult to do things such as very heavy manual labor, riding a bike, running, swimming fast or playing competitive sports.		

Section 7: We would like to know how your breathing **usually** affects your daily life. Mark True or False as it applies to you because of **your lung/respiratory problem**.

	True	False
I cannot play sports or active games.		
I cannot go out for entertainment or recreation.		
I cannot go out of the house to do the grocery shopping.		
I cannot do household chores.		
I cannot move far from my bed or chair.		

Here is a list of other activities that your lung/respiratory problem may prevent you from doing. (You do not have to fill these in, they are just to remind you of ways in which your shortness of breath may affect you):

- Going for walks or walking the dog
- Doing activities or chores at home or in the garden
- Having sexual intercourse
- Going to church, or place of entertainment
- Going out in bad weather or into smoky rooms
- Visiting family or friends or playing with children

Please write in any other important activities that your lung/respiratory problem may stop you from doing:

Now, would you mark the one statement which you think best describes how your breathing problem affects you:

- ☐ It does not stop me from doing anything I would like to do.
- ☐ It stops me from doing one or two things I would like to do.
- ☐ It stops me from doing most of the things I would like to do.
- ☐ It stops me from doing everything I would like to do.

Thank you for filling out this questionnaire. Please check to be sure that you have answered all questions.

Your name:

Today's date:

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy ☐ 0 ☒ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 I am very sad

		SCORE
I never cough	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 I cough all the time	<input type="text"/>
I have no phlegm (mucus) in my chest at all	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 My chest is completely full of phlegm (mucus)	<input type="text"/>
My chest does not feel tight at all	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 My chest feels very tight	<input type="text"/>
When I walk up a hill or one flight of stairs I am not breathless	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 When I walk up a hill or one flight of stairs I am very breathless	<input type="text"/>
I am not limited doing any activities at home	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 I am very limited doing activities at home	<input type="text"/>
I am confident leaving my home despite my lung condition	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 I am not at all confident leaving my home because of my lung condition	<input type="text"/>
I sleep soundly	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 I don't sleep soundly because of my lung condition	<input type="text"/>
I have lots of energy	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 I have no energy at all	<input type="text"/>
		TOTAL SCORE <input type="text"/>

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Last Updated: February 24, 2012

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FORM A: FOR SELF-ADMINISTRATION BY THE RESPONDENT (revised 4-2000)
DUKE HEALTH PROFILE (The DUKE)
Copyright © 1989-2014 by the Department of Community and Family Medicine,
Duke University Medical Center, Durham, N.C., U.S.A.

Date Today: _____ Name: _____ ID Number: _____
Date of Birth: _____ Female _____ Male _____

INSTRUCTIONS: Here are some questions about your health and feelings. Please read each question carefully and check (✓) your best answer. You should answer the questions in your own way. There are no right or wrong answers. (Please ignore the small scoring numbers next to each blank.)

	Yes, describes me exactly	Somewhat describes me	No, doesn't describe me at all
1. I like who I am	12	11	10
2. I am not an easy person to get along with	20	21	22
3. I am basically a healthy person	32	31	30
4. I give up too easily	40	41	42
5. I have difficulty concentrating	50	51	52
6. I am happy with my family relationships	62	61	60
7. I am comfortable being around people	72	71	70

TODAY would you have any physical trouble or difficulty:

	None	Some	A Lot
8. Walking up a flight of stairs	82	81	80
9. Running the length of a football field	92	91	90

DURING THE PAST WEEK: How much trouble have
you had with:

	None	Some	A Lot
10. Sleeping.	102	101	100
11. Hurting or aching in any part of your body.	112	111	110
12. Getting tired easily	122	121	120
13. Feeling depressed or sad	132	131	130
14. Nervousness	142	141	140

DURING THE PAST WEEK: How often did you:

	None	Some	A Lot
15. Socialize with other people (talk or visit with friends or relatives).	150	151	152
16. Take part in social, religious, or recreation activities (meetings, church, movies, sports, parties).	160	161	162

DURING THE PAST WEEK: How often did you:

	None	1-4 Days	5-7 Days
17. Stay in your home, a nursing home, or hospital because of sickness, injury, or other health problem.	172	171	170

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PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME: _____ DATE: _____

Over the last 2 weeks, how often have you been
bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite —being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3

add columns + +

(Healthcare professional: For interpretation of TOTAL, TOTAL:
please refer to accompanying scoring card).

10. If you checked off <i>any</i> problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all	_____
	Somewhat difficult	_____
	Very difficult	_____
	Extremely difficult	_____

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A2663B 10-04-2005

BERLIN QUESTIONNAIRE

Height (m) _____ Weight (kg) _____ Age _____ Male / Female

Please choose the correct response to each question.

CATEGORY 1

1. Do you snore?

- ☐ a. Yes
- ☐ b. No
- ☐ c. Don't know

If you snore:

2. Your snoring is:

- ☐ a. Slightly louder than breathing
- ☐ b. As loud as talking
- ☐ c. Louder than talking
- ☐ d. Very loud – can be heard in adjacent rooms

3. How often do you snore

- ☐ a. Nearly every day
- ☐ b. 3-4 times a week
- ☐ c. 1-2 times a week
- ☐ d. 1-2 times a month
- ☐ e. Never or nearly never

4. Has your snoring ever bothered other people?

- ☐ a. Yes
- ☐ b. No
- ☐ c. Don't Know

5. Has anyone noticed that you quit breathing during your sleep?

- ☐ a. Nearly every day
- ☐ b. 3-4 times a week
- ☐ c. 1-2 times a week
- ☐ d. 1-2 times a month
- ☐ e. Never or nearly never

CATEGORY 2

6. How often do you feel tired or fatigued after your sleep?

- ☐ a. Nearly every day
- ☐ b. 3-4 times a week
- ☐ c. 1-2 times a week
- ☐ d. 1-2 times a month
- ☐ e. Never or nearly never

7. During your waking time, do you feel tired, fatigued or not up to par?

- ☐ a. Nearly every day
- ☐ b. 3-4 times a week
- ☐ c. 1-2 times a week
- ☐ d. 1-2 times a month
- ☐ e. Never or nearly never

8. Have you ever nodded off or fallen asleep while driving a vehicle?

- ☐ a. Yes
- ☐ b. No

If yes:

9. How often does this occur?

- ☐ a. Nearly every day
- ☐ b. 3-4 times a week
- ☐ c. 1-2 times a week
- ☐ d. 1-2 times a month
- ☐ e. Never or nearly never

CATEGORY 3

10. Do you have high blood pressure?

- ☐ Yes
- ☐ No
- ☐ Don't know

Categories and scoring:

Category 1: items 1, 2, 3, 4, 5.

Item 1: if 'Yes', assign 1 point

Item 2: if 'c' or 'd' is the response, assign 1 point

Item 3: if 'a' or 'b' is the response, assign 1 point

Item 4: if 'a' is the response, assign 1 point

Item 5: if 'a' or 'b' is the response, assign 2 points

Add points. Category 1 is positive if the total score is 2 or more points

Category 2: items 6, 7, 8 (item 9 should be noted separately).

Item 6: if 'a' or 'b' is the response, assign 1 point

Item 7: if 'a' or 'b' is the response, assign 1 point

Item 8: if 'a' is the response, assign 1 point

Add points. Category 2 is positive if the total score is 2 or more points

Category 3 is positive if the answer to item 10 is 'Yes' OR if the BMI of the patient is greater than 30kg/m².

(BMI must be calculated. BMI is defined as weight (kg) divided by height (m) squared, i.e., kg/m²).

High Risk: if there are 2 or more Categories where the score is positive

Low Risk: if there is only 1 or no Categories where the score is positive

Epworth Sleepiness Scale

Name: _____

Date: _____

Your age: (Yr) _____ Your sex: ☐ Male ☐ Female

How likely are you to doze off or fall asleep in the situations described below, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation:-

- 0 = would never doze
- 1 = Slight chance of dozing
- 2 = Moderate chance of dozing
- 3 = High chance of dozing

Situation	Chance of dozing
Sitting and reading	<input type="text"/>
Watching TV	<input type="text"/>
Sitting, inactive in a public place (e.g. a theatre or a meeting)	<input type="text"/>
As a passenger in a car for an hour without a break	<input type="text"/>
Lying down to rest in the afternoon when circumstances permit	<input type="text"/>
Sitting and talking to someone	<input type="text"/>
Sitting quietly after a lunch without alcohol	<input type="text"/>
In a car, while stopped for a few minutes in the traffic	<input type="text"/>
Total	<input type="text"/>

Score:

0-10 Normal range
10-12 Borderline
12-24 Abnormal

INSTITUTIONAL REVIEW BOARDS

University of Louisville
MedCenter One, Suite 200
501 E. Broadway
Louisville, Kentucky 40202-1798

Office: 502-852-5188
Fax: 502-852-2164

To: Folz, Rodney
From: The University of Louisville Institutional Review Board (IRB)
Date: Friday, August 16, 2013
Subject: Approval Letter

Tracking #: 13.0428
Title: Effectiveness of COPD disease management program at University of Louisville
Approval Date: 8/15/2013 12:00:00 AM
Expiration Date: 8/14/2014 12:00:00 AM

This study was reviewed on 08/15/2013 by the chair/vice chair of the Institutional Review Board and approved through the Expedited Review Procedure, according to 45 CFR 46.110(b), since this study falls under Expedited Category (5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non—research purposes (such as medical treatment or diagnosis).

This study was also approved through 45 CFR 46.116 (D), which means that it has been granted a waiver of informed consent because it meets the following criteria:

- ° The research involves no more than minimal risk to the subjects.
- ° The waiver or alteration will not adversely affect the rights and welfare of the subjects.
- ° The research could not practicably be carried out without the waiver or alteration.
- ° Whenever appropriate, the subjects will be provided with the additional pertinent information after participation.

The following items have been approved:

- Research Protocol, not dated
- HIPAA Complete Waiver, not dated

This study now has final IRB approval from 08/15/2013 through 08/14/2014. You should complete and return the Progress Report/Continuation Request Form EIGHT

weeks prior to this date in order to ensure that no lapse in approval occurs. The committee will be advised of this action at their next full board meeting.

Site Approval

If this study will take place at an affiliated research institution, such as Jewish Hospital/St Marys Hospital, Norton Healthcare, or University of Louisville Hospital, permission to use the site of the affiliated institution may be necessary before the research may begin. If this study will take place outside of the University of Louisville Campuses, permission from the organization should be obtained before the research may begin. Failure to obtain this permission may result in a delay in the start of your research.

Privacy & Encryption Statement

The University of Louisville's Privacy and Encryption Policy requires such information as identifiable medical and health records; credit card, bank account and other personal financial information; social security numbers; proprietary research data; dates of birth (when combined with name, address and/or phone numbers) to be encrypted. For additional information: <http://security.louisville.edu/PolStds/ISO/PS018.htm>.

1099 Information (If Applicable)

As a reminder, in compliance with University policies and Internal Revenue Service code, all payments (including checks, gift cards, and gift certificates) to research subjects must be reported to the University Controller's Office. Petty Cash payments must also be monitored by the issuing department and reported to the Controller's Office. Before issuing compensation, each research subject must complete a W—9 form.

For additional information, please contact the Controller's Office at 852—8237 or contro1l@louisville.edu.

The following is a link to an Instruction Sheet for BRAAN2 "How to Locate Stamped/Approved Documents in BRAAN2":

<http://louisville.edu/research/braan2/help/ApprovedDocs.pdf/view>

Please begin using your approved (stamped) document(s) at this time. The previous versions are no longer valid. If you need assistance in accessing any of the study documents, please feel free to contact our office at (502) 852—5188. You may also email our service account at hsppofc@louisville.edu for assistance.

Best wishes for a successful study. If you have any questions please contact the HSPPPO at (502) 852-5188 or hsppofc@louisville.edu.

Thank you.

EWTTKWNWO "XKCG"

""O crj ct'C"Lj cxcgk'O DDU.'O RJ "

QUALIFICATION SUMMARY:

- A doctorate degree in epidemiology with special interest in epidemiological research, health economics and outcome research, pharmacoepidemiology, research methodology, comparative effectiveness research
- Strong background in epidemiology and biostatistics
- Trained in advanced statistical methods including Hierarchical Linear Modeling and propensity score analysis
- 2 years of experience in analyzing administrative claims data
- More than 5 years of experience in SAS
- Team player with strong communication, statistical and analytical skills

EDUCATION:

Doctor of Philosophy (Ph.D.)

Aug 2010 – April 2014

Concentration: Epidemiology with minor in Biostatistics

University of Louisville, Louisville, Kentucky

Dissertation: Clinical and Cost Effectiveness of Chronic Obstructive Pulmonary Disease management program at the University of Louisville

Committee: Dr. Frank Groves (chair), Dr. Rodney Folz (advisor), Dr. Richard Baumgartner, Dr. Susan Muldoon, Dr. Guy Brock

Master of Public Health (M.P.H.)

Aug 2005-May 2009

Concentration: Epidemiology with minor in Biostatistics

University of Kentucky, Lexington, KY

Thesis: Comparison of 3 versus 4 and Protease Inhibitors (PI) versus non-PI

Combinations as Initial Highly Active Antiretroviral Therapy (HAART): Experience from 1998-2007

Committee: Dr. Steven Browning (chair), Dr. Richard Greenberg (advisor), Dr. Heather Bush

Bachelor of Medicine and Bachelor of Surgery (equivalent to MD)

September 1999 – March 2005

Sardar Patel University, Gujarat, India

PROFESSIONAL EXPERIENCE

Graduate Research Assistant August 2012-present

Department of Epidemiology, University of Louisville

Supervisor: Dr. Frank Groves, Dr. Rodney Folz

- Analyzed administrative claims data from United Healthcare retrospectively
- Prepared and submitted IRB documents
- Retrieved data from Electronic Medical Records
- Assisted supervisors in writing grant proposal
- Reviewed literature for research proposal

Graduate Fellow August 2010-July2012

Department of Epidemiology, University of Louisville

Supervisor: Dr. Richard Baumgartner

- Analyzed large data sets like NHANES, NHEFS using advanced statistical methods like logistic regression, linear regression, survival analysis
- Prepared manuscript for submission to peer review journals

Research Associate July 2008-April 2010

University of Kentucky

Supervisor: Dr. Juan Yepes

- Developed proposals under supervision of Principal Investigator
- Analyzed data from randomized controlled trial of Burning mouth disorder and dry mouth
- Assisted supervisor in grant writing, preparing IRB documents, recruiting subjects for trial and collected primary data.
- Prepared manuscript for peer review journal submission
- Provided Quality Assurance of analytic file
- Performed project related statistical analysis & interpreted results
- Communicated & disseminated study results effectively in the form of slide presentations

Research Assistant Aug 2006- June 2008

University of Kentucky

Supervisor: Dr. Richard Greenberg

- Assisted supervisor in IRB submission and literature review
- Manipulated and analyzed data using SAS and Microsoft Excel

STATISTICAL METHODS

- Ordinary Least Square regression
- General Linear Modeling
- Survey design adjusted multivariate analysis
- Longitudinal Data Analysis
- Survival Analysis and Cox Regression model

STATISTICAL SOFTWARE

- SAS

AFFILIATIONS

- American Public Health Association
- American Federal Medical Research
- American Thoracic Society

PUBLICATIONS

- Myint T, Anderson AM, Sanchez A, Farabi A, Hage C, Baddley JW, Jhaveri M, Greenberg RN, Bamberger DM, Rodgers M, Crawford TN, Wheat LJ. Histoplasmosis in patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS): multicenter study of outcomes and factors associated with relapse. *Medicine*. Jan 2014;93(1):11-18
- Brimhall J, Jhaveri MA, Yepes JF. Efficacy of cevimeline vs. pilocarpine in the secretion of saliva: a pilot study. *Special care in dentistry : official publication of the American Association of Hospital Dentists, the Academy of Dentistry for the Handicapped, and the American Society for Geriatric Dentistry*. May-Jun 2013;33(3):123-127
- Luftman V, Martin CA, Guenther G, Arnold SM, Mullett TW, Jhaveri M. The power of videotaped personal statements of patients with lung cancer: a recruitment strategy for smoking prevention and cessation programs. *Oncology nursing forum*. Jan 2011;38(1):11-14

- Lommel K, Bamford J, Jhavari M, Martin C, Crofford L. A pilot study: pain, fatigue and stress in maternal relatives of adolescent female psychiatric inpatients assessed for juvenile primary fibromyalgia syndrome. *International journal of adolescent medicine and health*. 2011;23(1):59-63
- Jhavari MA, Mawad HW, Thornton AC, Mullen NW, Greenberg RN. Tenofovir-associated severe bone pain: I cannot walk! *Journal of the International Association of Physicians in AIDS Care*. Sep-Oct 2010;9(5):328-334
- Jhavari MA, Browning SR, Bush H, Thornton A, Greenberg RN. Comparison of 3-drug versus 4-drug and PI versus non-PI combinations as initial HAART: experience from 1998 to 2007. *Journal of the International Association of Physicians in AIDS Care*. Sep-Oct 2009;8(5):299-307

PRESENTATIONS

Poster Presentations

- Malhar Jhavari, Frank Groves, Bryan Beatty, Rodrigo Cavallazzi, MD, MPH, R. Folz, MD, PhD. Clinical Effectiveness of the University of Louisville Chronic Obstructive Pulmonary Disease Management Program
Poster presented at American Thoracic Society; San Diego, CA (May 2014)
- Thein Myint, Albert M. Anderson, Alejandro Sanchez, Ali Farabi, Chadi Hage, John W. Baddley, Malhar Jhavari, Richard N Greenberg. Outcomes after withdrawal of antifungal therapy for AIDS-associated histoplasmosis and factors associated with relapse
Poster presented at Infectious Disease week (ID week); San Diego, CA (Oct 2012)
- Juan Yepes, Malhar Jhavari, Andrew Hoellein. Knowledge and Attitudes of Dental Students towards HIV Infection and AIDS
Poster presented at Annual Meeting of Hispanic Dental Association; Carefree, AZ (Nov 2008)
- Anand G. Vaishnav, Creed Pettigrew, Michael Dobbs, Stephan Ryan, Malhar Jhavari, Lisa Bellamy. JCAHO Primary Stroke Center Core Measures: Influence of Stroke Care Unit
Poster presented at American Academy of Neurology; Chicago, IL (May 2008)
- Kiyoun Lee, Elien Hahn, Malhar Jhavari, Riker, R, Sara Head. Indoor Air Quality and Enforcement of Smoke-free Policies in public venues and schools

Poster presented at International Conference on Environmental Epidemiology;
Paris, France
(Aug 2006)

Oral Presentation

- Malhar Jhaveri, Heather Bush, Steven Browning, Alice Thornton, Richard Greenberg. Comparison of 3 versus 4 Drugs as Initial HAART: University of Kentucky Experience from 1998-2007
Presented at American Federal Medical Research Southern Regional Conference; New Orleans, LA (Feb 2009)

HONORS/AWARDS AND ACTIVITIES:

- First Place Doctoral student award at Research Louisville conference (Sep 2013)
- Inducted into the University of Kentucky Delta Epsilon Iota society (Jan 2008)
- Student Facilitator in a "22nd Kentucky Governors Safety and Health Conference", Louisville, KY (May 2006)
- Certificate for excellent work on Tobacco Cessation Clinic, WHO conducted Pulse Polio Immunization program and Ministry of Health and Family Welfare (Jul 2004).