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Controlled Trial of Oral Glucocorticoids in Outpatients with Acute COPD exacerbation Who Present to the Emergency Department

A Randomized, Double-Blind, Placebo-Controlled Pilot Study

By:

© Shawn David AARON M.D.F.R.C.P

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Abstract

Background: In North America, the prevalence of chronic obstructive pulmonary disease (COPD) amongst elderly patients is increasing, and COPD exacerbation is now a common cause for Emergency Department (ED) patient visits. Over 900 patient visits were logged at the Ottawa General and Civic Hospital's Emergency Departments in 1996 because of COPD exacerbation. Fifty-two percent of these ED patient visits for COPD resulted in a discharge home.

Although exacerbations of COPD occur commonly, the optimal therapy of this condition remains unknown. Inhaled bronchodilators and antibiotics have been proven to be effective, however the use of systemic glucocorticoids for treatment of COPD exacerbation remains controversial since there is a lack of controlled trials demonstrating their efficacy . A review of 1996 ED records suggests that 49% of COPD patients are being discharged from the ED with a prescription for oral prednisone. Given this wide practice variation, it was felt that a state of clinical equipoise exists which justifies the need for a randomized, double-blind, placebo-controlled trial examining whether oral glucocorticoids should be used to treat patients with COPD exacerbation who are discharged home from the ED. This thesis will report on the results of the pilot study which was undertaken to establish the feasibility of a larger, definitive clinical trial.

Objectives: The primary objective of the pilot study was to ensure that a larger clinical trial will be feasible. Secondary objectives of the pilot study were: to assess the rate of patient relapse in order to determine whether this clinical variable could serve as the primary outcome variable for the definitive study, to verify the sample size estimates for the larger trial, to evaluate patient referral rates and trial recruitment, and to verify the enrollment process and allow for pre-testing of the data collection and data analysis process.

Design: Randomized, double-blind, placebo-controlled pilot trial. Patients who presented to the Emergency Departments at The Ottawa General or Ottawa Civic Hospital with acute COPD exacerbation were randomized to treatment with a 10 day course of prednisone or placebo prior to being discharged home from the ED. All patients received a 10 day course of oral antibiotics and 30 days of inhaled bronchodilators.

Outcomes: The primary outcome variable was the percent improvement in forced expiratory volume

in one second (FEV_1) over the 10 day treatment period. Secondary outcomes included improvements in oxygenation, improvements in subjective dyspnea scores (assessed by The Baseline and Transitional Dyspnea Indexes), improvements in disease-specific quality of life (assessed by the Chronic Respiratory Disease Index Questionnaire), relapse rates at 10 and 30 days and adverse effect rates. All outcomes were assessed 10 days after randomization, with the exception of patient relapse which was assessed at 10 and 30 days after randomization.

Results: A total of 67 referrals to the study were received over the four month pilot period, of these twenty eligible patients were randomized into the study. Nineteen patients successfully completed the study, eleven in the placebo group and eight in the prednisone group. Recruitment rates were approximately 60% of that anticipated. Based on the results of the pilot data, a recalculation of the sample size needed for the definitive clinical trial suggested that 30-day relapse could be used as the primary outcome variable if 212 patients were to be enrolled in the definitive study.

Patients treated with prednisone in the pilot study improved their FEV_1 by a mean of 40.3 ± 44.4% over the 10 day assessment period compared to a mean improvement of 13.9 ± 23.8% in the placebo-treated patients (p=0.14). The mean percent oxygen saturation in the prednisone group increased by 1.6 ± 1.9% in the prednisone group compared to a 0.18 ± 2.8% increase in mean oxygen saturation in the placebo group (p=0.38). Patients reported similar Day 1 dyspnea scores on the Baseline Dyspnea Index, however by Day 10 the 'functional impairment' and 'magnitude of effort' components of the Transitional Dyspnea Index trended towards greater improvements for the prednisone-treated patients than for placebo-treated patients (p = 0.08 and p= 0.06 respectively). Overall, the total Transitional Dyspnea Index mean score was 2.44 points higher in the prednisone-treated group, reflecting a greater improvement in subjective self-reported dyspnea from Day 1 to Day 10 in those treated with prednisone, however this improvement was not statistically significant (95% CI, -1.36 to 6.24, p=0.19).

Both treatment groups showed net improvement in disease-specific quality of life as assessed by improvements in The Chronic Respiratory Disease Index Questionnaire scores measured on Day 1 and Day 10 of the trial. The prednisone-treated group consistently scored greater 10 day improvements than the placebo-treated groups across all four domains of the quality of life index, however none of the differences between the two groups reached statistically significant levels.

Patient relapse occurred at a greater rate than expected. Relapse occurred by Day 10 in 45% of placebo-treated patients and 12% of prednisone-treated patients (p=0.18), and by Day 30 in 45% of placebo and 25% of prednisone-treated patients (p=0.63). Kaplan-Meier survival curves did not show a statistically significant survival difference between the two treatment groups (log-rank test p =0.29). A logistic regression model using risk of 30 day relapse as the outcome variable was constructed in order to attempt to adjust for the influence of suspected clinically significant covariates on the treatment effect. The adjusted odds ratio for the treatment effect was found to be 0.15, however this apparent protective effect of steroid treatment was not statistically significant (95% CI of the odds ratio, 0.002- 13.70). The overall frequency of self-reported adverse events was similar in the two treatment groups.

Conclusions: In summary, the pilot study was completed successfully and demonstrated that a larger, definitive trial is feasible. Relapse occurred at a greater rate than was expected in the placebo group, and it was shown that the rate of 30-day relapse could be used as the primary outcome variable for the definitive clinical trial. The pilot study involved a relatively small number of patients, and therefore did not have statistical power to show any difference in results between the two groups. Nevertheless, the pilot data suggests a trend towards improved expiratory airflow, dyspnea scores, disease-specific quality of life, and relapse rates in the prednisone-treated patients compared to those patients on placebo. Naturally, this trend could easily be reversed in a larger study, and therefore a larger trial will be needed in order to definitively establish whether prednisone is superior to placebo for outpatient therapy of COPD exacerbation.

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1.0 Introduction

Chronic obstructive pulmonary disease (COPD) exacerbation represents an important clinical and public health problem which results in hundreds of Emergency Department patient visits to Ottawa-area hospitals each year. The optimal therapy for acute COPD exacerbation remains unknown. Oral glucocorticoids are frequently, but inconsistently, prescribed for COPD exacerbation, despite a lack of current available evidence demonstrating their efficacy, and despite practice guidelines which do not support the routine use of glucocorticoids for managing outpatient COPD exacerbation [1,2]. As a result, there is therefore a need to objectively determine whether outpatients with COPD exacerbation benefit from treatment with a course of oral glucocorticoids following their acute presentation.

In order to best answer this important clinical question a three-staged plan of research was developed. The plan of research began with a literature and chart review to document the extent of the clinical problem, and was followed by a pilot study which I designed in collaboration with colleagues from The Division of Respiratory Medicine. The pilot study consisted of a randomized, double-blind, placebo-controlled, clinical trial of prednisone for treatment of outpatients who present to the Emergency Department with COPD exacerbation. The last stage of the research plan, which is currently in progress, will consist of the definitive, larger clinical trial. This thesis will describe the process, and the results, of the pilot study which was conducted from January 5 to May 4, 1998.

2.0 Background

2.1 Definition of Chronic Obstructive Pulmonary Disease:

The definition of chronic obstructive pulmonary disease has evolved considerably since The British Medical Research Council first defined chronic bronchitis in 1965 as a disease characterized by "chronic cough and sputum production for three months in two successive years in the absence of other diseases recognised to cause sputum production."[3]

Today, the definition of COPD has been refined to reflect its hallmark characteristic of chronic airflow obstruction. Airflow obstruction refers to a diminished expiratory flow of air through the airways of the lung, and is objectively measured by means of spirometry. The degree of airflow obstruction is quantified by determining the forced expiratory volume in one second (the FEV_1), in relation to reference values.

In 1997 The British Thoracic Society defined COPD as "a chronic, slowly progressive disorder characterised by airflow obstruction that does not change markedly over several months. Most of the lung function impairment is fixed, although some reversibility can be produced by bronchodilator (or other) therapy."[2] According to British guidelines a diagnosis of COPD in clinical practice requires: "1) a history of chronic progressive symptoms (cough and/or wheeze and/or breathlessness) and 2) objective evidence of airways obstruction that does not return to normal with treatment".

In contrast, The 1995 American Thoracic Society (ATS) definition of COPD is somewhat different and harder to operationalize. The ATS definition states that "chronic obstructive pulmonary disease is a disease state characterized by the presence of chronic airflow obstruction due to chronic bronchitis or emphysema or a combination of the two." [1]

Chronic bronchitis is clinically defined as the presence of chronic productive cough for 3 months in each of two successive years in a patient in whom other causes of chronic cough have been excluded.[3] However, it should be noted that the presence of chronic bronchitis does not necessarily signify the presence of airways obstruction or a diagnosis of COPD. Patients with chronic bronchitis who do not show spirometric evidence of airflow obstruction are not classified as having COPD

according to 1997 British, [2] or 1995 American Thoracic Societies definitions.[1]

Emphysema is defined in terms of anatomic pathology as an abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of bronchiolar walls, without obvious fibrosis.[1] In reality, most patients do not undergo lung biopsy in order to make a diagnosis of emphysema, so clinically patients are usually diagnosed with emphysema based on a typical history of smoking, chronic progressive dyspnea, chronic airflow obstruction, and chest radiograph and/or CT scan evidence of emphysematous lung destruction.[4] This highlights a weakness of the American definition, since technically it relies on pathologic evidence to make a diagnosis of emphysema, whereas the British definition allows for clinical and physiologic criteria for making a diagnosis of COPD without requiring pathologic evidence.

The airflow obstruction of COPD, unlike that of asthma, is chronic, progressive, and is by definition, largely irreversible.[5] Reversibility of airflow obstruction is determined by testing the patient's expiratory flow rate response to inhaled bronchodilator. Classically, patients with COPD, unlike asthmatics, are said to be relatively unresponsive to bronchodilator (ie. relative percent increase in FEV_1 of < 15%)[5], although several studies have shown that patients with COPD can exhibit widely varying levels of reversibility post-bronchodilator making them difficult to distinguish from asthmatic patients based on this criteria alone.[5, 6]

Patients with asthma, whose airflow obstruction and whose symptoms of breathlessness are reversible, are not considered to have COPD.[1] Often the most difficult diagnostic problem is distinguishing COPD from the persistent airflow limitation of chronic asthma in older subjects. Although the distinction may be difficult, a history of heavy smoking, evidence of emphysema radiologically, and chronic hypoxemia favour the diagnosis of COPD. In contrast, onset in childhood, atopy and marked improvement on spirometry with administration of bronchodilators favour the diagnosis of asthma.[1]

Distinguishing patients with asthma from those with COPD will be important for the validity of this study. Previous large clinical trials have already established the efficacy of using steroids to treat acute asthma exacerbation, and have demonstrated that Emergency Department patients with acute asthma exacerbation treated with outpatient glucocorticoids have reduced relapse rates, reduced use of beta-agonist bronchodilators, and reduced hospitalisation rates.[7-9] It would thus be

unethical to include known asthmatics into this trial since these patients should not be randomized to placebo. Furthermore, the inclusion of asthmatics would jeopardize the validity of the results since their inclusion should bias the study results in the direction of a positive treatment effect. For these reasons, the trial inclusion and exclusion criteria have been purposefully designed to exclude patients with known or suspected asthma.

2.2 Epidemiology of COPD

COPD is a major cause of morbidity and mortality in North America. In 1985 in the United States, COPD accounted for 5% of office visits to physicians and 13% of hospitalizations.[7] In Canada, COPD remains a significant public health burden; more than 50,000 patients are admitted to hospital every year for treatment of emphysema and chronic bronchitis, and many more require outpatient therapy for flares of their disease.[10]

Analysis of morbidity data abstracted from the US National Health Interview Survey shows that in 1985 the age-adjusted prevalence rate of COPD in persons aged 55 to 84 was 110 per 1,000 for males and 120 per 1,000 for females.[11, 12] This estimate may be somewhat inflated however, since the data represents self-reported prevalence of COPD, and firm criteria for the diagnosis of COPD were not employed. Estimates of Canadian health-professional-diagnosed COPD prevalence rates, derived from the 1994-95 National Health Survey, indicate a COPD prevalence rate of 4.7% in persons aged 55-64, 5.4% in those 65-74 and 8.3% in persons ≥ 75.[13] In 1985, according to US National Center for Health Statistics (NCHS) National Hospital Discharge Survey Data, the age-adjusted rate for hospital discharges for COPD was 14 per 1,000 and 10 per 1,000 for males and females respectively over age 55.[11, 14] In Canada, the number of hospital separations with COPD as the primary discharge diagnosis increased from 42,102 in 1981-82 to 55,782 in 1993-94.[13] Recent trends suggest that disease prevalence and hospital discharge rate is stable in men, but increasing among women, reflecting a 40 year societal trend towards increased smoking among females.[7] In fact in Canada, the rate of age-specific hospital separations in women ≥ 75 increased from 504 per 100,000 in 1981 to 1033 per 100,000 in 1994.[13]

Mortality rates for COPD have been increasing. In 1991 COPD caused more than 85,500 deaths in the US, making the disease the fourth leading cause of death in the country.[1] In the United States, according to death certificate information compiled by the NCHS, the 1985 age-adjusted death rate from COPD amongst persons 55-84 years old was 200 per 100,000 and 70 per 100,000 amongst males and females respectively.[15] In the US, age-adjusted death rates for COPD rose 47% between 1979 and 1993,[7]. In Canada, the total number of deaths from COPD increased from 4438 in 1980 to 8583 in 1995. Age-specific mortality rates remained stable in all groups except amongst those aged ≥ 75 in which it increased from 2.5 per 1,000 in 1980 to 3.8 per 1,000 in 1995.[13] The

importance of COPD-associated mortality will likely continue to increase given the aging population and the heavy smoking history of the current cohort.

Approximately 90% of all COPD patients have a history of smoking.[10] Although rates of cigarette smoking declined amongst males in Canada from 1970 to 1990[16], overall morbidity and mortality from COPD continue to increase due to the long latency period before the development of clinical disease.[17]

2.3 Natural History of COPD

COPD is a disease characterized by chronic symptoms of cough and breathlessness which progress over time. The disease, by definition, is characterized by chronic, progressive airflow obstruction. Reports on the natural history of patients with COPD show accelerated rates of decline in lung function. In COPD patients who smoke, the forced expiratory volumes in one second (FEV_1) declines by 50-75 ml per year [18, 19], versus an expected decline in FEV_1 of 15-25 ml per year in age-matched controls who do not have COPD. Patients with advanced COPD are at risk of dying of their disease; five year survival rates for patients with an initial FEV_1 of less than 1.0 litre are 45 to 50 percent.[18, 20].

Individuals with COPD are prone to acute exacerbations of their illness. These acute exacerbations of COPD are characterized clinically by symptoms of worsening dyspnea, cough, sputum production and sputum purulence, as well as by worsening of airflow obstruction.[21] It is difficult to predict expected exacerbation rates for individual patients, however most patients with COPD experience one to four exacerbations per year.[22] As airflow obstruction becomes more severe, exacerbations often occur more frequently. Age-adjusted US data suggests that COPD exacerbations account for an average 1.2 office visits and 0.1 to 0.23 hospitalizations per year per prevalent case.[7]

Acute exacerbation of COPD can predict a poorer than expected patient outcome. A recent prospective cohort study of 1,016 patients who were admitted to hospital for acute COPD exacerbation and who had an arterial $PaCO_2 \geq 50$ mm Hg, revealed that 11% of patients died during the index hospital stay, and that 60 day and 2 year mortality was 20% and 49% respectively.[23] Although this study did not include a control group, the relatively high 2 year mortality rate suggests

that acute COPD exacerbation with hypercarbia may be associated with a greater short-term risk of subsequent death.

2.4 Etiology of COPD Exacerbations

Worsening of pulmonary function during a COPD exacerbation is most commonly caused by respiratory infection, but can also occur secondary to environmental triggers (e.g., humidity, pollution, exposure to smoke or occupational irritants), cardiac dysfunction, or progression of the underlying disease.[24] Studies using viral cultures and serology have established that viral, and, to a lesser extent, mycoplasma infections, are associated with approximately one third of acute exacerbations of chronic bronchitis.[25] Three bacterial pathogens, *Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis*, are frequently implicated in flares of COPD, however these bacteria can be found in the upper respiratory tracts of healthy people, and are often found in the sputum of patients with COPD during periods of clinical quiescence, as well as during periods of disease exacerbation.[26] Determining whether these bacteria are simply commensals or whether they are responsible for clinical deterioration is therefore difficult. However, several clinical trials have supported the use of antibiotics for treatment of COPD exacerbation, suggesting that in some patients, bacterial infection of the airways may play a causal role in provoking COPD exacerbation.

2.5 Airway inflammation in COPD

Histologic and immunohistochemical studies of the airways of patients with stable COPD have revealed evidence of chronic inflammation. Lobar bronchial biopsy specimens from patients with COPD show infiltration of the airway wall with lymphocytes, and macrophages and increased expression of markers of lymphocyte activation.[27] Recent studies have also shown that patients with COPD have significantly increased numbers of CD3+ and CD8+ T-lymphocytes in subepithelial bronchial biopsies as compared to control smokers and non-smokers.[28] Similarly, levels of the inflammatory cytokines, tumour necrosis factor and interleukin-8, are elevated in the sputum of stable COPD patients compared to controls, suggesting that COPD is associated with a chronic inflammatory response within the airways.[15] Although it seems reasonable to assume that airway

inflammation plays a similar role in the pathogenesis of worsening of airflow obstruction seen during acute exacerbations of COPD, there is to date suprisingly little data which exists characterizing the inflammatory responses seen in acute COPD exacerbation.

2.6 Treatment of COPD Exacerbation

Current Canadian, U.S., and European Thoracic Society guidelines recommend that exacerbations of COPD be treated with appropriate supplemental oxygen therapy, plus bronchodilator therapy with $beta_2$-agonists and anticholinergic aerosols.[1, 4, 29] Antibiotics are usually prescribed since it has been shown that they may be of help in resolving an acute exacerbation and are valuable at decreasing the risk of further deterioration.[21] The most comprehensive study of antibiotic therapy for COPD exacerbation showed that treatment with a broad-spectrum antibiotic increased the 21 day successful recovery rate from 55% to 68% in the antibiotic-treated group ($p < 0.01$), and decreased the deterioration rate from 19% to 10% ($p<0.05$).[21] A recent meta-analysis of 9 randomized trials of antibiotics for COPD exacerbation demonstrated an overall summary effect size of 0.22 (95% CI 0.10 to 0.34) indicating a modest benefit in the antibiotic-treated group.[30]

At present time, there is a paucity of available evidence and lack of clear recommendations contained in clinical practice guidelines as to whether prednisone should be used in the treatment of acute exacerbations of COPD. The evidence for and against the use of systemic glucocorticoids in the treatment of exacerbations of COPD is summarized below.

2.7 *Rationale for Use of Glucocorticoids for COPD*

Several of the physiological and pharmacological actions of glucocorticoids are of theoretic benefit in patients with COPD. Glucocorticoids have the ability to inhibit or suppress the inflammatory process. Laboratory studies have shown that glucocorticoids: 1) modify neutrophil function by inhibiting enzyme release, chemotaxis, and margination; 2) suppress the release of bioactive inflammatory mediators; and 3) modify tissue responses to inflammatory mediators by altering the availability and binding affinity to various receptors.[31, 32] Many of the inflammatory mediators that are inhibited by glucocorticoids, such as thromboxane, platelet activating factor, and histamine are known to cause airway constriction. Inhibition of inflammation, and of the production

and release of inflammatory mediators, may thus have theoretic benefits in COPD exacerbation.[33]

2.8 Potential Adverse Effects of Glucocorticoids in Patients with COPD

2.81 Short-term adverse effects:

A prospective randomized controlled trial evaluating the complication rate of a short course of glucocorticoids (1-3 weeks) in patients with COPD has not been published. Albert et al reported that the frequency of side effects in COPD patients with acute respiratory failure treated with 3 days of IV methylprednisolone was similar to placebo.[34] Unpublished results from the SCCOPE trial (Systemic Corticosteroids in COPD Exacerbations)[35], a trial using intravenous and oral steroids in the treatment of hospitalized patients with COPD exacerbation, demonstrated that hyperglycemia was the only short-term side-effect seen more frequently in the steroid-treated group.

However, short courses of glucocorticoids can be associated with side effects which may be important to patients with COPD exacerbation. Short courses of glucocorticoids can increase the risk of infection. The strongest evidence for this comes from a meta-analysis of 71 controlled clinical trials in which patients were randomized to treatment of their illness with steroids or placebo.[36] When all diagnostic groups were considered, systemic steroids were found to be associated with a relative risk of 1.6 (95% CI, 1.3 to 1.9) of lethal and nonlethal infections. However an increase in the incidence of infection was not seen in the subgroup of patients with pulmonary disease (n=364).

Short-term steroid use is also associated with acute psychiatric side-effects. A prospective study of 676 patients treated with short-term steroids for a variety of illnesses showed that 3.1% developed acute psychosis or inappropriate euphoria. [37] Finally, atrophy and myopathy of skeletal and respiratory muscles are well-known side-effects which may occur with short term administration of glucocorticoids. Short courses of supra therapeutic doses of glucocorticoids in rats and hamsters have been shown to cause reduction in diaphragm weight and atrophy of type IIb diaphragmatic muscle fibres.[38, 39]

2.82 Long-term adverse effects:

A clinical study involving 21 consecutive patients admitted to hospital with acute

exacerbations of COPD or asthma has suggested that patients who have been treated with numerous courses of systemic steroid are more at risk for generalized and respiratory muscle weakness than those patients who have not received steroids. A multiple regression analysis of the relationship between maximal inspiratory muscle strength (Pimax) and quadriceps force (QF) and steroid dose in these patients, showed that the average daily dose of steroids used over the previous 6 month period independently accounted for 32% of the variance in Pimax and for 51% of the variance of QF.[40] This potential contribution of steroids to reduced respiratory muscle strength in COPD patients is of great clinical significance since respiratory muscle function of many patients with COPD is already compromised due to hyperinflation, malnutrition, and detraining. Any additional steroid-induced reduction of respiratory muscle force could theoretically cause further respiratory compromise.[41]

Finally, epidemiological data exists which suggests that long-term use of glucocorticoids in patients with COPD may be harmful. When data from the Swedish Long-Term Home Oxygen Registry were analysed using multivariate regression analysis models to determine predictors of survival in COPD patients, oral steroid usage showed no tendency to improve survival in men and steroid use was associated with an increased mortality rate in women with COPD (relative risk of death 2.13; 95% CI, 1.38 to 3.29).[42] Similar studies from The Netherlands assessing the independent contribution of corticosteroids on mortality using a Cox proportional hazards model and adjusting for age, FEV_1, smoking and sex, has shown that the chronic use of oral steroids was associated with increased risk of mortality (RR =1.33, p=0.002).[43]

2.9 Glucocorticoids for COPD Exacerbation- Evidence from the Literature

A MEDLINE search of the published literature was undertaken to look for trials which examined the use of oral or parenteral steroids for acute management of COPD exacerbation. The search terms used were the following: (exp lung diseases, obstructive or chronic bronchitis tw. or emphysema tw.) and (exp steroids or prednisone.tw.). The reference lists of retrieved studies were manually searched in order to try to find further studies. Three published clinical trials, as well as one study published in abstract form only were found. Preliminary data from two unpublished trials recently presented at an international meeting are also summarized below. A summary of the

retrieved clinical trials is found in table 1.

2.91 Glucocorticoids for hospitalized patients:

Albert et al studied 44 patients admitted to hospital with COPD exacerbation and randomized them to either methylprednisolone 0.5 mg/kg every 6 hours for 72 hours, or to placebo.[34] They found that 12 of 22 steroid treated patients had prebronchodilator FEV_1 increases of 40% or more at the end of 72 hours of therapy compared to. 3 of 21 placebo treated patients (p=0.01). They did not find a difference in oxygenation, and mortality and hospital duration time were not assessed.

A large trial, which has not yet been published, was recently presented at the 1998 American Thoracic Society annual meeting.[35] The SCCOPE trial was a multicenter, placebo-controlled study which randomized patients admitted to hospital with COPD exacerbation to treatment with placebo, or to treatment with 3 days intravenous methylprednisolone and then either 2 weeks or 8 weeks of oral prednisone. All patients received antibiotics and inhaled bronchodilators. The trial's primary endpoint was treatment failure within 6 months of entry (a composite outcome defined as death, intubation, readmission for COPD, or need for pharmacologic intensification of treatment). The study was designed as an equivalence trial and actually required 1200 patients to show a 25% difference in failure rates between the two groups. Unfortunately the trial only enrolled 271 patients. The study showed that the 30 day and 90 day failure rate was 10% higher in the placebo group as compared to the active group. However, at 6 months the two groups had identical failure rates. Mean hospital stay was slightly lower in the steroid-treated groups (8.4 vs. 9.7 days, p=0.03). FEV_1 was significantly greater on days 2 and 3 in the steroid-treated groups, however this effect was lost by 14 days (although it should be noted that the analysis was by intention-to-treat and a significant proportion of patients had crossed over from placebo to open-label prednisone by day 14).

Another recent trial, published in abstract form only, randomized 57 hospitalised COPD patients to treatment with 30 mg/day of prednisolone for 14 days or placebo.[44] Seven patients withdrew due to treatment failure, 2 in the steroid-treated group and 5 in the placebo-treated group. Lung function was marginally better in the steroid-treated group at discharge from hospital; FEV_1 was 42% predicted in the treatment group compared to 34% predicted in control group, however statistical tests were lacking. The rate of further exacerbations after discharge from hospital was similar in both groups. The authors concluded that steroids were associated with fewer dropouts but

did not prevent further exacerbations after discharge and were therefore of little benefit. However, it is difficult to judge the validity of this conclusion in the absence of a more complete presentation of the study data.

A similar trial, published only in abstract form randomized 30 inpatients with acute COPD exacerbation to therapy with either steroids or placebo for an 11 day course.[45] The authors observed a statistically significant improvement in pulmonary function in both groups, however there was no additional improvement in the pulmonary function of the steroid-treated group over that of the placebo-treated group after one month of follow-up. The authors concluded that steroids were of little benefit.

2.92 Glucocorticoids for ambulatory patients:

Emerman et al studied patients with acute COPD exacerbation in the emergency department.[46] They randomized 96 patients to 100 mg of methyl-prednisolone or placebo within 30 minutes of arrival to the ED. They did not find a significant treatment effect. Change in FEV_1 was similar at 4.5 hours in both groups (37% improvement in the steroid treated group compared to 43% improvement in the control group), and there was no difference in percent of patients admitted to hospital (33% vs. 30%), or the number who relapsed within 24 hours (10% vs. 15%). It should be noted however, that this trial studied the acute effects of therapy over only 4.5 hours following only one dose of systemic steroids. Therefore inferences from this study may be limited, since the duration of therapy and follow-up may have been too brief to discern a treatment effect.

The only longitudinal trial studying steroid use in outpatients with COPD exacerbation was performed by Thompson et al.[47] Twenty-seven outpatients with COPD exacerbation were recruited from the emergency department and from outpatient clinics. Patients were randomized to receive a 9 day taper of prednisone (60 mg, 40 mg, then 20 mg/day each for 3 days). Unfortunately, because of the small numbers of patients randomized, the baseline characteristics of the prednisone and the placebo groups were somewhat different, and suggest that the placebo treated group may have been more chronically ill before entering the trial (the placebo group had a baseline FEV_1, before exacerbation of 1.15 ± 0.49 litres compared to 1.59 ± 0.67 litres in the prednisone-treated group). This may have biased the results in favour of the prednisone-treated group, since obviously the prednisone-treated group had more potential for improvement back to their higher previous baseline

status. Results from this small trial showed that patients in the prednisone-treated group had a significant improvement in FEV_1 on day 10 but not day 3 of the trial. Overall, patients in the prednisone-treated group improved their FEV1 by 0.05 litres per day vs. 0.00 litres per day for control patients (p=0.006). Prednisone treated patients also had a more rapid improvement in arterial oxygenation , but no significant change in dyspnea scale scores when compared to placebo-treated patients. Eight of the 14 placebo treated patients required hospital admission or open-label prednisone compared to none of the 13 actively-treated patients (p=0.002).

In addition to data from these three clinical trials, several retrospective studies have been published suggesting a possible benefit to glucocorticoids for COPD exacerbation. Murata and colleagues conducted a retrospective review of 352 patients with COPD exacerbation who were treated and released from the emergency department.[48] Thirty-two percent of ED visits resulted in relapse, defined as an unscheduled revisit to the ED within 14 days of treatment. A multiple logistic regression model comparing visits that resulted in relapse versus those that did not showed that patients who had visits which resulted in relapse had lower entry and discharge FEV_1's, required greater number of treatments with nebulized bronchodilators in the ED, had more frequent use of parenteral adrenergic drugs, and had less frequent use of oral prednisone on discharge. The same investigators have also published a retrospective case-control study of 30 COPD patients with a history of multiple relapses.[49] They compared 45 emergency department visits in which steroids were prescribed to an equal number of matched visits in which they were withheld and found that the 48 hour relapse rate for steroid-treated visits was 9% compared to 33% for the non-steroid treated visits (p=0.005).

ble 1.

Glucocorticoids for COPD Exacerbation

Summary of Published and Unpublished Randomized, Controlled, Clinical Trials:

Author, year (reference)	n	Patient Population	Treatment Protocol	Outcome Measures	Results	Author's Conclusions	Comments
lbert, 1980 [34]	44	Inpatients	IV methyl-prednisolone x 72 hours or placebo	FEV_1. PaO_2.	Control group: mean FEV_1 improved 20%. Steroid group: mean FEV_1 improved 40% ($p<0.001$) No change in PaO_2.	Steroids improved airflow more than placebo	Clinical outcomes not assessed.
rbland, 1998 CCOPE [35]	27 1	Inpatients	Three arms. IV methyl-prednisolone x 72 hours followed by 2 or 8 weeks of oral prednisone, or placebo	Treatment failure rate. FEV Mean hospital stay (days).	30 and 90 day failure rates were 10% higher in placebo group, but not different at 6 mos. FEV_1 greater on day 2 and 3 in steroid group compared to controls.	Steroids are useful at preventing treatment failures	Primary endpoint was 6 mo. failure rate, therefore negative study, however underpowered for its equivalency trial design
lavies, 1998 [44]	57	Inpatients	Thirty milligrams of prednisone daily x 14 days.	FEV_1. Dropout rate.	Control group: FEV_1 34% predicted at discharge. Five dropouts due to lack of efficacy. Steroid group: FEV_1 42 % predicted at discharge. Two dropouts due to lack of efficacy.	Steroids associated with fewer dropouts due to lack of efficacy.	Abstract only, no statistical tests available.

Author, year (reference)	n	Patient Population	Treatment Protocol	Outcome Measures	Results	Author's Conclusions	Comments
Rostom, 1994 [45]	30	Inpatients	IV methyl-prednisolone x 72 hours followed by 11 days of oral prendnisone, or placebo	FEV_1.	No improvement of FEV_1 in steroid group compared to controls.	Steroids of no benefit	Many patients lost to follow-up, data is incomplete.
Emerman, 1989 [46]	96	Emergency Department patients	IV methyl-prednisolone 125 mg. x 1 dose	FEV_1 at 4.5 hours. No. of patients admitted. Relapse rates.	Control group: 43% improvement in FEV_1. Steroid group: 37% improvement in FEV_1. (p = NS), No difference in relapse or admission rates between the two groups.	Steroids of no benefit	Duration of therapy and F/U may have been too brief to discern treatment effect.
Thompson, 1996 [47]	27	Outpatients-clinics and ED	Nine days of tapering oral prednisone	FEV_1. Failure rate. Dyspnea scale.	Control group: FEV_1 improved 0.00 L/d. Failure rate 8/14. Steroid group: FEV_1 improved 0.05 L/d (p=0.006), Failure rate 0/13.	Steroids improve airflow obstruction and prevent treatment failures	Groups unbalanced with respect to baseline characteristics, small number of patients randomized.

2.10 Glucocorticoids for COPD exacerbation- Clinical Guidelines

Current American Thoracic Society Guidelines for care of patients with COPD state that "corticosteroids can be useful if there is an asthmatic component in a patient who demonstrates responsiveness to beta-agonist therapy, although there is limited information supporting the use of intravenous and oral steroids in the management of COPD exacerbations."[1]

Current British Thoracic Society Guidelines state that for treatment of acute COPD exacerbations "Oral corticosteroids may be prescribed in some cases. These should not be used unless: the patient is already on oral corticosteroids; there is a previously documented response to oral corticosteroids; airflow obstruction fails to respond to an increase in bronchodilator dosage; this is the first presentation of airflow obstruction." The guidelines conclude by stating "there is a need for further research into the place of oral corticosteroids in the context of an acute exacerbation of COPD".[16]

2.11 Summary

COPD exacerbation represents an important clinical and public health problem. The optimal treatment of acute COPD exacerbation remains unknown. Although experimental data strongly supports the use of oral glucocorticoids for treating outpatient exacerbations of asthma, the data is weak to support the same treatment in the COPD population. The risks and benefits of short courses of prednisone are unclear for COPD and current available evidence is inconclusive. There is therefore a need to objectively study this issue and determine whether patients who present to the Emergency Department with COPD exacerbation should be discharged home on oral prednisone. A randomized, double-blind, placebo-controlled clinical trial is warranted and offers a unique opportunity to answer this important clinical question.

2.12 Results of the Emergency Department COPD Chart Review.

A detailed Emergency Department chart review was done to investigate the number of visits made for COPD exacerbation to the Ottawa General and Civic Hospital Emergency Departments in 1996. Data was accessed through the OCH Emergency EPIS Database and through The OGH Emergency Discharge Coding Database. Data was collected on the number of ED visits, disposition of the patient following each visit, and relapse rates. Results are summarized below, and are presented in Tables 2 and 3.

Table 2 depicts a summary of 1996 COPD-related admission, discharge and relapse rates for The Ottawa General and Civic Hospitals. In 1996, The Ottawa General Hospital recorded 368 ED visits for COPD exacerbation. Of these visits, 187 (51%) resulted in admission to hospital and 181 (49%) resulted in discharge from the Emergency Department. Excluding repeat visits, 142 individual patients at OGH were discharged from the ED in 1996. At The Ottawa Civic Hospital 546 ED visits were recorded; 252 (46%) resulted in admission to hospital and 294 (54%) resulted in discharge from the ED. Excluding repeat visits, 216 individual patients at OCH were discharged from the ED in 1996.

Relapse rates, defined as a repeat visit to the same Emergency Department for symptoms of COPD exacerbation, are outlined in table 2. Of the 475 ED visits that resulted in discharge from both hospitals, 12.0% resulted in a relapse within 10 days, and 18.9% resulted in relapse within 30 days.

Table 3 depicts data retrieved from a more detailed analysis of the charts of the 142 patients who were discharged home from the OGH ED in 1996. Data from these patient charts was collected in order to determine Emergency Department therapy of the patients' COPD exacerbation. Patient characteristics were also abstracted from the entire chart in order to determine whether the patient would meet the criteria for trial eligibility.

One hundred and thirty-eight of 142 charts were retrieved (97.2%), four patients had charts which had gone missing from Medical Records and data on these patients was not available. 70 of 138 patients (51%) had been recently placed on prednisone or had received a prescription for prednisone on discharge from the Emergency Department. 54 of 138 patients (39%) had been recently placed on antibiotics or had received a prescription for antibiotics on discharge from the Emergency Department.

Figure 1 depicts a flow diagram of 30-day relapse events vs. treatment received. Of those patients who relapsed within 30 days of their visit to the Emergency Department only 39% were prescribed prednisone upon discharge from the ED (or had already been prescribed prednisone before presentation to The Emergency Department). In contrast, 51% of those patients who did not experience a 30-day relapse were prescribed, or were already taking, prednisone on discharge from The ED, ($\chi^2 = 1.13$, $p = 0.29$).

Finally, a feasibility review was undertaken to determine that a sufficient number of eligible patients would be available at the two hospitals in order to support the definitive larger study. The charts of 138 of the 142 COPD patients who were discharged from The OGH ED in 1996 were analyzed (four charts were unavailable from Medical Records) in order to determine the proportion of patients who would fit the eligibility criteria for the proposed clinical trial. In total, 41 of 138 patients (30%) definitely met all study eligibility criteria and an additional 19 of 138 patients (14%) were judged to possibly fulfill study eligibility criteria according to information contained in the chart. Assuming the COPD patients who present to the OGH ED are similar to those who present to the OCH ED, then approximately 35% of the 358 individual patients who presented to both hospitals with COPD exacerbation in 1996 would have been eligible for the trial. Based on this estimate, 125 eligible patients would have been available in 1996 for potential recruitment into the trial.

2.13 *Conclusions Derived from the Chart Review:*

1) A sufficient number of patients with acute COPD exacerbation should be available for the definitive study.

2) There appears to be a wide practice variation concerning the treatment of COPD exacerbation in the ED- only 49% of ED patients were prescribed steroids on discharge. Given this wide practice variation, a state of clinical equipoise exists which ethically justifies the need for the pilot study and definitive trial.

3) Relapse is fairly common and can serve as an objective clinical outcome variable.

RESULTS OF THE 1996 EMERGENCY DEPARTMENT COPD RECORDS REVIEW:

Table 2: Summary of COPD Admission and Relapse Rates:

Hospital	#ED Visits for COPD	# Admissions for COPD	# Discharges home	10 day relapse rate	30 day relapse rate
OGH	368	187 (51%)	181 * (49%)	10.0%	17.7%
OCH	546	252 (46%)	294 ** (54%)	13.3%	19.7%
Both	914	439 (48%)	475 (52%)	12.0%	18.9%

* 181 discharges /142 individual patients

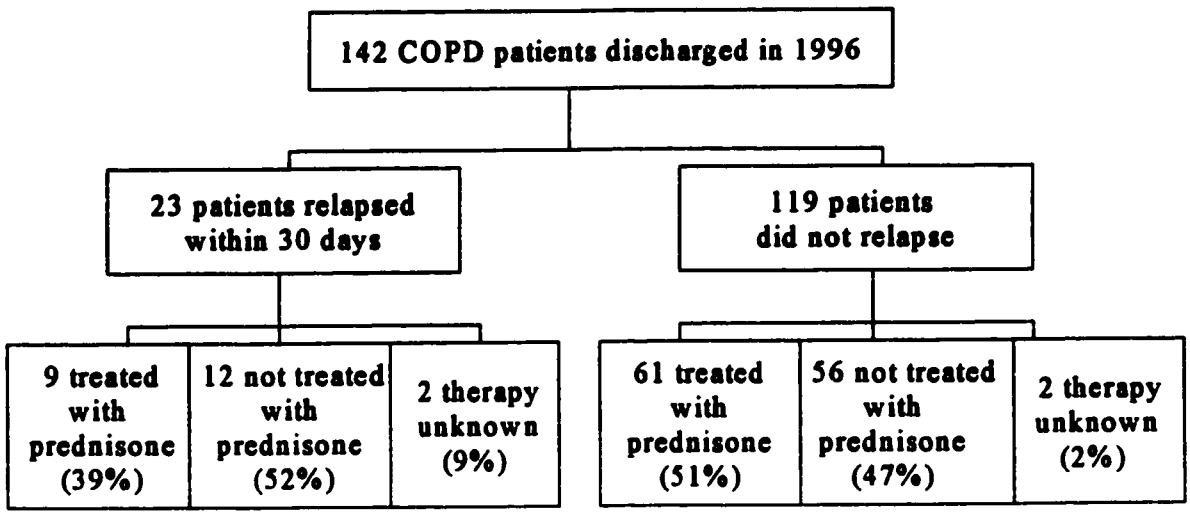
** 294 discharges / 216 individual patients

Table 3: Emergency Department Therapy for Patients Discharged Following Acute COPD Exacerbation.

Hospital	No. of COPD patients discharged from ED in 1996	No. of charts retrieved	No. of patients who received antibiotics on discharge (%)	No. of patients who received prednisone on discharge (%)
OGH	142	138	54 (38%)	70 (49%)

Figure 1: Thirty-day relapse rates vs. treatment received

Ottawa General Hospital 1996.



3.0 Objectives

This thesis will describe the process, and the results, of the pilot study which I designed in collaboration with colleagues from The Ottawa Hospital, Division of Respiratory Medicine, and which was conducted from January 5 to May 4, 1998. This pilot study was a randomized, placebo-controlled clinical trial, and was designed to be a prelude to a larger, definitive, clinical trial. The definitive clinical trial will attempt to ascertain whether oral glucocorticoids are effective at treating acute exacerbation of chronic obstructive pulmonary disease in patients discharged from the Emergency Department.

Specific Objectives of the Pilot Study:

. ***Primary Objective:***

The primary objective of the pilot study was to ensure that a larger clinical trial will be feasible.

Secondary Objectives:

The specific secondary objectives of the pilot study were:

1) To assess the proportion of patients who relapse in the two treatment groups, in order to determine whether this clinical variable could serve as the primary outcome variable for the definitive study.

2) To verify the sample size estimates for the larger trial.

3) To evaluate patient referral rates and trial recruitment.

4) To verify the enrollment process- did the inclusion/exclusion criteria allow for the intended group of patients to be entered into the study?

5) To allow for pre-testing of the data collection and data analysis process.

The three major objectives of the definitive clinical trial will be :

1) To determine whether a 10 day course of oral glucocorticoids will improve airflow obstruction

in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) who are discharged from The Emergency Department.

2) To compare the frequency of 10 day and 30 day relapse events in patients receiving oral glucocorticoids compared to controls after the treatment of acute COPD exacerbation in the Emergency Department.

3) To compare rates of patient-centered outcomes, including improvements in subjective dyspnea scores and improvements in disease-specific quality of life measured at day 10 following an Emergency Department visit.

The primary outcome variable of the definitive trial will be either percent improvement in airflow obstruction (objective 1 above) or relapse rate (objective 2 above). The choice of primary outcome variable will depend on the results of the pilot study.

4.0 Experimental Methods

4.1 Study Design

This pilot study was a randomized, double-blind, placebo-controlled clinical trial. Patients were randomized to treatment with oral prednisone or to treatment with identically labelled placebo capsules. The study was run out of The Emergency Departments of The Ottawa General and Ottawa Civic Hospitals and recruited patients from January 5, 1998 to May 4, 1998. Data collection was completed on June 4, 1998.

4.2 Patient Selection

4.21 Inclusion Criteria

Inclusion criteria were chosen to conform to current ATS definitions of COPD. The criteria were also selected to ensure that the study population was reflective of those patients in the ED who are ordinarily identified and diagnosed as having COPD exacerbation.

Patients were considered to fulfill the diagnosis of COPD if they met the following criteria:

1) Patients with a previous diagnosis of chronic bronchitis, emphysema or COPD established by their physician. In the event that the patient had not been previously labelled as having COPD, he/she was still eligible for the study if the treating emergency department physician felt that the clinical history was compatible with a diagnosis of COPD, and not asthma.

   Clinical history necessary to support a new diagnosis of COPD:

   a) Patient must have a history of chronic shortness of breath or chronic cough with sputum production.

   b) Symptoms should be constant and chronic and not fluctuate on a day-to-day basis.

2) Patients must have had evidence of airflow obstruction on presentation at the emergency department, defined as an $FEV_1 \leq 70\%$ of predicted and a FEV_1 / FVC ratio $\leq 70\%$.

3) Patients must have chronic airflow obstruction, defined as an $FEV_1 \leq 70\%$ of predicted

and a FEV_1 / FVC ratio ≤ 70%. The FEV_1 and FVC used for this criterion was taken from postbronchodilator spirometry results obtained at a time of clinical stability either before, or 1 month after the emergency room visit.

4) Patients must be ≥ 35 years old.

5) Patients must have a minimum history of 15 pack-years smoking.

6) Patients must be experiencing an acute exacerbation of COPD and must meet at least one of the following three clinical criteria for acute COPD exacerbation as defined by Anthonisen[21]: increased chronic baseline dyspnea , increased sputum volume or increased sputum purulence. The above complaints had to have necessitated the emergency department visit.

4.22 Exclusion criteria:

Patients excluded were those with:

1) Significant reversible airflow obstruction in the emergency room: Significant reversible airflow obstruction was defined as at least a ≥ 20% and a ≥200 ml improvement in FEV_1 from baseline after inhalation of bronchodilator.

2) Physician diagnosed asthma, eczema, allergic rhinitis or nasal polyposis.

3) Use of oral or injectable corticosteroids (but not inhaled steroids) during the month preceding trial entry.

4) History of chronic lung disease other than COPD. Patients with a history of bronchiectasis, cystic fibrosis, and interstitial lung disease were excluded. Patients with lung cancer were excluded, unless the cancer has been completely resected with no evidence of residual disease.

5) Pneumonia or congestive heart failure on emergency room CXR.

6) Patients not able to perform an FEV_1 assessment.

7) Patients with known adverse reaction or intolerance to systemic steroids.

8) Patients with severe uncontrolled diabetes mellitus (emergency room blood sugar > 15 mmol/l), severe renal (Cr > 200, or on dialysis), hepatic (biopsy proven cirrhosis or chronic

hepatitis), or cardiac failure (echocardiogram-documented grade III or IV left ventricular dysfunction and symptomatic heart failure- NYHA class III or IV), patients with ongoing gastrointestinal bleeding .

9) Inability to provide informed consent or comply with the study protocol due to cognitive impairment, language barrier, or distance > 100 kilometres from the study centre.

10) Patients admitted to hospital.

11) Patient has previously participated in the study.

4.3 Treatment Protocols

4.31 Experimental Manoeuvre:

Eligible patients were randomly allocated to receive either:

Oral prednisone, 40 mg capsules to take once daily for 10 days, or

placebo capsules identical in taste and appearance, to be taken daily for 10 days.

Medications were prepared by one central pharmacy and labelled only with a study number so as to ensure concealment of allocation.

This dose and duration of administration of prednisone was chosen based on previous studies in asthmatics which demonstrated that a 10 day course of 40 mg/day of prednisone was as safe and was as effective as a tapering prednisone course in achieving relief of airflow obstruction and prevention of asthmatic relapse.[24,50]

4.32 Other study manoeuvres:

1) A standardized emergency department protocol and order sheet for treatment of COPD exacerbation was distributed - the order sheets specified that patients should not receive intravenous or oral glucocorticoids in the emergency department. All other decisions regarding treatment and care of the patients were left to the treating emergency physician.

2) Both groups of patients were placed on an antibiotic. Patients were prescribed trimethoprim-sulfamethoxasole (septra) 2 tablets twice daily for 10 days, or in the event of a sulfa allergy, they received doxycycline 100 mg twice daily for 10 days.

3) Both groups of patients were provided with inhaled salbutamol and inhaled ipratropium metered dose inhalers. Education concerning use of the inhalers was provided to all patients and inhalation technique was verified. Patients were advised to use ipratropium 3 puffs four times daily and salbutamol 2 puffs four times daily for the duration of the trial period of 30 days.

4) Those patients taking inhaled corticosteroids and/or theophyline preparations before entering the trial were advised to continue on these medications.

4.33 Protocol for dealing with patients who relapsed:

The patient's family doctor was notified by fax when the patient entered the study. Patients who made an unscheduled visit to the emergency department or to the family doctor on or before day 10 because of self-reported worsening of dyspnea were considered to have relapsed and were classified as treatment failures. In the case of treatment failures, the physician treating the patient was advised to take the patient off the study medication, and to treat the patient with open-label prednisone. Patients were seen by study personnel on the same day of their relapse, or as soon as possible thereafter, and they were asked to complete the study measurements which had been scheduled for day 10.

4.4 Measures of Compliance

Compliance with the trial medication and antibiotic regimen was assessed through patient questionnaire and pill counts. Patients were asked to return unused pills and pill containers on study day 10 to verify compliance with the drug regimen. Unfortunately, there is no commercially available assay to monitor for blood levels of prednisone, and therefore laboratory testing for compliance was not feasible.

4.5 Baseline Assessment

Recorded information for all patients on admission into the trial included: age, gender, height, weight, ethnic origin, past medical history, duration of COPD, smoking history, current medication use, allergies, and recent respiratory symptoms. Previous pulmonary function tests were also recorded if available. A CXR, baseline and postbronchodilator spirometry, and pulse oximetry was obtained on all patients as part of routine emergency room care.

4.6 Outcome Measures

4.61 Primary outcome measure

The primary outcome measure was improvement in airflow obstruction. This was determined by assessing the percent change in the postbronchodilator FEV_1 at study day 10 from the postbronchodilator FEV_1 obtained before discharge from the emergency department.

FEV_1 was chosen as the primary outcome variable since it is a direct, sensitive, measure of the underlying physiologic abnormality[1]. FEV_1 is an objective measurement and is

highly reproducible.[51] The percent change in FEV_1 has previously been shown in the clinical trials of Albert [34] and Thompson [47] to be a sensitive measure of improvement in airflow obstruction in a similar patient population.

Although change in FEV_1 has been correlated with changes in patients' ratings of dyspnea and quality of life [52, 53], we chose not to use dyspnea index or quality of life as the primary outcome variables, since patient reporting of quality of life and dyspnea is necessarily subjective, and patient scores on these questionnaires may be affected by the confounding effects of steroids on mood and affect, independent of the effects of steroid on the actual disease process. [52]

In the event that we were unable to obtain spirometric measures on day 10, then measurements taken within ± 2 days were accepted. Spirometry was performed with the patient in the sitting position according to established American Thoracic Society criteria.[51] A minimum of two forced flow-volume loops of good quality were obtained. If the FEV_1 and FVC values were not within 10% of one another, an additional measurement was taken. The flow-volume loop with the best FEV_1 and FVC was used.

4.62 Secondary outcomes

Secondary outcomes were assessed at day 10, with the exception of relapse rates which were assessed at 10 days and 30 days after randomization. Secondary outcomes included:

1) The absolute change in postbronchodilator FEV_1 on study day 10 compared to day 1.

2) Absolute improvement in oxygenation measured by pulse oximetry done on room air, or if the patient was on home oxygen, oximetry was performed on the patient's usual oxygen prescription.

3) The proportion of patients who relapse within 10 and 30 days- relapse was defined, as per Chapman et al [54], as an unscheduled visit to a physician's office or a return to the emergency department because of a patient's perception of worsening dyspnea.

4) Improvement in subjective dyspnea score as assessed by The Mahler Baseline and Transitional Dyspnea Indexes. [55] The Mahler index is a two-part, interviewer-administered dyspnea index that rates dyspnea according to three categories: functional impairment,

magnitude of task, and magnitude of effort. The baseline dyspnea index (BDI) is used to rate the severity of dyspnea at a single point in time and the transition dyspnea index is used to assess changes from that baseline. At baseline, dyspnea in each of three categories is rated on a 5 point scale from 0 (severe) to 4 (unimpaired). Ratings for each of the three categories are added to form a baseline total dyspnea score (range, 0-12). The transition dyspnea index (TDI) is used to rate changes in each of the three categories using a 7-point scale from -3 (major deterioration) to +3 (major improvement). Ratings form the transition index can be added to form a dyspnea transition total score (range, -9 to +9).

Interobserver agreement for the baseline index has been observed at 92%, while the agreement for the transition index was 90%.[56] A correlation of $r = 0.60$ ($p < 0.001$) was reported between the baseline total score and the 12 minute walk test, and the transition total score has been significantly correlated with the change in 12 minute walk ($r = 0.33$, $p < 0.05$). The BDI has also been seen to correlate strongly with other measures of dyspnea (the MRC and Oxygen Cost Diagram), ($r = 0.53$ - 0.83), and moderately with the FEV_1 ($r = 0.43$).[56]

5) Improvement in disease-specific quality of life as assessed by the Chronic Respiratory Disease Index Questionnaire (CRQ).[57] The CRQ evaluates four aspects of quality of life in patients with obstructive lung disease: dyspnea, fatigue, emotional function, and mastery. Each domain includes four to seven items, and each item is scored on a scale of 1 to 7 (1- extremely short of breath to 7- not at all short of breath). This questionnaire has been demonstrated in the COPD population to be reliable, valid, and responsive to change. [57, 58] In previous clinical trials evaluating drug treatment protocols, changes in the CRQ correlated with changes in spirometric values, exercise performance, and subjective ratings of improvement by both the patients and physicians. [59] Correlations improved further when patients were given information about their previous responses, and the developers of the CRQ recommend providing patients with feedback on their previous responses when they repeat the test more than one time.[60]

6) Adverse effect rates assessed at 10 days by patient questionnaire.

Table 4: Summary of the Data Collection Schedule:

Day 1	Day 3	Day 10	Day 30
Baseline data collection in ED	Phone call to ensure compliance	Visit to clinic or at patient's home	Phone call to determine relapse
spirometry		spirometry	spirometry- only if no pre-study stable spirometry available
oximetry		oximetry	
Mahler baseline dyspnea index		Mahler transition dyspnea index	
CRQ		CRQ	
		adverse effects questionnaire	

4.7 Randomization and stratification

Patients with acute COPD exacerbation were screened by the emergency department physicians, and if considered eligible, were referred to on-call study personnel who assessed the patient and determined if the patient fulfilled eligibility criteria. Study personnel were on call by pager system 24 hours a day, seven days a week in a rotating one-in-five call schedule. The principal investigator (myself) was on continuous second call to handle queries from the study employees or patients. After informed consent was obtained from eligible patients randomization was performed. The randomization process consisted of a computer-generated random listing of the two treatment allocations blocked by groups of four and stratified by emergency department. Randomization was through central allocation of a randomization schedule and was coordinated by the Ottawa General Hospital Pharmacy Research Department. Physicians and research staff were unaware of the treatment allocation prior to randomization.

4.8 Blinding

The study was double-blinded. Medications were prepared by one central pharmacy and labelled only with a study number so as to ensure concealment of allocation. The prednisone and placebo were packaged in capsule form and had identical taste and appearance.

4.9 Sample Size Considerations

Patients were recruited for the pilot study over a four month period. All consecutive patients randomized over the four month pilot period were included in the study . Twenty patients were randomized from Jan. 5 1998 to April 5 1998.

Before the pilot was performed a total of 124 patients (62 per group) were estimated to be required for the larger clinical trial. This sample was calculated to provide a power of 80% to detect a 20% difference between improvement in FEV_1 in the placebo and treatment groups, with a probability of type I error (two-tailed alpha) of 5%.

A 20 % difference in improvement in FEV_1 was chosen as the smallest difference having clinical importance based on American and Canadian Thoracic Society recommendations stating that a 20% improvement in FEV_1 in chronic COPD patients is a significant improvement which justifies long-term steroid use in these patients [1, 29, 61]. In addition, I conducted a survey of 10

Ottawa-area chest physicians to determine their minimal clinically important difference. The physicians were asked the question "What minimum percent improvement in FEV_1 would you theoretically require in order to justify using a 10 day course of prednisone for a patient with COPD exacerbation?" The median response for these 10 surveyed respirologists was a 20% improvement in FEV_1, (mean ± SD, 16.9% ± 4.6% improvement).

4.10 Sample size calculations

The sample size estimate was based upon the following assumptions:

The outcome measure used to plan the study was the change in FEV1 at Day 10 from baseline. The baseline FEV_1 and its standard deviation were estimated from data from the study by Thompson et al. to be 0.90 ± 0.26 litres. At Day 10, placebo patients were assumed to improve by 15% from baseline and prednisone patients by 35% for a hypothesized minimal clinically important difference of 20%. As patients improved, both groups were assumed to have a larger standard deviation of 0.49 at Day 10 as per Thompson's study.

Assuming a correlation of .8 between Baseline and Day 10 FEV1 measures, the standard deviation of the change from baseline was estimated to be 0.32. In a preliminary estimate, a sample of 104 patients (52 per groups) were needed to detect a 20% improvement (i.e. an absolute improvement of 0.18 litres) based on the two-sided t-test for two independent groups with an 80% power and a 5% false-positive rate; using the formula

$$2N = \frac{4 * (Z_\alpha + Z_\beta)^2 * \sigma^2}{\delta^2}$$

where 2N = total sample size

Z_α= 1.96 (standard normal deviate for a two-tailed $\alpha = 0.05$)

Z_β=0.84 (standard normal deviate for $\beta = 0.20$)

σ = standard deviation around the mean of the outcome measurement. The standard deviation is estimated at .32 litres

δ = A 20% difference between improvement in FEV_1 in the placebo and prednisone groups on Day 10 of the trial. A 20% difference corresponds to an absolute greater improvement in FEV_1 of 0.18 litres in the treatment group from baseline, as compared to the placebo group. Substituting the values of the various parameters into the formula yields

$$2N = \frac{4 * (1.96 + 0.84)^2 * 0.32^2}{0.18^2} = 104$$

That is, 104 patients are needed to find a 20% difference between improvement in FEV_1 in the placebo and prednisone groups with a two-tailed $\alpha = 0.05$ and 80% power. Simulated FEV_1 data were then analysed using an ANCOVA model to verify the adequacy of the planned sample size for the large clinical trial: [62]

Assuming FEV1 measures were normally distributed according to treatment (i.e. prednisone and placebo) and assessment (i.e. Baseline and Day 10), four cohorts were generated. The simulated FEV1 changes were subjected to an analysis of covariance (ANCOVA) model including the following explanatory factors: treatment, centre, baseline FEV1 and treatment by centre interaction. For simplicity, we assumed FEV1 change correlated with baseline level with equal slope between the two treatment groups. Imbalance between centres at baseline was characterized according to the mean level difference equal to 0, .25 of baseline standard deviation, .5 SD, 1 SD and 1.5 SD (where the baseline standard deviation was 0.26). Test of treatment effect in the ANCOVA model was then subjected to a power analysis. Table 5 summarized the results the simulated ANCOVA (p-values of various effects) and of the power analysis of treatment effect.

Table 5: Simulated ANCOVA and Power Analysis of Treatment Effect

Centre Difference	2N	Power	Least Significant Number (N)*	p-value Rx ^	p-value Centre^	p-value FEV_1^	p-value Rx by centre Interaction^
0 SD (equal)	104	.60	83	.03	.11	<.001	.94
.25 SD	104	.72	64	.01	.06	<.001	.68
.5 SD	104	.83	52	.004	.03	<.001	.46
1 SD	104	.95	36	<.001	<.001	<.001	.16
1.5 SD	104	.99	24	<.001	.003	<.001	.04

*Least significant number is the sample size required to produce a significant test for a sample with the same profile (i.e. sums of squares and mean squares as derived from the simulated ANCOVA).

^Test of effects from the simulated ANCOVA model.

Assuming an attrition rate of 20%, a total of 124 patients (104 + (.20 * 104)), are needed for the study.

4.11 Final Analysis

4.11.1 Principal analysis of the primary outcome measure

The final analysis will be performed on an "intention to treat" basis. Using this approach, patients will be included in the analysis according to the group to which they were randomized. Those patients who relapse within the first 10 days of the trial will have the post-bronchodilator FEV_1 value done on the day of relapse counted as the Day 10 value for purposes of the analysis (ie. endpoint analysis, with the last observation carried forward).

The principal analysis of the difference between the percent improvement in postbronchodilator FEV_1 in the placebo and prednisone groups from day 1 to day 10 of the trial will be assessed using parametric procedures (independent t tests) initially. Student's t-test with equal variances will be used for these analyses if the p-value of Levene's test for homogeneity of variance is greater that 0.10, otherwise Students t-test with unequal variances will be used. However, if the Kolmogorov-Smirnov test of normality suggests that the data is not normally distributed ($p < 0.10$), a nonparametric test (Wilcoxon Rank Sum) will also be performed.

In the event that the two treatment groups appear to be imbalanced at baseline with respect to a major baseline covariate, such as stable FEV_1 or Day 1 FEV_1, then an analysis of covariance model with the imbalanced variable as the covariate will be conducted. The analysis of covariance will be done if the stable FEV_1 is imbalanced between the two groups since higher stable FEV_1's in one group compared to the other could bias the results in favour of that group. In theory, patients in the group with higher stable FEV_1's could have more room for improvement back to their baseline lung function and could therefore show proportionately greater changes in % improvement in FEV_1 from day 1 to day 10. The analysis of covariance will thus serve to adjust for the possible confounding effect of different stable FEV_1, or Day 1 FEV_1, distributions in the two treatment groups.

The ANCOVA will be performed as per methods described by Kleinbaum et al.[63] First, the two straight line regression equations of percent change in FEV_1 on the covariate will be generated. The two straight lines will be compared using a partial F test for parallelism using the model $Y = \beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ + E$, where Z is a dummy variable identifying the treatment group (0 if placebo, 1 if treatment) and with the null hypothesis for the test for parallelism Ho: $\beta_3 = 0$. After the

assumption of parallelism is assured, (ie. when regressing the percent change in FEV_1 on the covariate the slopes between the two treatment groups are parallel at a significance level of 0.10) then the ANCOVA analysis will be performed. In this approach, a regression model will be fitted of the form $Y = \beta_0 + \beta_1 X + \beta_2 Z + E$. Adjusted mean scores for both treatment groups will be obtained by evaluating the model at $Z = 0$ and $Z = 1$ when X is set equal to the overall mean of the covariate for the two groups. Finally, a partial F test of the hypothesis Ho: $\beta_2 = 0$ will be used to determine whether these adjusted mean scores are significantly different.

4.11.2 Analysis of the secondary outcome variables

Absolute changes in FEV_1 and oxygen saturation for the two treatment groups will be compared using parametric procedures (independent t tests) initially, or with nonparametric methods if the data is not normally distributed. Differences in scores of the Transitional Dyspnea Indexes in the two groups, and differences from day 1 to day 10 in the scores of the four components of the Chronic Respiratory Questionnaire, will be compared using independent t tests. Relapse rates at 10 and 30 days will be compared using Fisher's exact chi-square tests.

Of all the outcome variables assessed for this study, the outcome variable which is arguably the most clinically important is the proportion of patients who experience a 30-day relapse. A logistic regression model will be developed using the pilot data, with 30-day relapse as the dependent variable. The logistic regression will be done in an attempt to adjust for the influence of suspected clinically significant covariates on the treatment effect. Variables which will be assessed for potential inclusion in the model will be those that are considered: 1) clinically important variables that could potentially influence the outcome; and/or 2) variables which are mal-distributed in the two treatment groups at baseline.

The selection of variables for the logistic model will begin with a univariate analysis of each variable. The independent variables will then be screened for inclusion into the final model by adding each variable individually to the basic logistic model containing the constant term and the variable 'treatment'. Any variable which appears to appreciably change the beta coefficient for the variable 'treatment' will be considered to be a possible confounder and will be retained in the model. In addition, any relevant variable which shows a significant relationship with the treatment variable (judged by a likelihood ratio test for the model, $p < 0.10$) will be retained. Using this approach a final logistic model will be generated and an adjusted odds ratio for the treatment effect will be obtained.

Survival analysis will be used to compare number of days to relapse in the two treatment groups. Kaplan-Meier survival curves will be constructed to describe time to relapse and the curves will be compared using the log-rank test statistic.

All *p* values will be reported as two-sided. All data will be presented as means ± standard deviations unless otherwise stated. Odds ratios will be reported with 95% confidence intervals.

All analyses will be performed with SPSS software (™) version number 8.0.

4.12 Ethical Considerations

In the introduction, I have outlined the importance of COPD exacerbation as a common public health problem. There is currently no convincing evidence that treating outpatient COPD exacerbation with corticosteroids provides any significant benefit to patients who are already being treated with standard therapy of antibiotics and bronchodilators. Given the uncertainty regarding treatment approaches in this population and the relative absence of clinical trials in this field, I believe that a state of clinical equipoise exists which ethically justifies the need for a trial.

A Safety Data Monitoring Committee will be created for the larger trial for the purpose of interim analysis and possible early termination of the trial. As a further safety measure, those patients who complain of worsening dyspnea during the first 10 days of the trial will be withdrawn from the study, and their physician will be offered the option of placing the patient on open-label prednisone. This will ensure that assignment to the placebo arm will not be hazardous to the patient. Ethical approval for the pilot and the larger study was granted from the Ottawa General and Civic Hospitals Research Ethics Committees.

5.0 Results:

5.1 Trial Profile

Sixty-seven patients were referred to the study during the four month pilot phase, of these, 23 patients fulfilled eligibility criteria for admission into the trial (Figure 2). Twenty of the eligible 23 patients were enrolled into the trial, three patients refused consent. Nineteen of twenty completed the 30-day study. One patient in the prednisone-treated group withdrew after 3 days on the advice of her family physician and refused further attempts at follow-up. Complete data was therefore available for 11 patients in the placebo group and 8 patients in the prednisone group.

There were two protocol violations related to improper enrollment of patients into the pilot study. One patient (who died 6 days after enrollment) was dialysis-dependant and should have been excluded based on exclusion criteria #8, and the second patient was discovered on day 10 of the trial to have been on prednisone 21 days before trial entry when he brought in his old pill bottles to the study investigators. Both patients were retained in the intention-to-treat analysis.

5.2 Patient Characteristics

Age, sex, smoking history, presenting symptoms, and mean study Day 1 FEV_1 were comparable between groups (Table 6). Because of the small numbers of patients enrolled in the pilot study there were imbalances with respect to mean stable FEV_1, history of coronary artery disease, and use of inhaled steroids between the two groups (Table 6).

5.3 Improvements in Airflow Obstruction

Figure 3 depicts the absolute changes in FEV_1 from day 1 to day 10 for the placebo and prednisone-treated patients. The mean improvement in FEV_1 was 0.15 ± .27 litres for the placebo-treated group and 0.26 ± .25 litres for the prednisone-treated group. The data were not normally distributed (Kolmogorov-Smirnov (KS) test p=.06 for placebo group and p=.20 for prednisone group) and the data were therefore analysed using the Wilcoxon rank-sum test. The mean absolute improvement in FEV_1 was not significantly different between the two groups (p=0.20).

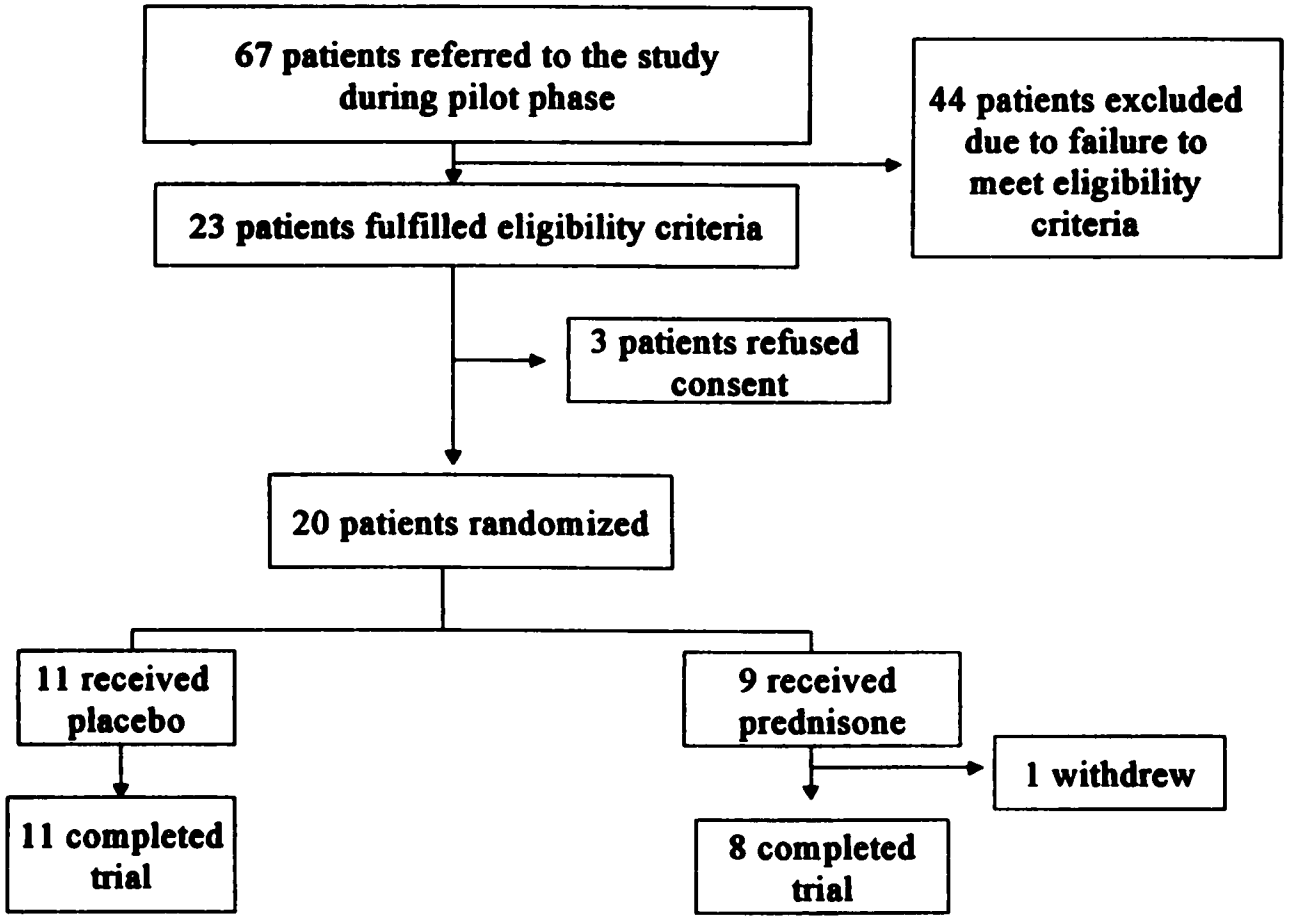
The percent change in FEV_1 from baseline, ie. (Day 10 FEV_1 - Day 1 FEV_1) / Day 1 FEV_1, is depicted in Figure 4. Placebo-treated patients improved their FEV_1 by a mean of 13.9 ± 23.8% over the 10 day period compared to an improvement of 40.3 ± 44.4% in the prednisone-treated

group. KS tests for normality were equivocal (KS p= 0.11 and 0.12 for the two respective groups), and data were therefore analysed using both parametric and non-parametric tests. Levene's test for equality of variances was significant p= 0.05, and therefore the two groups were assumed to have unequal variances for the purposes of the parametric test. The mean percent improvement in FEV_1 was not significantly different between the two groups (independent t-tests assuming unequal variances p= 0.16, Wilcoxon rank-sum test p= 0.14).

5.4 Improvements in Oxygen Saturation

Figure 5 depicts the distribution of oxygen saturation responses for the prednisone and placebo-treated groups. The mean change in oxygen saturation (Day 10 - Day 1) was slightly, but not significantly greater in the prednisone-treated patients compared to placebo treated patients. Five of the eight patients treated with prednisone improved their oxygen saturation over the 10 day period compared to 6 of the 11 placebo-treated patients. The placebo group showed a 0.18 ± 2.8% increase in mean oxygen saturation compared to a 1.6 ± 1.9% increase in mean oxygen saturation in the prednisone group (Wilcoxon p = 0.38).

Figure 2: Trial Profile



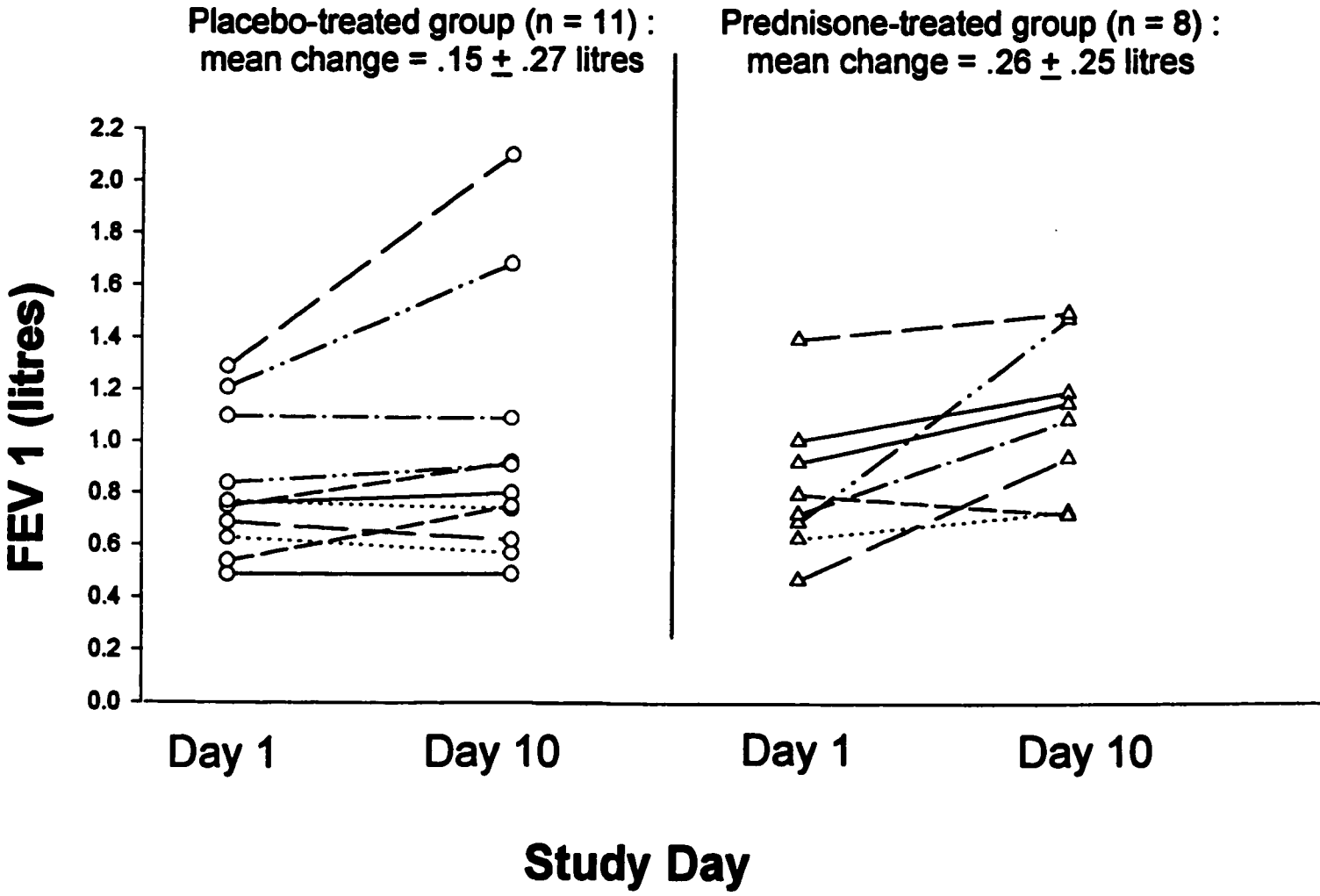
Reasons for exclusion	No.
Admitted to hospital	11
Asthma	8
Current use of steroids	6
Spirometric exclusion	6
CXR - pneumonia or CHF	4
Patient already enrolled in study	2
History of atopy	1
Referred to wrong study	1
Not acute COPD exacerbation	1
Severe diabetes	1
Lung cancer	1
No French or English	1
Lives > 100 km from Ottawa	1

Reason for withdrawal	
Advice of Family Physician	1

Table 6: Baseline Characteristics of All Patients Randomized to the Pilot Study:

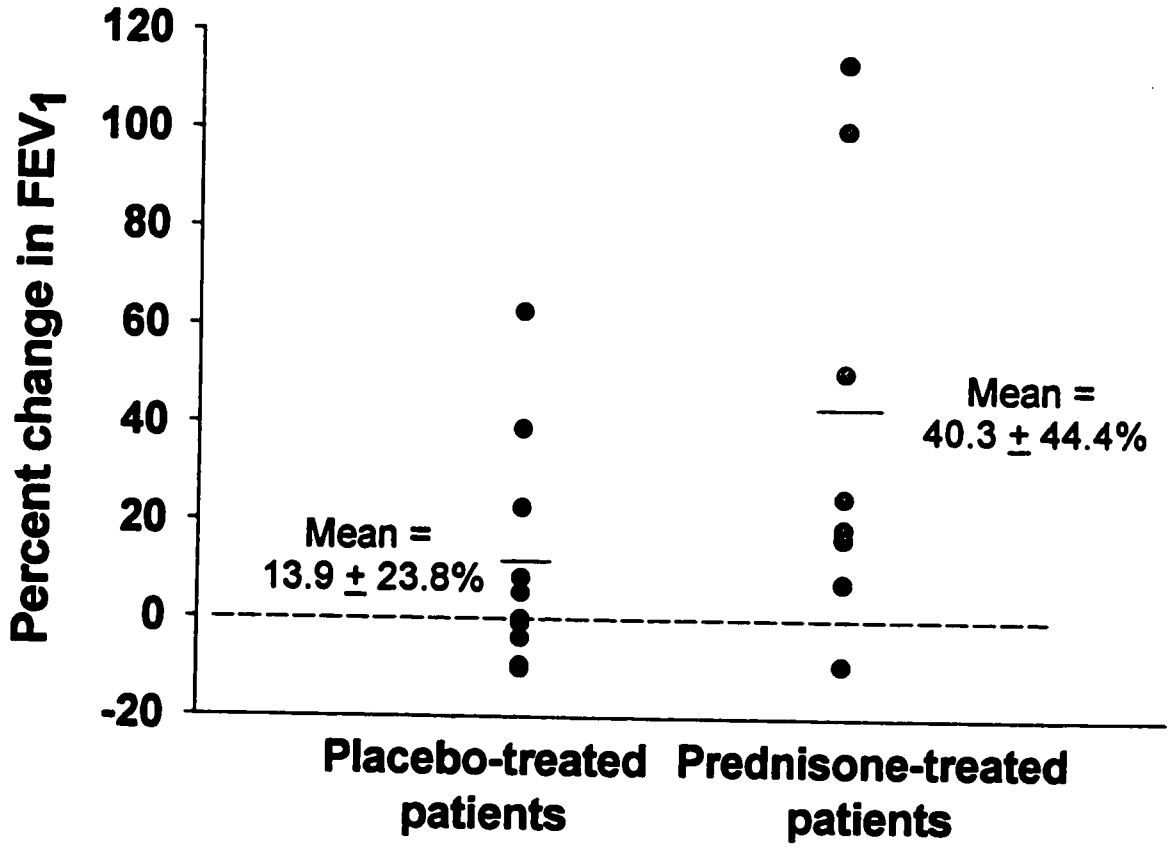
Characteristic	Placebo (n=11)	Prednisone (n=9)
Sex (M/F)	5/6	3/6
Mean age ± SD	70.1 ± 5.2 y	67.2 ± 5.2 y
Smoking status		
Smoker	4 (36%)	3 (33%)
Ex-smoker	7 (64%)	6 (67%)
Pack-year history ± SD	52 ± 20	43 ± 14
Duration of COPD (years)		
0-5	2 (18%)	4 (45%)
6-10	4 (36%)	2 (22%)
>10	2 (18%)	2 (22%)
Unknown	3 (27%)	1 (11%)
Mean stable FEV_1 (L) ± SD	1.22 ± .47	0.93 ± .40
Mean stable FEV_1 %predicted ± SD	48 ± 18%	38 ± 12%
Mean stable FEV_1/FVC (%) ± SD	53 ± 14%	43 ± 9%
Presenting symptoms		
Dyspnea	11 (100%)	8 (89%)
Cough	9 (82%)	7 (78%)
Sputum production	8 (73%)	7 (78%)
Mean study day 1 FEV_1 (L) ± SD	0.82 ± .27	0.85 ± .30
Mean study day 1 FEV_1 %predicted ± SD	33 ± 13%	36 ± 14%
Mean study day 1 FEV_1/FVC (%) ± SD	47 ± 10%	45 ± 10%
Concurrent medical conditions		
CAD	9 (82%)	2 (22%)
CHF	2 (18%)	1 (11%)
Renal dysfunction	3 (27%)	0 (0%)
Liver dysfunction	1 (9%)	0(0%)
Diabetes	2 (18%)	1 (11%)
COPD medication use		
Inhaled steroids	5 (45%)	8 (89%)
Ipratropium	7 (64%)	5 (56%)
Antibiotics	5 (45%)	2 (22%)
Theophyline	1 (9%)	2 (22%)
Home oxygen	1 (9%)	0 (0%)

Figure 3: Absolute Change in FEV_1 From Day 1 to Day 10
Placebo and Prednisone-Treated Groups:



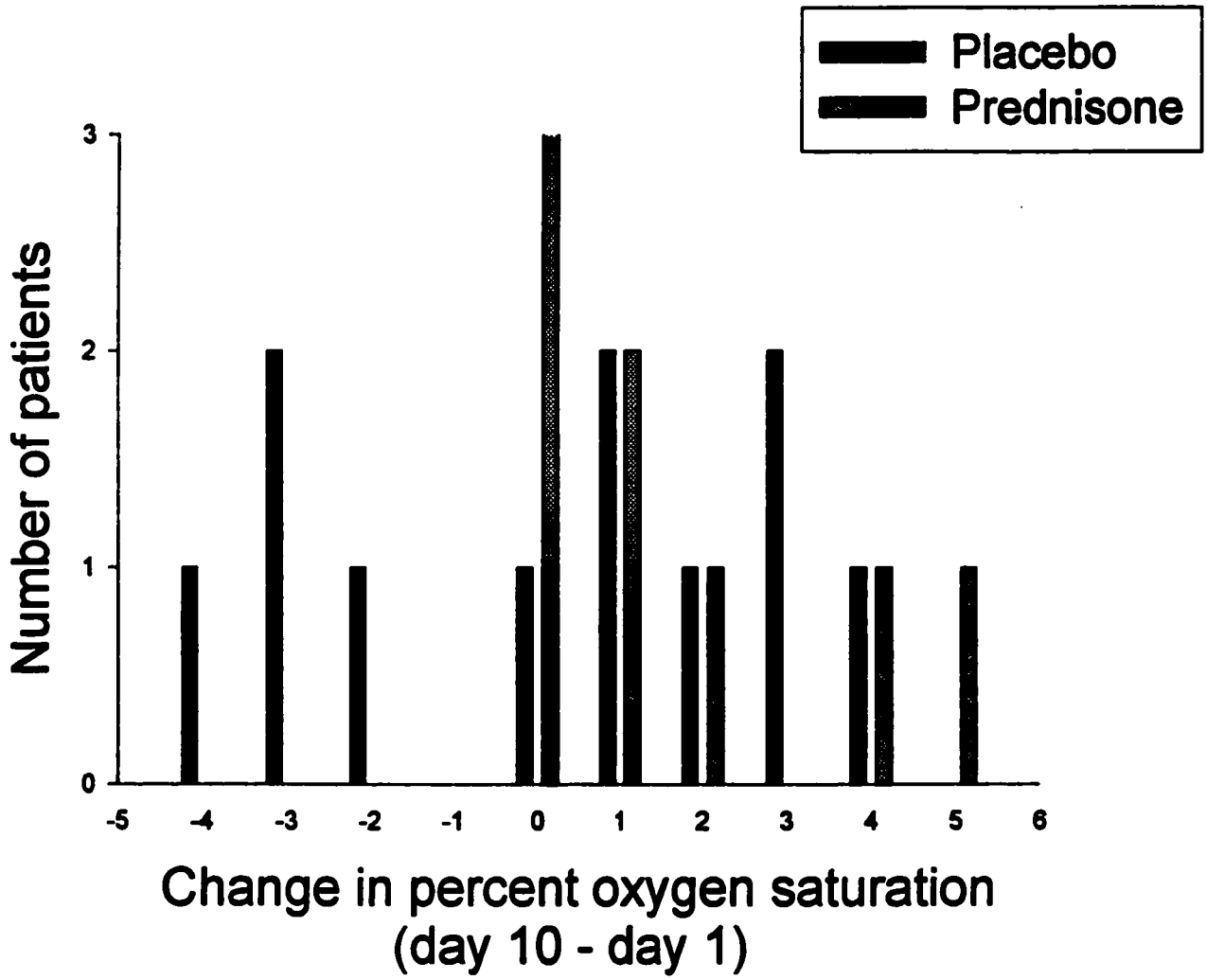
Six of the eleven patients in the placebo-treated group experienced an improvement in FEV_1 over the ten day trial period compared to seven of the eight patients treated with prednisone. Nevertheless, the mean absolute improvement in FEV_1 was not significantly different between the two groups ($p = 0.20$).

Figure 4: Percent Change in FEV_1 From Day 1 to Day 10
Placebo and Prednisone-Treated Groups



The percent change from baseline in FEV_1 was calculated as (Day 10 FEV_1 - Day 1 FEV_1) / Day 1 FEV_1. The mean percent improvement from Day 1 in FEV_1 was not significantly different between the two treatment groups ($p = 0.14$).

Figure 5: Distribution of Oxygen Saturation Responses for the Prednisone and Placebo-Treated Groups.



Mean change in oxygen saturation (day 10 - day 1) was slightly, but not significantly greater in the prednisone-treated patients compared to placebo-treated patients. The placebo group showed a 0.18 ± 2.8% increase in mean oxygen saturation compared to a 1.6 ± 1.9% increase in mean oxygen saturation in the prednisone group (Wilcoxon p=0.38).

5.5 ANCOVA Adjustment for the Effect of Stable FEV_1 on Percent Change in FEV_1

Mean stable FEV1 was 1.22 ± .47 litres in the placebo-treated group compared to 0.93 ± .40 litres in the prednisone-treated group (Table 6). In order to adjust for the possible confounding effect of different stable FEV_1 distributions observed in the two treatment groups an analysis of covariance (ANCOVA) was performed. The ANCOVA was performed on data from 18 of the 19 patients who completed the trial since data on stable FEV_1 were unavailable for 1 patient from the placebo-treated group who did not return for 30-day spirometric testing.

The two straight-line regression equations of %change in FEV_1 on stable FEV_1 were:

Y(placebo) = -27.09 + 34.96 X and

Y(prednisone) = 35.87 + 4.86X

The two straight lines were compared using a regression model $Y = \beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ + E$, where Z was the indicator variable identifying the treatment group (0 if placebo, 1 if treatment) and where the null hypothesis for the test for parallelism was Ho: $\beta_3 = 0$. The ANOVA table for the test for parallelism is displayed below:

	Source of variation	Sum of Squares	df	Mean square
1	Regression (X,Z)	4454.8	2	2227.4
	Residual	17418.7	15	1161.2
	Total	21873.5	17	
2	Regression (X,Z,XZ)	5154.1	3	1718.0
	Residual	16719.4	14	1194.2
	Total	21873.5	17	

From the ANOVA table, the partial F test : F(XZ| X,Z) = (5154 - 4454) / 1194

$F_{1,14} = 0.586$, p = 0.46, therefore Ho is not rejected and the two lines are assumed to be parallel.

Given that the parallel straight-line assumption of the model is appropriate, an analysis of covariance model was then used to adjust for the covariate, baseline FEV_1, using a regression model of the form $Y = \beta_0 + \beta_1 X + \beta_2 Z + E$.

The least-squares fitting of the model yielded the following estimated model:

$$Y = -15.01 + 23.70X + 33.27Z$$

using X = 1.08 (the mean stable FEV_1 for both groups) yielded the following adjusted mean scores pictured in the table below:

Treatment	Unadjusted % improvement in FEV_1	Adjusted % improvement in FEV_1
Placebo	13.9	10.6
Prednisone	40.3	43.9

These results indicate that when the covariate 'stable FEV_1' is adjusted for that the difference between the two groups in %improvement in FEV_1 is further magnified. To test whether this difference in adjusted mean scores was significant a partial F test of the hypothesis Ho: $\beta_2 = 0$ was computed using the ANOVA table pictured below:

	Source of Variation	Sum of Squares	df	Mean square
1	Regression (X)	497.1	1	497.1
	Residual	21376.4	16	1336.0
	Total	21873.5	17	
2	Regression (X,Z)	4454.8	2	2227.4
	Residual	17418.7	15	1161.2
	Total	21873.5	17	

Partial F test: $F(Z|X) = (4454 - 497) / 1161$

$F_{1,15} = 3.40, p = 0.09$

Therefore, the ANCOVA adjustment for the covariate, stable FEV_1, does not significantly change the results of the analysis, ie. there is still no significant difference ($p=0.09$) observed in the percent improvement in FEV_1 between the two treatment groups after the adjustment at level of significance 0.05.

5.6 Results: The Baseline and Transitional Dyspnea Indexes:

The baseline dyspnea index (BDI) was used to rate the severity of dyspnea on Day 1 of the trial. The BDI consists of three components (functional impairment, magnitude of task, and magnitude of effort) and a total score. At baseline, on Day 1 of the trial, dyspnea in each of the three categories was rated on a 5 point scale from 0 (severe) to 4 (unimpaired). Ratings for each of the three categories were added to form a baseline total dyspnea score (range, 0-12). The transition dyspnea index (TDI) was used on Day 10 to rate changes in each of the three categories using a 7-point scale ranging from -3 (major deterioration) to +3 (major improvement). Ratings from the transition index were added to form a dyspnea transition total score (range, -9 to +9).

Results of the BDI are summarized in Table 7. On Day 1 of the trial the BDI scores for the two patient groups were not significantly different across any of the three components of the measurement tool. However, the placebo-treated patients did score slightly lower than the prednisone-treated patients across all 3 components of the BDI, indicating that on Day 1 these patients tended to report slightly more dyspnea.

The TDI was administered on Day 10 of the trial to assess the change in severity of dyspnea from baseline. Results of the TDI are summarized in Table 8. At Day 10 the 'functional impairment' and 'magnitude of effort' components of the TDI trended towards greater improvements for the prednisone-treated patients than for placebo-treated patients. These trends almost approached statistical significance ($p = 0.08$ and $p= 0.06$, for the 'functional impairment' and 'magnitude of effort' components respectively). Conversely, the magnitude of task component of the TDI did not show a greater improvement in the steroid-treated patients. Overall, the total TDI mean score was 2.44 points higher in the prednisone-treated group, reflecting a trend to a greater improvement in subjective self-reported dyspnea from Day 1 to Day 10 in those treated with prednisone, however this improvement was not statistically significant (95% CI, -1.36 to 6.24, $p=0.19$).

Table 7: Baseline Dyspnea Index Scores (Day 1):

Baseline Dyspnea Index (BDI) Component	Placebo group (n =11)	Prednisone group (n=9)	Mean difference (95% CI)	p
Functional impairment grade, mean ± SD	0.73 ± 1.01	1.22 ± 1.48	0.49 (-0.69, 1.67)	0.39
Magnitude of task grade, mean ± SD	0.82 ± 0.60	1.00 ± 0.71	0.18 (-0.43, 0.79)	0.54
Magnitude of effort grade, mean ± SD	1.82 ± 1.40	2.00 ± 1.00	0.18 (-0.99, 1.35)	0.75
Total BDI Score, mean ± SD	3.36 ± 2.06	4.22 ± 2.44	0.86 (-1.25, 2.97)	0.40

Table 8: Transitional Dyspnea Index Scores (Day 10):

Transitional Dyspnea Index (TDI) Component	Placebo group (n =11)	Prednisone group (n=8)	Mean difference (95% CI)	p
Functional impairment grade, mean ± SD	0.18 ± 1.99	1.50 ± 1.07	1.32 (-0.18, 2.82)	0.08
Magnitude of task grade, mean ± SD	0.45 ± 1.86	0.25 ± 1.58	-0.20 (-1.88, 1.48)	0.80
Magnitude of effort grade, mean ± SD	0.55 ± 2.02	1.88 ± 0.64	1.33 (-0.08, 2.74)	0.06
Total TDI Score, mean ± SD	1.18 ± 5.40	3.63 ± 1.92	2.44 (-1.36, 6.24)	0.19

5.7 Results: The Chronic Respiratory Index Questionnaire:

Disease-specific quality of life was assessed by the Chronic Respiratory Disease Index Questionnaire (CRQ). The CRQ evaluates four aspects of quality of life in patients with obstructive lung disease: dyspnea, fatigue, emotional function, and mastery. Each domain includes four to seven items, and each item is scored on a scale of 1 to 7 (1- extremely short of breath to 7- not at all short of breath). Higher scores imply better self-reported disease-specific quality of life. Patients were tested with the CRQ on Day 1 of the trial and again on Day 10. Patients were provided with feedback on their previous responses when they repeated the test on day 10. The outcome variable of interest was the change in the CRQ scores from Day 1 to Day 10.

Previous work by the investigators who developed this index has shown that a change in score in any domain of the CRQ of 0.5 or greater represents the minimal clinical important difference that is noticeable to patients, and that changes in any domain of the CRQ greater than 1.0 and greater than 1.5 represent moderate improvements and large improvements respectively in disease-specific quality of life.[64, 65]

Table 9 depicts the results of the Day 1 CRQ scores. There was no significant difference in score across any of the four domains of the CRQ between the two treatment groups at baseline when the patients entered into the trial.

Table 10 documents improvement in the CRQ scores across the four domains from Day 1 to Day 10 of the trial. Both treatment groups showed net improvement in scores. The prednisone-treated group consistently scored greater improvements than the placebo-treated groups across all four domains of the quality of life index, however none of these differences between the two groups reached statistically significant levels. For the prednisone-treated group the mean improvement in 3 of 4 domains of the CRQ was greater than 1.5 indicating that these patients had large improvements in dyspnea, emotional function, and fatigue over the 10 day period, whereas in the placebo group only the fatigue domain showed an improvement greater than 1.0.

Table 9: Baseline CRQ Scores (Day 1):

CRQ domain	Placebo group (n=11)	Prednisone group (n=9)	Mean difference (95% CI)	p
Dyspnea	3.10 ± 0.93	2.51 ± .099	-0.59 (-1.50, 0.32)	0.19
Fatigue	2.61 ± 0.90	2.86 ± 1.30	0.25 (-0.79, 1.28)	0.62
Emotional Function	3.66 ± 1.32	3.79 ± 1.34	0.13 (-1.12, 1.39)	0.83
Mastery	3.20 ± 1.35	3.70 ± 2.00	0.50 (-1.08, 2.08)	0.51

Table 10: Changes in CRQ scores (Day 10 - Day 1)

CRQ domain	Placebo group (n=11)	Prednisone group (n=9)	Mean difference (95% CI)	p
Dyspnea	0.69 ± 2.09	1.92 ± 1.79	1.23 (-0.70, 3.16)	0.20
Fatigue	1.09 ± 1.93	1.78 ± 1.15	0.69 (-0.93, 2.31)	0.38
Emotional Function	0.61 ± 1.56	1.41 ± 1.56	0.80 (-0.73, 2.33)	0.29
Mastery	0.84 ± 1.50	1.53 ± 1.50	0.69 (-0.78, 2.16)	0.34

5.8 Results: Relapse

The proportion of patients in the two treatment groups who experienced a relapse event within ten and thirty days is displayed in Table 11 below. Relapse was defined as an unscheduled visit by the patient to the Emergency Department or to another physician because of worsening dyspnea. Relapse occurred on, or before Day 10 in 45.5% of placebo-treated patients and 12.5% of prednisone-treated patients and on, or before Day 30 in 45.5% and 25.0% of placebo-treated patients and prednisone-treated patients respectively. Although the prednisone treated patients tended towards lower relapse rates the difference between the two treatment groups was not statistically significant.

Kaplan-Meier survival curves showing the probability of remaining relapse-free for patients receiving prednisone and those receiving placebo are shown in Figure 6. The survival difference between the two treatment groups was not statistically significant, log-rank test $p = 0.29$. Median survival could not be evaluated from the data in either group since relapse rates over 30 days did not reach 50%, 75th percentile survival time was 4 days in the placebo-treated group compared to 21 days in the prednisone-treated group.

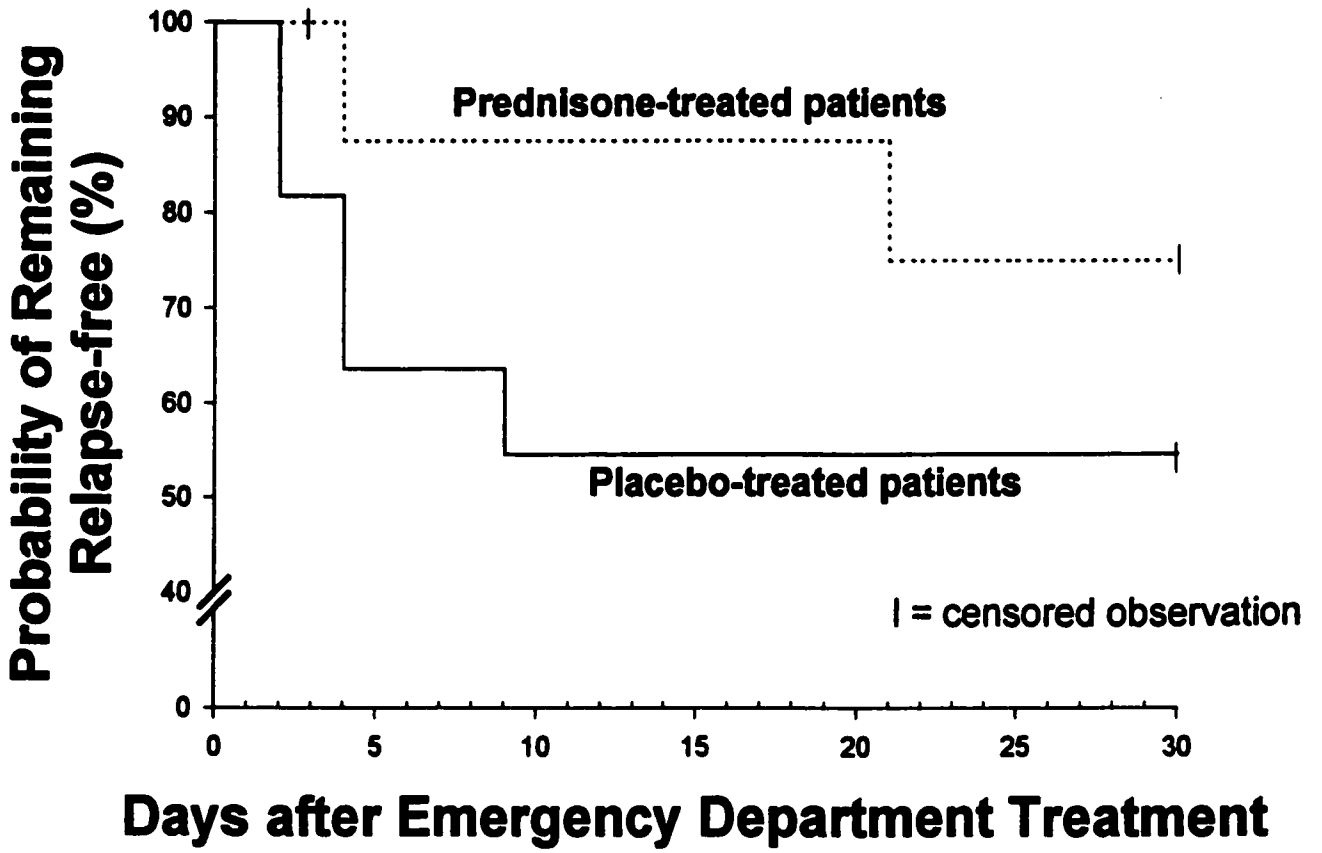
Table 11: Ten and thirty-day relapse events in the two treatment groups:

Treatment group	10 day relapse proportion	30 day relapse proportion
Placebo	45.5%	45.5%
Prednisone	12.5%	25.0%

χ^2 (Fisher's exact test) p=0.18 for 10 day relapse

χ^2 (Fisher's exact test) p=0.63 for 30 day relapse

Figure 6: Kaplan-Meier Survival Curve Showing the Probability of Remaining Relapse-Free for Patients Receiving Prednisone (broken line) and Those Receiving Placebo (solid line).



The survival curves suggest that the prednisone-treated group showed a trend to longer relapse-free survival. However the survival difference between the two treatment groups was not statistically significant, log-rank test $p = 0.29$.

5.9 Results: Logistic Regression Model for 30 Day Relapse:

The logistic regression for 30 day relapse was done to adjust for the possible influence of suspected clinically significant covariates on the treatment effect. Variables which were assessed for potential inclusion into the logistic model were: 1) clinically important variables that could potentially influence the outcome, such as age, sex, study site, smoking status, and Day 1 FEV_1, 2) variables which were mal-distributed in the two treatment groups at baseline, such as mean stable FEV_1, history of coronary artery disease, and use of inhaled steroids. Table 12 illustrates results of the univariate logistic regression models for 30 day relapse rate.

Because of the small number of patients entered into the pilot study, estimates became unstable when a large number of independent variables were added into the model, and forward stepwise regression methods yielded models with only one variable in addition to the treatment variable . It was therefore decided to limit the number of independent variables allowed into the model by first screening for confounding effects of each individual independent variable when it was added to the basic logistic model containing only the constant term and the 'treatment' variable. Any variable which appreciably changed the beta coefficient for the variable 'treatment' was considered to be a possible confounder and was retained in the model. In addition, the variables 'site', 'sex' and 'age' were thought to be important covariates which could potentially modify the effect of the treatment variable, and these variables were therefore screened for significant interaction effects with the treatment variable. A significant interaction effect was judged to be one where the addition of the interaction term to the main effects model yielded a likelihood ratio test statistic of $p < 0.10$.

Table 13 illustrates the results of the variable screening procedure. The variables 'age', 'history of CAD', and 'stable FEV_1', had a significant effect on the beta coefficient for the 'treatment' variable and were therefore considered to be confounders and were chosen for the main effects model. The interaction term sex*treatment improved the basic model (likelihood ratio test p=0.04) and therefore the variables sex and the interaction term sex*treatment were retained for assessment in the model as well.

Table 14 illustrates the results of the main effects model which was constructed using the retained variables 'treatment', 'age', 'sex', 'history of CAD', and 'stable FEV_1 (% pred)'. This model, although not meant to be a predictive model for relapse, still demonstrated a reasonable ability to characterize 30 day relapse. The likelihood ratio test for the main-effects model, compared to a

model containing only the constant term, was G=8.348, df=5, p = 0.13. The Hosmer-Lemeshow goodness of fit test showed a $\chi^2 = 4.016$, df=6, p=0.78.

Using this main-effects model the adjusted odds ratio for the treatment effect was found to be 0.15 (95% CI, 0.002 - 13.70). This compares to the univariate unadjusted odds ratio for the treatment effect of 0.40 (95% CI, 0.05 - 2.93) (see table 12). Thus, treatment with prednisone may have been protective in that it was associated with an odds ratio for 30-day relapse of 0.15 (controlling for the variables, 'age', 'sex', 'history of CAD', and 'stable FEV_1 (%pred.)'. However, because of the small number of patients studied, the standard error around the beta-coefficient was very wide and the 95% confidence interval overlapped one, indicating that this apparently favourable odds ratio result was not statistically significant.

Finally, the main effects model was also subject to an assessment for possible significant interactions. The interaction term 'sex * treatment' was tested since it was considered to have possible biological significance and since its addition to the basic model containing the constant and the treatment variable had previously been shown to improve the fit of the basic model (likelihood ratio test p=0.04). When the sex*treatment term was added to the main effects model pictured in Table 14 the likelihood ratio p value was 0.21. However, the inclusion of this interaction terms into the main-effects model produced an unstable model with uninterpretable odds ratios. It was concluded that although the sex*treatment interaction term may be significant, the size of this data set was too small to allow its inclusion, and that any possible interaction effect of sex and treatment will need to be assessed in the more definitive larger trial.

Table 12: Univariate logistic regression models for 30 day relapse:

All univariate models were compared to the model containing the constant term only.

Variable	Odds Ratio	95% CI of the odds ratio	-2 Log-likelihood	χ^2	*p*
Constant			25.01		
Treatment	0.40	(.05-2.93)	24.16	0.85	0.36
Sex	0.38	(.06-2.55)	23.98	1.03	0.31
Site	0.40	(.05-2.93)	24.16	0.85	0.36
Age	1.12	(.91-1.38)	23.74	1.27	0.26
Current smoker	0.56	(.08-4.14)	24.68	0.33	0.56
Inhaled steroids	0.67	(.10-4.54)	24.84	0.17	0.68
History of CAD	1.33	(.20-8.70)	24.92	0.10	0.76
Stable FEV_1	0.93	(.13-6.77)	22.91	0.00	0.95
Stable FEV_1 (% pred.)	0.97	(.91-1.04)	22.18	0.74	0.39
Day 1 FEV_1	2.21	(.06-85.8)	24.83	0.18	0.67
Day 1 FEV_1 (% pred.)	1.00	(.92-1.09)	25.01	0.00	0.99

Table 13: Results of the variable screening procedure:

Highlighted variables indicate those which appreciably changed the beta coefficient for the variable 'treatment' or those which demonstrated a significant interaction effect with the treatment variable. All models were compared to the original model containing the constant term and the treatment variable.

Model #	Variables in the model	β treatment	-2 Log-Likelihood	χ^2	*p*
1	constant, treatment (ct)	-0.916	24.15		
2	ct + site	-1.05	23.10	1.05	0.31
3	ct + site + site*treatment		21.78	1.32	0.25
4	ct + sex	-0.884	23.23	0.92	0.34
5	ct + sex + **sex*treatment**		18.87	4.36	**0.04**
6	ct + age	**-0.527**	23.52	0.63	0.43
7	ct + age + age*treatment		23.27	0.24	0.62
8	ct + smoke	-0.926	23.82	0.33	0.56
9	ct + inhaled steroids	-0.905	24.16	0.01	0.98
10	ct + **history of CAD**	**-1.36**	23.95	0.21	0.59
11	ct + stable FEV_1	-0.903	23.37	0.79	0.37
12	ct + **stable FEV_1 (% pred.)**	**-1.15**	22.17	1.98	0.16
13	ct + day 1 FEV_1	-0.899	24.01	0.14	0.71
14	ct + day 1 FEV_1 (%pred.)	-0.917	24.16	0.01	0.98

Table 14: The Main Effects Model:

Variable	Coefficient	Standard Error	Odds Ratio (± 95% CI)
Treatment	-1.919	2.315	0.147 (0.002 - 13.70)
Age	0.307	0.224	1.359 (0.875 - 2.11)
Sex	-3.900	2.302	0.202 (0.001- 1.84)
History of CAD	-1.785	2.262	0.167 (0.002 - 14.11)
Stable FEV_1 (% pred.)	-0.086	0.592	0.918 (0.817 - 1.03)

5.10 Profile of Adverse Effects:

There was one death amongst the study participants. The patient, who was assigned to the placebo group, relapsed on day 3 and was hospitalized and placed on open-label glucocorticoids. Three days after being withdrawn from the study (ie. 6 days after being enrolled in the study), the patient sustained a myocardial infarction and died in hospital.

The overall frequency of adverse events during treatment was similar in the two treatment groups, occurring in 82% of the placebo-treated group and 88% of the prednisone-treated group. The most common adverse effects related to changes in appetite- 63% of prednisone-treated patients reported an increase in appetite compared to 27% of those on placebo. No patients treated with prednisone reported a decrease in appetite, but 18% of those on placebo reported decreased appetite. Weight gain was reported in 25% of prednisone-treated patients compared to 9% of those treated with placebo.

Anxiety and depression were the next most common reported adverse effects, occurring in 12% of prednisone-treated patients compared to 45% of placebo-treated patients. Nausea and/or vomiting occurred in 38% of prednisone-treated patients and 27% of placebo-treated patients. Epistaxis was reported in 18% of patients taking placebo, but did not occur in the prednisone-treated patients. No other significant adverse effects were reported, however this pilot study was not powered to detect other rare, but possibly important adverse effects.

6.0 Discussion

6.1 Summary and Interpretation of the Results of the Pilot Study:

In this study, outpatients with acute COPD exacerbation who were treated with prednisone following a visit to the Emergency Department showed a trend towards greater improvement of their expiratory flows (FEV_1) at ten days compared to patients treated with placebo. Specifically, the mean absolute and percent change in FEV_1 over the ten day follow-up period tended to be higher in the prednisone-treated patients compared to the placebo-treated patients. The results also suggest that a greater proportion of patients in the prednisone-treated group experienced a net improvement in FEV_1 from Day 1 to Day 10. An analysis of covariance which was done to adjust for baseline imbalances in the mean stable FEV1 further accentuated the observed difference in mean improvement in FEV_1 between the prednisone and placebo-treated groups.

Although none of the differences in expiratory airflow reached statistically significant levels, this pilot study involved a relatively small number of patients, and was therefore unable to detect clinically important differences between the two treatment groups. However, results of the pilot study are nevertheless interesting, since the data does indicate a trend towards an improved physiologic outcome for the prednisone-treated patients compared to those patients treated with placebo.

Secondary outcome variables also showed a trend towards greater improvement in the prednisone-treated patients. The other physiologic outcome variable, the mean change in oxygen saturation, trended towards a greater improvement in prednisone-treated patients compared to those treated with placebo.

Other investigators have previously noted that improvements in expiratory airflow obstruction result in less dynamic hyperinflation of the lung, which in patients with COPD has been shown to be the major physiologic stimulus leading to dyspnea.[66] It would therefore be expected that improvements in FEV_1 would correlate with improvements in these patients' subjective sense of dyspnea. This was observed in the pilot study. The two treatment groups had similar Baseline Dyspnea Index scores and thus reported similar subjective levels of dyspnea on Day 1 of the trial. However, those patients who received prednisone experienced a trend towards greater improvement

in their level of dyspnea by Day 10 as reflected by higher Transitional Dyspnea Index (TDI) scores. Similarly, this study used an additional tool for measuring patient dyspnea, namely, the dyspnea component of the Chronic Respiratory Index Questionnaire (CRQ). Results of the CRQ were similar to those of the TDI, that is, those patients treated with prednisone experienced a trend towards greater improvement from day 1 to day 10 on the dyspnea component of the CRQ compared to those who received placebo.

Improvements in disease-specific quality of life tended to be greater in the prednisone-treated patients. Although no results demonstrated statistical significance, all four components of the Chronic Respiratory Index Questionnaire (dyspnea, fatigue, emotional function and mastery) showed a trend towards greater improvement from day 1 to day 10 for those patients treated with prednisone. The mean improvements in the CRQ scores at Day 10 for the prednisone-treated patients were 1.92, 1.78, 1.41 and 1.53 points for the dyspnea, fatigue, emotional function, and mastery domains respectively. These changes should be interpreted in the context that the minimal important difference in the change in quality of life score per item has been previously established to be 0.5, and that changes greater than 1.5 have been shown to represent large changes in quality of life.[64, 65] Therefore, although the mean improvements in CRQ scores were not significantly different for the prednisone group compared to the placebo group, it is nevertheless apparent that the prednisone-treated group experienced large positive changes over the 10 day period in 3 of the 4 domains measured by the disease-specific quality of life questionnaire. In contrast, changes observed in the placebo-treated group were more modest, with only the fatigue domain showing an improvement greater than 1.0 point over the 10 day period.

An analysis of relapse showed that the proportion of patients who experienced a relapse event was somewhat higher than expected for both treatment groups. Our previous chart review had predicted 30-day relapse proportions of 18-20%. However, thirty-day relapse proportions in this study were 45% and 25% for the placebo and prednisone groups respectively. This discrepancy in expected relapse proportions can be explained by considering that in our initial chart review a relapse was only established if the patient re-presented to the same Emergency Department. However, for the purposes of this trial, relapse was defined as an unscheduled visit to any ED, or to any physician, because of worsening dyspnea. Our higher than expected rate of relapse suggests that many patients

do not necessarily return to the ED to which they originally presented, and suggests that the problem of patient relapse may have been underestimated in previous studies which relied only on Emergency Department data to establish a definition of relapse.

This small pilot trial showed that 10 and 30 day relapse proportions tended to be lower in the prednisone group. Although relapse proportions were not statistically different between the two treatment groups, the patients in the prednisone-treated group showed an absolute risk of 30-day relapse which was 20% lower than placebo-treated patients. Similarly, the survival distributions comparing the probability of remaining relapse-free, tended to be more favourable for the prednisone-treated patients. A logistic model of risk of 30 day relapse, adjusting for potentially significant covariates, also suggested a favourable odds ratio associated with the administration of prednisone, however confidence intervals were very wide, owing to the small number of patients studied, and results were therefore not statistically significant.

This study did make use of an intention-to-treat endpoint analysis. Those patients who relapsed within the first 10 days of the trial were taken off their study medications and had the primary and secondary outcomes measured on the day of relapse. These values were counted as the day 10 value for the purpose of the analysis (ie. the last observation was carried forward). One would therefore intuitively expect that the group which contained proportionately more patients who relapsed within the first 10 days of the study might do less well with respect to the other outcome variables, and this seems to have been the case.

It is reassuring, from the investigators' standpoint that all the outcome variables tended to move concordantly in the same direction, ie. that improvements in FEV_1 mirrored improvements in dyspnea scores and disease-specific quality of life. This makes sense since previous studies have shown that there is a modest correlation between FEV_1 and these other variables.[53, 56, 66, 67]

The placebo-treated patients did demonstrate overall mean improvements in airflow obstruction, dyspnea scores, and quality-of-life scores over the 10 day period. However, the magnitude of improvement in these outcome variables was less marked than in the prednisone-treated group. Overall net improvement was not unexpected in the placebo-treated patients, since study participants did receive co-interventions such as bronchodilators and antibiotics which were administered to both treatment groups and which are known to be effective therapies for COPD exacerbation.

In summary, this pilot study involved a relatively small number of patients, and therefore did not have statistical power to show any significant difference in results between the two groups. Nevertheless, the pilot data does suggest a trend towards improved expiratory airflow, dyspnea scores, disease-specific quality of life, and relapse proportions in the prednisone-treated patients compared to those patients on placebo. Naturally, this trend could easily be reversed in a larger study, and therefore a larger trial will be needed in order to definitively establish whether prednisone is superior to placebo for outpatient therapy of COPD exacerbation.

Impact of the Pilot Study on a Larger Definitive Clinical Trial:

6.2 Determination of the Primary Outcome Variable:

Originally, the primary outcome variable for the definitive trial was to have been the percent improvement in FEV_1, and the sample size for the definitive trial was calculated to provide adequate power to detect a 20% difference in improvement in FEV_1 between the placebo and the prednisone groups. The major advantage to using the percent improvement in FEV_1 as the primary outcome variable was felt to be its feasibility, since it is objective, easy to measure and reproducible, and its sample size advantage, since it is a continuous variable which can be measured in all the study participants (as opposed to relapse which occurs in only a minority of study participants).

However, it can be argued that although the FEV_1 is an important, objectively-measured, physiologic variable, it nevertheless is a surrogate outcome measure, which may correlate with, but which cannot be said to consistently reflect the state of an individual patient's health. As such the FEV_1 suffers from many of the disadvantages of a surrogate outcome measure, including difficulties with interpretation of its meaning, since some clinicians may not be familiar with the measurement, as well as lack of acceptance, since it may not be accepted as being a meaningful outcome by some clinicians or by patients.

One of the major objectives of this pilot study was therefore to determine whether a more clinically relevant variable could serve as the primary outcome variable. Thus, the pilot study set out to obtain preliminary estimates of relapse proportions in the two treatment groups in order to determine whether patient relapse could realistically serve as the primary outcome variable for the definitive clinical trial.

Using relapse proportion as the primary outcome variable for the definitive trial would have several clear advantages. Relapse represents a well-defined clinical outcome which is understandable to patients and their physicians. It therefore should not suffer from problems with acceptance or difficulties with interpretation of its meaning. Relapse is clinically important, since by definition, a patient who relapses is one who seeks out additional medical care because of worsening dyspnea. Thus, relapse represents a well-defined means of measuring failure of treatment in this clinical

situation. Finally, relapse is an important economic outcome, since those patients who relapse would be expected to generate higher costs. The potential economic cost of relapse would be related to costs associated with a second visit to a physician, to costs due to prescription of additional medications or treatments, to possible costs associated with hospitalization of a proportion of relapsed patient, as well as to potential time lost from work for patients and their families.

The potential disadvantage to using 30-day relapse as the primary outcome variable would be its potential for inter-individual variation, since each patient's perception of dyspnea, and his/her threshold for initiating a physician visit, would be expected to be somewhat different. However, since the study format is that of a randomized controlled trial, any unmeasured potential confounders which could influence relapse rates, such as patient dyspnea thresholds or individual patient anxiety levels, should be expected to be balanced out between the two randomized treatment groups.

In summary, the proportion of patients who relapse represents a more clinically and economically relevant outcome measure than the change in FEV_1. Relapse was easy to measure in the pilot study, and it occurred with sufficient frequency in the pilot study to suggest that the definitive trial could conceivably be powered to detect a meaningful difference in relapse between the two groups. The sample size estimates which follow will illustrate how the definitive trial will be designed in order to be powered to detect a difference in patient relapse.

Impact of the Pilot Study on a Larger Definitive Clinical Trial:

6.3 Verification of Sample Size Estimates for the Larger Trial:

The sample size for the definitive clinical trial was originally calculated to ensure a power of 80% to detect a 20% difference in improvement in FEV_1 between the two treatment groups. Using percent improvement in FEV_1 as the primary outcome variable, and assuming a 20% attrition rate, it was originally estimated, using data from the trial by Thompson et al [47] that 124 patients would be needed for the definitive clinical trial (see methods section, p.39). In fact, results from the pilot study support this estimated sample size. The baseline FEV_1 for the 20 patients enrolled in our pilot study was 0.84 ± 0.28 litres and the absolute improvement in FEV_1 for the 19 patients who completed the study was 0.19 ± 0.26 litres. Both of these values are quite similar to the data from Thompson's study. Repeating the sample size calculations using our pilot data yielded an estimated sample size of 90 patients needed to find a 20% difference between improvement in FEV_1 in the placebo and prednisone groups with a two-tailed $\alpha = 0.05$ and 80% power.

However, results from the pilot study suggested that relapse occurred more commonly than previously suspected and that relapse could therefore be used as the primary outcome variable for the definitive clinical trial. In consultation with colleagues it was decided that a 20% reduction in 30-day relapse proportions would be the minimal clinically important difference that would be important to detect. From the pilot data the prednisone and placebo-treated patients had a 25% and 45% rate of 30-day relapse respectively. Using the formula for calculation of dichotomous response variables with two independent samples:

$$2N = 2^2 / (p_c - p_i)^2$$

where p_i = the event rate in the intervention group =0.25

p_c = the event rate in the control group = 0.45

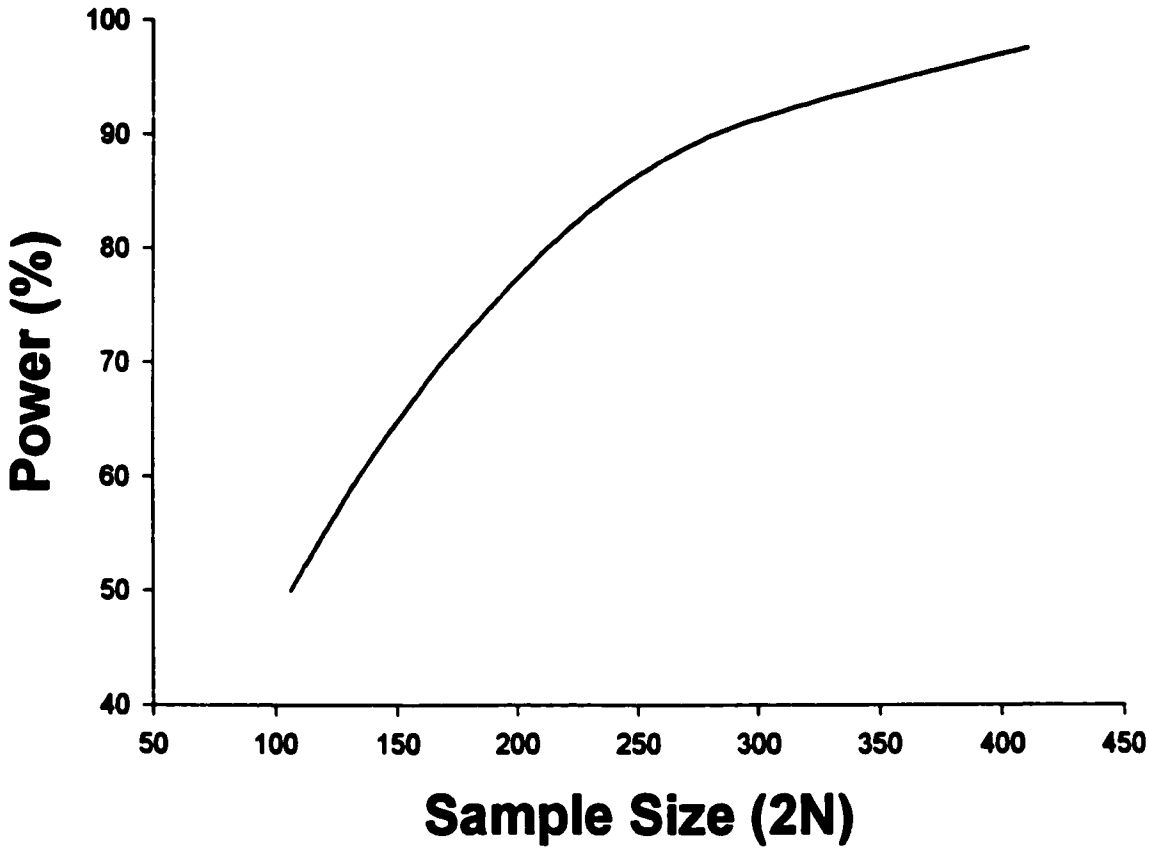
$p_a = (p_c + p_i)/2 = 0.35$

$Z_\alpha = 1.96$ and $Z_\beta = 0.84$.

2N = 176

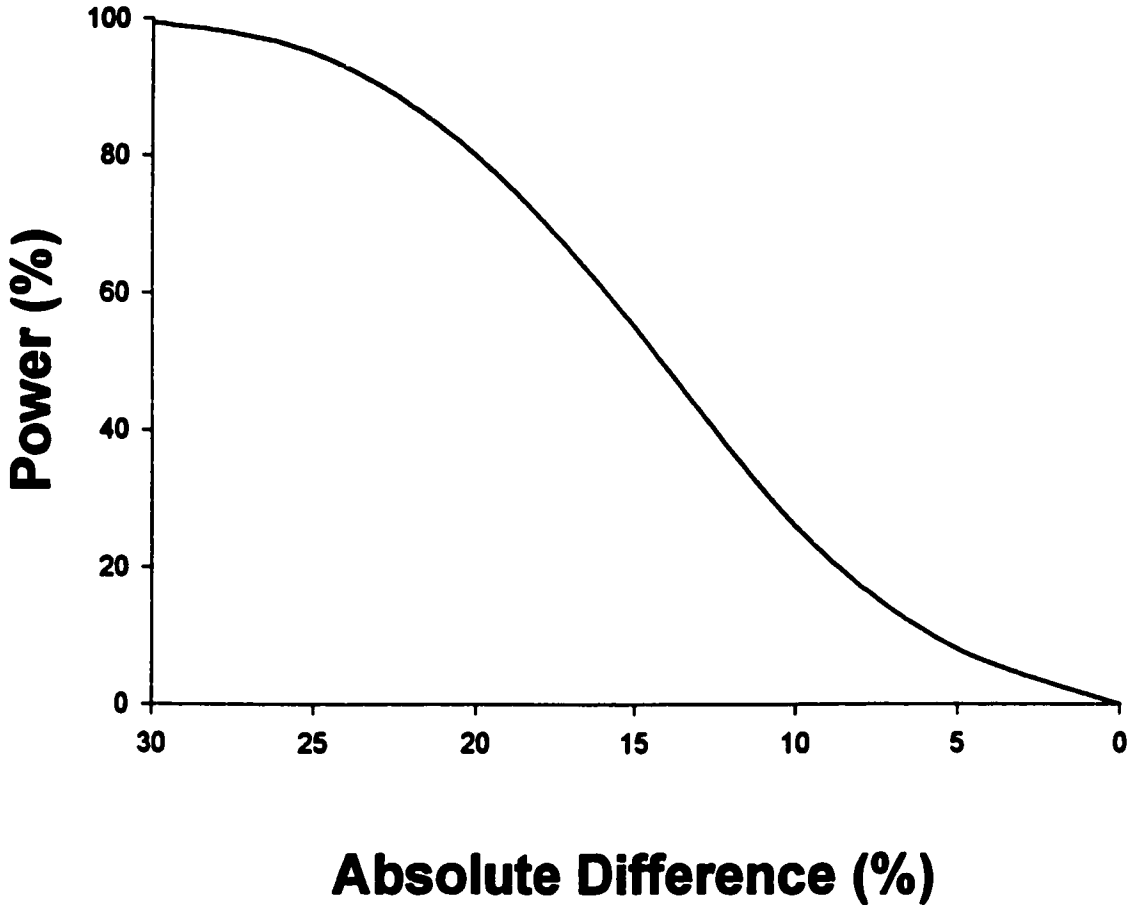
Assuming 20% attrition, 2N = 212. Therefore, 212 patients are needed to demonstrate a 20% difference in 30 day relapse rates with $\beta = 0.20$ and two-tailed $\alpha = 0.05$.

Figure 7: Graphical representation of power as a function of sample size for the definitive trial



A sample size of 212 is needed to achieve a power of 80% in order to detect an absolute difference of 20% in rates of 30-day relapse between the placebo group and the control group (assuming 20% attrition and a control group relapse rate of 45%). In order to achieve 90% power a sample size of 282 would be needed.

Figure 8: Power to Detect Absolute Differences: Total Sample of 212.



A total sample size of 212 will enable the definitive trial to detect an absolute difference in 30-day relapse rates of 20% with 80% power, and an absolute difference in relapse rates of 25% with 95% power.

The implication of changing the primary outcome variable for the definitive clinical trial is that the total sample size will need to be increased from 124 to 212 patients. Unfortunately, if 124 patients are enrolled in the larger trial (as originally was planned) this would only guarantee a power of 0.57 to detect a 20% difference in relapse proportions.

Currently neither the required number of patients, nor the financial resources, are available to mount a trial of this magnitude at only one study centre. The definitive trial will therefore need to be expanded to involve centres outside The Ottawa-Carleton area, and further financial resources will need to be obtained in order to fund a multi-centre study.

Impact of the Pilot Study on a Larger Definitive Clinical Trial:

6.4 Need for an Interim Analysis and Organization of a Data Monitoring Committee:

Originally, the definitive trial did not have a built-in planned interim analysis. It was initially felt that there was no significant risk associated with receiving placebo, since any patient who relapsed would be taken out of the study and placed on open-label prednisone. Therefore a Data Monitoring Committee and interim analyses were not felt to be needed. However, after reviewing results of this pilot study, which suggests a trend towards improved expiratory airflow, dyspnea scores, disease-specific quality of life, and relapse rates in the prednisone-treated patients, it has become clear that for ethical, scientific, and economic reasons an independent Data Monitoring Committee will need to be set up for the purpose of conducting an interim analysis. An interim analysis will need to be conducted, not only to ensure the safety of the patients, but also to ensure that the trial is not needlessly prolonged.

An interim analysis will be performed once 50% of patients have been accrued to determine if either of the two therapies is beneficial or hazardous. O'Brien-Fleming group sequential stopping rules[68, 69] were chosen to maintain an overall significance level of 0.05. Significance boundaries will be symmetrical with $\alpha = 0.005$ ($Z_I = 2.77$) for the interim analysis and $\alpha = 0.048$ for the final analysis. The Data Monitoring Committee will be blinded to treatment group (ie. treatment groups will be labelled as A or B for the purposes of the interim analysis). The Data Monitoring Committee will monitor the outcome event of interest, 30 day-relapse rate, and if this variable shows test statistics which fall outside of the stopping boundary on the interim analysis then the trial will be terminated and the null hypothesis will be rejected.

Impact of the Pilot Study on a Larger Definitive Clinical Trial:

6.5 Randomization and Data Collection:

Randomization was through central allocation of a randomization schedule and was coordinated by the Ottawa General Hospital Pharmacy Research Department. The randomization process consisted of a computer-generated random listing of the two treatment allocations blocked by groups of four, and was supposed to have been stratified by emergency department. However, when the randomization code was broken for the twenty patients enrolled in the pilot study it became apparent that randomization had not gone according to plan. Of the first eight patients enrolled at The Civic site, only three patients were randomized to treatment with prednisone (rather than four patients as would have been expected with block of four randomization). It was subsequently discovered that the Pharmacy Research Department had failed to stratify randomization by site, so that the first two patients randomized at The Civic Site were grouped in a block of four patients with two patients from the General Site.

Ultimately, this failure to stratify randomization by site did not have a large impact on the pilot study, although it did result in a minor imbalance in the number of patients randomized to placebo vs. prednisone (11 vs. 9). However, for the purposes of the larger trial, randomization will obviously be repeated, this time stratified by the three sites, as well as by the type of patient (Emergency Department patients vs. respirology patients). Although the investigators will obviously not have access to the randomization schedule, I will ensure that an independent outside auditor reviews the randomization lists before the trial begins to ensure that stratification is properly performed.

The research assistants involved in the pilot study were all trained Respiratory Therapists who were certified to do spirometric testing. In addition, all the assistants received pre-study training in ATS standards and techniques for performing proper spirometry. Nevertheless, despite this, a potential weakness of the pilot study is that it failed to include a validation of the data collection methods; specifically the pilot should have included some sort of evaluation to ensure that the individual research assistants were performing the spirometric testing accurately and that the results were reproducible. For the purposes of the larger study, a subset of twenty enrolled patients will be

independently tested by two or more research associates to ensure that the spirometric results are reproducible. Furthermore, the accuracy of the study results will be verified in these twenty patients by comparing the study results to the results of same-day spirometric testing done by certified pulmonary function technicians in the hospital pulmonary function labs.

Impact of the Pilot Study on a Larger Definitive Clinical Trial:

6.6 Classification of Patients:

The validity of this trial depended on the correct classification and selection of patients. In order to ensure validity, it was imperative that only patients with suspected COPD exacerbation, and not asthma were enrolled into the study. In acute asthma exacerbation, previous large clinical trials, and a meta-analysis, have demonstrated that outpatient steroids reduce relapse rates, reduce use of beta-agonist bronchodilators, and decrease rates of hospitalisation in Emergency Department patients.[7-9] The same has not yet been conclusively shown in COPD patients.

Proper selection of patients can be difficult since patients with asthma exacerbation often appear to be clinically indistinguishable from those patients with exacerbation of COPD. Both asthmatic and COPD patients present acutely with symptoms of dyspnea, cough, and wheezing, they often have identical signs on physical examination, and both groups show evidence of expiratory obstruction to airflow on spirometric testing.

It would be unethical to include known asthmatics into this trial since these patients should not be randomized to placebo. Furthermore, the inclusion of asthmatics would jeopardize the validity of the results since their inclusion should bias the results towards a positive treatment effect. For these reasons, it was important that the trial inclusion and exclusion criteria be rigidly designed to exclude patients with suspected asthma, even at the expense of limiting patient eligibility and to some extent, limiting generalizability of the results.

Unfortunately, no guidelines exist in the literature which provide a rigid classification system to help distinguish COPD patients from asthmatics for purposes of clinical trials. Epidemiologic studies have depended mainly on the presence of symptoms (productive cough, wheezing, and dyspnea on effort) and spirometric abnormalities for the diagnosis of COPD, however these findings are nonspecific. The situation is complicated by the fact that chronic long-standing asthma can cause irreversible airflow obstruction; an Australian study of 100 asthmatic patients showed a significant negative correlation between the duration of asthma and the highest FEV_1 which was achieved after high-dose prednisone therapy ($r= -0.47$, $p<0.001$)[70]. These results suggest that patients with longstanding asthma develop irreversible airflow obstruction, which may make them difficult to

distinguish from patients with COPD.

Epidemiologic studies have also demonstrated that physician bias may play a role in diagnostic labelling of patients with airflow obstruction. The Tucson Epidemiologic Study of Obstructive Lung Disease prospectively followed 3,239 subjects who did not have a diagnosis of obstructive airways disease for 7 years. Three hundred and fifty one of these patients developed asthma, emphysema or chronic bronchitis during the follow-up period. The investigators found that older males who presented with new symptoms of dyspnea and wheeze were more likely to be diagnosed with emphysema by their physicians than females with identical symptoms, even when smoking status was corrected for (21.8% of males were diagnosed with emphysema vs. 3.7%of females with identical symptoms, $p<0.05$ by chi-square analysis).[71] Conversely, older females were more likely to be diagnosed with asthma than older males (9.2% vs. 2.9%, $p<0.05$). This data suggests that patients may be mislabeled by their physicians.

We attempted to avoid mislabeling patients by ensuring that the study inclusion criteria conformed to, or were actually more strict, than American and British Thoracic Society guidelines for the diagnosis of COPD. Thus enrolled patients needed to have a significant smoking history (COPD, except in rare cases, does not occur in lifetime non-smokers), be older than age 35 (COPD, except in rare cases, does not occur in young patients), and meet clinical symptomatic and historical criteria for the diagnosis of COPD. Furthermore, patients needed to show spirometric evidence of significant airflow obstruction on presentation to the ED.

We attempted to exclude asthmatics from our trial population by excluding patients with a history of diagnosed asthma, patients with atopy (which is often associated with asthma), or patients with evidence of significant reversible airflow obstruction (≥20% improvement in FEV_1 post-bronchodilator). Furthermore, to ensure that the study patients met clinical criteria for diagnosis of COPD, and that potential asthmatics would be excluded, the patients were required to have had spirometric evidence of chronic airflow obstruction taken at a time of clinical stability, either before, or 1 month after entry into the trial . In this manner, we obtained a population of patients who met all the clinical and laboratory criteria for COPD, and who were very unlikely to be asthmatic.

Of the twenty patients enrolled in the pilot study, 13 had previous available spirometries done at a time of clinical stability which indicated chronic irreversible airflow obstruction consistent with

COPD. Six of the remaining seven patients who did not have accessible pre-study stable spirometries were tested 4-6 weeks after enrollment in the study, when they were clinically stable, to determine if they fulfilled criteria for chronic airflow obstruction. One patient refused this follow-up spirometric testing. Of the six patients tested, five had persistent chronic airflow obstruction, however one patient (who had been randomized to the placebo group) improved her FEV_1 from 52% of predicted on day 1 to 76% of predicted by day 10 and to 78% of predicted by day 30. According to our study criteria, this patient would not qualify as having chronic airflow obstruction since her stable FEV_1 was greater than 70% of predicted (although our study criteria are somewhat stricter than British Thoracic Society guidelines which allow for an FEV_1 of < 80% predicted as being consistent with mild COPD[2]). For the purposes of the larger trial a secondary analysis will be performed excluding such patients who are found not to fulfill study criteria for chronic airflow obstruction after completion of the 30 day trial period.

In summary, the enrollment process of the pilot study worked reasonably well, however there were 2 protocol violations. The study was able to successfully distinguish asthmatics from patients with COPD with the exception of 1 patient who was enrolled in the study and was subsequently found not to have significant chronic airflow obstruction. Thus, it appears that the pilot study was able to ensure that at least 90% of participants met strict criteria for the diagnosis of chronic airflow obstruction and COPD. Based on the pilot study's successful classification of patients it was decided that the definitive trial will continue to employ the same inclusion and exclusion criteria used in the pilot study.

The definitive trial will have a planned secondary analysis excluding those patients who are found not to fulfill study criteria for chronic airflow obstruction. However based on the pilot data, it is not expected that the validity of the primary intention-to-treat analysis for the definitive trial will be threatened by the inadvertent randomization of asthmatics.

Impact of the Pilot Study on a Larger Definitive Clinical Trial:

6.7 Referral and Recruitment Rates:

Twenty patients were recruited into the pilot study, an average of five patients per month. This level of recruitment was somewhat less than expected since the trial was projected to average a recruitment rate of 8-10 patients per month. Thus recruitment averaged approximately 60% of predicted.

Flaws in recruitment are the major cause of failure of clinical trials.[72] Recruitment often fails because investigators overestimate many-fold the pool of available patients who meet the inclusion criteria and would be willing to enroll in a particular trial.[73] For this pilot study, the pre-trial recruitment strategy included a detailed chart review with special emphasis placed on determining the proportion of available patients who met study eligibility criteria. The number of eligible patients was carefully estimated from 1996 data, and it is therefore unlikely that the pool of available, eligible patients was grossly over-estimated.

The pilot study's difficulties with patient recruitment can be traced to several sources:

1) Referral rates from the two ED's were lower than expected.
2) The "funnel effect" of recruitment- the pool of potential patients became progressively smaller as it passed through the screening and informed consent process. Ultimately, the pilot study enrolled only 20 of 67 (30%) of referred patients.

6.71 Pilot Study Referral Rates:

One major potential weakness of the pilot, and the larger study, is that patient recruitment is dependant on referrals of appropriate patients by Emergency Department staff. In the absence of active participation by Emergency Department staff the trial cannot hope to succeed.

The pilot study had 67 referrals from The Emergency Departments of The Civic and General Hospitals over the four month winter study enrollment period (see figure 1). This number of referrals was somewhat less than expected, since data from my pre-study chart review (see table 1, page 22)

had indicated that 475 visits (358 individual patients) were discharged from the two ED's for COPD exacerbation in 1996. Based on 1996 data, we had expected 158 potential visits to result in discharge over the four month period, and we had anticipated approximately 100 referrals. Study personnel were available on 24-hour call every day of the week through a central number so access to study personnel should not have affected referral rates or patterns.

Physicians in the ED were asked to perform a preliminary screen prior to telephoning study personnel. They were instructed that patients with asthma, those taking oral corticosteroids, and those patients who were being admitted to hospital were not eligible for the study. This likely had an effect on the overall number of referrals since some patients were appropriately screened out by the Emergency Department physicians and were therefore not referred.

Several early events had a negative effect on referral rates and recruitment. The trial commenced immediately before a major ice-storm hit Eastern Ontario and West Quebec. Only 5 referrals were received during the 14 day ice-storm period. Of these 5 referrals, 3 referred patients were eventually admitted to hospital, and thus became ineligible for the trial, because they lacked electrical power at home and their Emergency Department physician was therefore uncomfortable not keeping them in hospital. Similarly, other potentially eligible patients were not referred by ED physicians during this period because the physicians assumed that lack of power and poor road conditions made participation in a clinical trial too difficult for patients. Also in January, several potential patient referrals from the Ottawa Civic ED site were not received by study personnel. Ultimately it was discovered that the ED unit coordinator had written the wrong study phone number into her telephone directory. When this problem was corrected, referrals from the Civic site increased.

Study orientation sessions had involved physicians as well as all the respiratory therapists and many of the registered nurses working in the ED. RN's and respiratory therapists were encouraged to refer patients to the study, however only 4 of 67 referrals (6%) originated from these potential sources. The reason most often cited by the nurses and respiratory therapists for their low referral rates was that they frequently lacked information about the patients' diagnosis and ultimate disposition and therefore did not feel comfortable making decisions as to whether their patient would be potentially eligible for the study.

Ninety-four percent of referrals were from staff physicians or residents working in the Emergency

Department. Twenty referrals were received from residents during the first two months of study enrollment, however only four referrals were received in the last two months of the study. This failure to garner referrals from residents in March and April likely related to our failure to provide an orientation to the new residents who rotated into the ED and replaced those residents who had received a thorough study orientation in January and February.

Finally, an analysis of overall referral patterns indicated that the number of referrals was greatest from mid February to mid March when 32 referrals were received. However the number of referrals subsequently dropped, so that in April only 6 referrals were received. A subsequent review of the Emergency Department records at the Civic and General Hospitals showed that only 14 patients presented with COPD exacerbation to the two hospitals from April 10-24, 1998. Of these 14 patients, four were referred to the study, nine did not meet trial eligibility criteria, and one potentially eligible patient was missed. The unexpectedly low rate of COPD presentation in April is unexplained, however it may have been due to warmer weather and the resultant drop in viral respiratory tract infections which are known to trigger exacerbations of COPD.

6.72 Measures to Improve Study Recruitment:

Based on the results of the pilot study, we have adapted the following changes in order to improve referral rates from the Emergency Department and stimulate recruitment of patients into the definitive study. The first measure will be to ensure a greater study presence within the ED's. Posters will be placed in all the participating ED's and pocket cards will be given out to ED staff. In addition, a study co-ordinator will be hired to liaison daily with ED staff in the participating hospitals in order to promote the study amongst ED staff-members. She will attend monthly resident orientation sessions to educate new ED residents about the study. The coordinator will also be available to recruit potentially eligible patients into the study during working hours. Her duties will also involve trouble-shooting to ensure that the study is running smoothly, and that the trial is not interfering with Emergency Department routine. Finally, she will conduct bi-weekly reviews of the Emergency Department logs while the trial is ongoing to ensure that referrals are not being missed. If certain Emergency Department medical staff are discovered to be not referring patients than further

efforts will be made to educate these physicians about the importance of the trial. Hopefully, the above measures will significantly improve study referral rates above those of the pilot study.

The number of referrals will also be increased simply by adding additional study sites. The definitive trial will add 1-2 study sites in the Ottawa area (The Queensway-Carleton Hospital and possibly The Riverside Site of The Ottawa Hospital) to try to improve recruitment. Adding these additional sites in the Ottawa area will be advantageous since the trial will then have city-wide exposure, and since recruitment of additional patients from the Ottawa area should not substantially increase the cost or complexity of the trial.

In order to reach a revised enrollment goal of 212 patients within 1-2 years several study sites outside of The Ottawa-Carleton area will also need to be added. Proposed study sites include The Toronto Hospital, University Hospital in London, Ontario, and The Niagara District Regional Hospital. Funding will be applied for in order to finance the multi-center aspect of this trial.

Another option to expand recruitment will be to increase the number of potential sources of patients available for the trial. Although the trial was originally designed to evaluate the efficacy of prednisone for COPD exacerbation in patients who present to the Emergency Department, the study could easily be modified to evaluate the use of prednisone for outpatients with COPD exacerbation who present, on an urgent basis, to the Emergency Department or to their respirologist's clinic or office. Advantages to using those patients who present to their respirologist would be that the trial could tap into an otherwise unavailable pool of patients with well-established diagnoses of COPD. Furthermore, it would be relatively simple to access these patients since most of the Ottawa-area respirologists are familiar with the trial and its objectives and would likely be agreeable to referring patients. In addition, the potential clinical implications of the trial's results would be expanded since the trial would be then be generalizable to a larger population of outpatients with COPD exacerbation.

Potential disadvantages to this approach would be a threat to the internal validity of the study. Specifically, those patients who present to their respirologist might be more or less ill than those who go to the Emergency Department for their urgent health care. These patients might therefore theoretically respond differently to the study intervention and might have somewhat different event rates. However, because the eligibility criteria for the study are otherwise identical, I expect that the

two groups of patients will be clinically and biologically similar to one another. Relapse rates, defined as a revisit to any physician or to the ED because of dyspnea, should be similar in both patient groups, as should responses to treatment.

Nevertheless, randomization will be stratified so that the proportion of patients who present to their respirologist outside of the ED are balanced between the two treatment options. *A priori* subgroup analysis will be specified so that secondary analyses can be done separating the ED patients from the respirology patients, however these subgroup analyses will likely be limited by a relative lack of power.

Finally, one other method to increase recruitment rates would be to liberalize the inclusion and exclusion criteria to allow for easier passage of screened patients into the study. However I do not feel that this is a feasible option. The trial, as it is currently designed, is an efficacy study designed to enroll only those patients with outpatient COPD exacerbation who have well-documented irreversible airflow limitation, who do not have asthma, pneumonia or congestive heart failure, and who have not been recently using systemic glucocorticoids . Liberalization of the eligibility criteria could pose a potential threat to the internal validity of the trial. For example, if patients who were currently, or had recently taken, oral glucocorticoids were allowed into the trial's placebo group this would result in contamination, and would bias the results against finding a significant treatment effect. Conversely, inclusion of patients with suspected asthma could bias the results of the study towards finding a positive treatment effect, since outpatient use of prednisone has been previously demonstrated to improve airflow and relapse rates in patients with asthma exacerbation.[54] For these reasons, restricted eligibility criteria are necessary, even at the expense of diminished recruitment rates and diminished study generalizability.

Table 15: Summary: Impact of the Pilot Study on the Larger Definitive Clinical Trial.

Results of the Pilot Study	Impact on the Definitive Trial
Proportion of patients who relapsed within thirty days: 45% control group, 25% prednisone group.	1) Primary outcome variable changed from percentage improvement in FEV_1 to 30 day relapse proportions. 2) Sample size increased from 124 to 212 patients.
Trend towards improved primary and secondary outcomes in the prednisone-treated patients.	Data Monitoring Committee and an interim analysis established for larger trial.
Failure of stratification of randomization process.	Independent review of randomization schedule implemented before definitive trial.
Successful classification of COPD patients	Inclusion/exclusion criteria for definitive trial to mirror that of pilot study.
Referral and recruitment rates lower than anticipated.	1) More aggressive trial promotion instituted. 2) Expansion of the definitive trial to include additional ED's outside the study centre. 3) Recruitment of outpatients who present on an emergency basis to respirologists.

7.0 Conclusion:

The aim of this thesis was to describe the process, and the results of a randomized, placebo-controlled clinical pilot trial of oral glucocorticoids for the management of acute outpatient exacerbations of COPD. The pilot study enrolled 20 patients over a 4 month period, and was successful in meeting its primary objective, since experience with the pilot study suggests that a larger, definitive clinical trial is certainly feasible.

Results of the pilot study are intriguing since the pilot study suggests that the patients treated with prednisone trended towards greater 10-day improvements in expiratory airflow, dyspnea scores, and disease-specific quality of life measurements than the placebo-treated patients. Ten and thirty-day relapse events also tended to occur less frequently in the prednisone-treated patients compared to the placebo-treated patients. However, it should be cautioned that the overall number of patients studied in this pilot project was very small and none of the results reached levels of statistical significance. Thus, the real importance of the results of this pilot trial is that they lend justification to the need for a larger, similarly-designed definitive trial exploring this clinical issue.

The pilot study, while it was successful, did highlight the challenges of research in the Emergency Department setting. The patient referral and recruitment rates were lower than expected, proper stratification of randomization was not achieved, and the time and expense involved in running a clinical trial from the ED for 24 hours a day was considerable. Many valuable lessons were learned from this pilot study which will hopefully help to improve recruitment rates and facilitate the administration of the larger, definitive clinical trial.

Finally, results from this pilot study suggest that 30-day patient relapse is an easily measured, objective, and relatively frequent event which can be used as the primary outcome variable for the definitive clinical trial. My future research will therefore be directed towards organizing a multi-centre clinical trial to determine whether a 10 day course of oral glucocorticoids has an effect on the proportion of patients who experience a 30-day relapse in the outpatient COPD patient population.

APPENDICES

APPENDIX I

Patient Consent and Information Form

PATIENT INFORMATION FORM:

Controlled Trial of Oral Glucocorticoids in Outpatients with Acute COPD Exacerbation Who Present to the Emergency Department

OGH Principal Investigator: Dr. Shawn Aaron

PATIENT INFORMATION

COPD stands for chronic obstructive pulmonary disease. The disease is also known as chronic bronchitis or emphysema. COPD causes narrowing of the airways, making it more difficult to get air into the lungs; this can lead to symptoms of increasing breathlessness, as well as cough and chronic production of phlegm. Your treating physician in the emergency room has diagnosed you as having COPD and feels that this is responsible for your current symptoms.

Occasionally, patients with COPD develop worsening symptoms of breathlessness, cough, or phlegm production. This worsening of symptoms is called "an exacerbation" and is often caused by infections within the airways. The standard treatment of these 'exacerbations' is with inhaled puffers which dilate the airways called *ventolin* and *atrovent*, plus antibiotics.

In the past several years a few studies have been published using corticosteroids to treat exacerbations of COPD. *Prednisone* is an example of a corticosteroid. Corticosteroids are natural hormones made in the body, which work to decrease inflammation (ie. they are anti-inflammatory substances). The three studies which have been published using corticosteroids for COPD exacerbation have had conflicting results. At present time we still don't know whether corticosteroids are useful at treating exacerbations of COPD. Some doctors put patients with exacerbations of COPD on corticosteroids, and some do not.

This study is designed to examine whether treating exacerbations of COPD with a corticosteroid drug called *prednisone*, in addition to antibiotics and puffers, will help patients who are discharged from the emergency room get better faster. Patients who have an exacerbation of COPD will all be placed on an antibiotic and puffers, which are standard

therapy for COPD exacerbation. In addition, patients will be randomly assigned to one of two treatment groups: 1) treatment with *prednisone*- one tablet daily for 10 days or 2) treatment with placebo- one tablet daily for 10 days. Placebo refers to an inert compound, which is identical in appearance with the drug being tested. Each patient who volunteers for the study will have an equal chance (50-50), of receiving one of the two treatments, either prednisone or placebo. Neither you, nor your physician, will be aware of which medication you are actually getting.

Prednisone, given for 10 days, is generally well tolerated and side effects are rare. *Prednisone* can cause a slight increase in appetite and occasional trouble sleeping. In patients with diabetes, prednisone can increase the blood sugar and make diabetes more difficult to control. On very rare occasions prednisone can cause mental depression or mood swings or skin rash or hives. Generally, all these side effects are completely reversible once the *prednisone* is stopped.

If you agree to enter the study you will be asked to take your study medication once a day for 10 days. You will be asked to do a simple breathing test to measure airflow called spirometry which involves breathing out a big breath into a tube. We will also ask you to rank the degree of your symptoms on a scale and to fill out a questionnaire which asks you questions about your symptoms and your quality of life. We will then see you again 10 days after your visit to the emergency room either in the hospital clinic or, if you cannot get to the clinic, we will come to your home. At these times the breathing test and the questionnaire will be repeated. We will call you at home 30 days after your emergency room visit and ask you several questions. No other tests or procedures will be carried out as part of this study.

We will be available for you, or your doctor, to contact 24 hours a day in the event that you feel you that you are getting worse or not getting better. You will be free to withdraw from the study at any time. In the event of research-related side effects or injury, you will be provided with appropriate medical treatment. While the research sponsor has not agreed to

provide additional financial compensation, you are not waiving your legal rights to pursue such claims by agreeing to participate in this study.

CONSENT

Participation in this study is voluntary and I understand that I am free to drop out of the study at any time. I further understand that if I do not join the study, or if I drop out at any time, the quality of my care will not change.

_____ has explained the purpose of this study to me, as well as the risks and benefits involved. Any questions that I had regarding the study have been answered. I know that I may ask questions now or in the future about the study procedures. I have been assured that my medical records relating to this study will be kept confidential and that no information will be released or printed that would disclose my personal identity without my permission.

I have read and understand the consent & patient information form, and agree to participate in this study. I have received a copy of the consent form.

If I have any questions/concerns regarding the study, at any time, I know that I am free to contact the Investigators (Dr. S. Aaron 737-8198) or the Research Employee on duty 239-4675.

November 6, 1997

FORMULAIRE DE RENSEIGNEMENTS POUR LES PATIENTS

Un essai contrôlé sur les corticostéroïdes oraux chez les patients avec une crise de BPCO aïgue qui se présentent à l'urgence

Chercheur principal: Dr Shawn Aaron

Renseignement au patient

"BPCO" signifie "broncho-pneumopathie chronique obstructive". On l'appelle aussi "bronchite chronique" ou "emphysème". La BPCO amène au rétrécissement des passages respiratoires, ce qui produit de la difficulté à inspirer. Ça peut aussi conduire à un manque d'oxygène, ainsi qu'une toux et la production chronique de flegme. Le médecin vous traitant à l'urgence croit que vous avez la BPCO et que ceci vous a amené à avoir les symptômes dont vous souffrez.

De temps en temps, les personnes avec la BPCO souffrent de difficulté respiratoire, de toux ou de production de phlegme plus aiguës. Cette détérioration est appelée "exacerbation" ou "crise" et se produit à cause d'infection dans les voies respiratoires. Le traitement standard pour cette exacerbation consiste d'inhalation "puffer", soit "Ventolin" ou "Atrovent", qui ouvre les voies respiratoires ainsi que des antibiotiques.

Dans les dernières années, quelques études décrivant l'utilisation de corticostéroïdes pour le traitement d'exacerbation de BPCO furent publiées. *Prednisone* est l'un de ces corticostéroïdes. Un corticostéroïde est une hormone normale produite par le corps pour diminuer l'inflammation (i.e. une substance anti-inflammatoire). Des trois études publiées décrivant l'utilisation de corticostéroïdes contre les crises de BPCO, toutes aboutissent à des résultats différents. Donc, à date, nous ne savons pas si les corticostéroïdes aident au traitement de crises de BPCO. Certains médecins traitent leurs patients en crise de BPCO avec des corticostéroïdes, d'autres ne le font pas.

Cette étude a pour but de voir si les patients congédiés de l'urgence après traitement pour exacerbation de BPCO avec le corticostéroïde *Prednisone*, en plus d'antibiotiques et de puffer, voient une amélioration plus rapide. Tous les patients se présentant à l'urgence pour crise de BPCO seront traités avec antibiotiques et "puffer", ce qui est le traitement standard. En plus, vous serez assignés, par hasard à un traitement dans un de deux groupes: 1) traitement avec *Prednisone* - une pilule par jour pour dix jours ou 2) traitement avec placebo - une pilule par jour pour dix jours. Un placebo est une substance inactive qui paraît identique au *Prednisone*. Si vous désirez participer, vous avez 1:1 chance de recevoir le *Prednisone* ou le placebo. Ni vous, ni votre médecin, sauront quel traitement vous recevrez.

Durant un traitement de 10 jours, le *Prednisone* est généralement bien toléré; les effets secondaires sont rares. Le *Prednisone* peut augmenter l'appétit et, de temps en temps, peut aussi amener l'insomnie. Pour patients diabétiques, le *Prednisone* peut augmenter le sucre sanguin ainsi provoquant des problèmes de contrôle. Très rarement, *Prednisone* peut causer une dépression, des sautes d'humeur, une éruption cutanée passagère ou de l'urticaire. Généralement, tous ces malaises se passent quand le *Prednisone* est arrêté.

Si vous acceptez de participer à cette étude, vous devrez prendre votre médicament une fois par jour pour 10 jours. Nous vous demanderons, aussi, de subir un test respiratoire pour mesurer le débit d'air en expirant dans un tube. Vous devrez aussi remplir un questionnaire sur vos symptômes et aussi sur votre qualité de vie. Nous vous reverrons 10 jours après votre visite à l'urgence, soit à la clinique de l'hôpital ou chez vous. A ce moment là, nous vous demanderons de répéter votre test respiratoire et de répondre au questionnaire. Par la suite, nous vous téléphonerons 30 jours après votre visite à l'urgence pour vous poser plusieurs questions. Il n'y aura pas d'autres tests ou procédures à subir.

Vous, ou votre medecin, pourrez nous rejoindre 24 heures par jour au cas que vos symptômes deviendraient plus sévère ou que vous ne vous sentez pas mieux. Vous avez le droit de vous retirer de cette étude à n'importe quel temps. Dans le cas d'effets secondaires ou de blessures reliés à l'éssai, vous recevrez le traitement médical approprié. Bien que le parrain de l'essai n'ait pas accepté de fournir une indemnité financière supplémentaire, vous ne renoncez pas à

vos droits légaux relatifs à de telles demandes d'indemnité en acceptant de participer à cette étude.

CONSENTEMENT Je participe volontairement à cette étude et je comprends que je peux m'en retirer librement à tout instant. Je comprends aussi que si je ne participe pas à l'étude, ou si j'abandonne à n'importe quel moment, la qualité de mes soins ne changera pas.
_____ m'a expliqué le but de cette étude, de même que les risques et les avantages. On a répondu à toutes les questions que j'avais au sujet de l'étude. Je sais que je pourrais poser des questions, maintenant ou à un moment ultérieur, au sujet de la march à suivre de l'étude. On m'a donné l'assurance que mes dossiers médicaux se rapportant à cette étude seront tenus confidentiels et qu'aucun renseignement ne sera divulgué, ni imprimé, qui pourrait divulger mon identité sans ma permission.

J'ai lu et je comprends le contenu de la formule de consentement et les renseignements à l'intention du patient, et j'accepte de participer à cette étude. J'ai reçu une copie de la formule de consentement. Si j'ai des questions ou des préoccupations au sujet de l'étude, n'importe quand, je sais que je peux librement prendre contact ave les enquêteurs (le docteur S. Aaron, au 737-8198) ou avec l'infirmière recherchiste 239-4675.

November 17, 1997

APPENDIX II

Doctor and Patient Information Letters

Controlled Trial of Oral Glucocorticoids in Outpatients with Acute COPD exacerbation Who Present to the Emergency Department

Dear Doctor _____,

Your patient _____, has been enrolled in a study entitled "Controlled trial of oral glucocorticoids in outpatients with acute COPD exacerbation who present to the Emergency Department." This is a study that is running out of the Emergency Departments of The Ottawa Civic and General Hospitals and The Queensway-Carleton Hospital.

Your patient was enrolled in this 10 day trial when he/she was discharged from the Emergency Department on _____ after presenting with an acute COPD exacerbation.

Your patient has been provided with antibiotics for 10 days (septra, or if allergic to sulfa-doxycline), ventolin, atrovent, plus either a 10 day course of prednisone 40 mg OD, or placebo. The trial is designed to discover whether a short course of prednisone is useful for treating outpatient COPD exacerbations. The trial is double-blind and placebo-controlled which means that neither your patient, nor the study investigators know which drug the patient is actually receiving.

If your patient has enrolled in this trial within the last 30 days, and if your patient makes an urgent appointment to see you in the office because of worsening shortness of breath, or if you are seeing this patient in the Emergency Room because of worsening symptoms of shortness of breath, then we would ask that you immediately call us at **239-4675**. We will be available 24 hours a day, 7 days a week, and we promise to call you back within 3 minutes of your call.

Once you speak with us we will make arrangements to see your patient again, and we can provide you with advice about whether your patient should be treated with steroids.

If you have further questions you can call us at **239-4675** at any time, or you can page the principal study investigator, Dr. Shawn Aaron, at The Ottawa General Hospital 737-8222.

Thank you

The Acute COPD Exacerbation Investigators

Controlled Trial of Oral Glucocorticoids in Outpatients with Acute COPD exacerbation Who Present to the Emergency Department

Dear Patient,

You have consented to be enrolled in a study entitled "Controlled trial of oral glucocorticoids in outpatients with acute COPD exacerbation who present to the Emergency Department." This is a study that is running out of the Emergency Departments of The Ottawa Civic and General Hospitals and The Queensway-Carleton Hospital.

We have provided you with puffers to take for 30 days, as well as antibiotic to take for 10 days and the study medication (either prednisone or a placebo) to take once daily for 10 days. It is important that you take all these medications as prescribed since these medications are necessary in order for your breathing to improve.

If you feel that your symptoms of breathlessness are getting worse despite the medications we have given you, we would advise you to see your family doctor immediately or go to the emergency room. We would also ask you to call us at **239-4675** if this happens. We will be available 24 hours a day, 7 days a week, and we promise to call you back within 3 minutes of your call. We will make arrangements to see you in the emergency department, or in your home if necessary, on the same day.

If you need to see your doctor urgently because of shortness of breath, or you need to go to the emergency room because of shortness of breath, we would ask you to bring the "Dear Doctor" letter that we have given you to show to your doctor.

If you have further questions you can call us at **239-4675** at any time, or you can page the principal study investigator, Dr. Shawn Aaron, at The Ottawa General Hospital 737-8222.

Thank you

The Acute COPD Exacerbation Investigators

APPENDIX III

The Study Data Collection Form

Study Site: _____ **Subject Number:** _____

CASE REPORT FORM

Controlled Trial of Oral Glucocorticoids in Outpatients with Acute COPD Exacerbation

Patient Initials: _____

Hospital Identifier _____

Research Associate _____

Date of Enrollment _____
yy / mm / dd

To be signed upon completion of study:

Signature of conducting investigator : _____

Date _____
yy / mm / dd

VISIT 1 (Emergency Department visit- study day 1)

Write the date in full: (ex. June 5, 1998): _____

DEMOGRAPHY

Age: _____

Date of birth : ____/____/____ (yy mm dd) Sex: Male ____ Female ____

Height: _____ cm Weight: _____ kg

Ethnic origin : ____ Caucasian

____ Oriental

____ Black

Other, specify: _____

SMOKING HISTORY

	Yes	*No*		
Is the patient currently a smoker?	____	____		
			Years	Months
If an ex-smoker, how long has it been since patient stopped smoking ?			____	____

Smoking history (current or past):

Average number of packs of cigarettes per day _____

Number of years spent smoking _____

Number of pack years smoked _____

VISIT 1

HISTORY OF COPD

How long ago was COPD (or emphysema/chronic bronchitis) diagnosed?

_____ years ago
or
_____ unknown.

For how many years has the patient had symptoms of breathlessness?

_____ years

RECENT SYMPTOMS: (check those that patient has experienced in past 7 days) :

Increasing shortness of breath _____

Increasing cough _____

Increasing sputum production _____

Change in sputum colour _____

Fever _____

Runny nose _____

CONCURRENT MEDICATIONS

Is the patient currently using any of the following medications at home ?

	Yes	*No*
Inhaled corticosteroids (flovent, becloforte, pulmicort, beclovent)	____	____
Ipratropium	____	____
Antibiotics	____	____
Theophyline (theodur, uniphyl, etc.)	____	____
Home oxygen	____	____

List any other medications patient is currently taking:

ALLERGIES

	Yes	*No*
Is the patient allergic to sulfa drugs (septra or bactrim)?	____	____

CONCURRENT MEDICAL CONDITION

Does the patient have a history of any of the following medical conditions?

	No	Yes	
Coronary artery disease (angina, heart attack)	☐	☐	_____
Congestive heart failure	☐	☐	_____
Renal disease	☐	☐	_____
Liver disease	☐	☐	_____
Diabetes	☐	☐	_____

PREVIOUS PFT'S:

Are previous PFT's available from the chart? Y _____ N_____

If yes, record the date of the last PFT's available before today's visit: _____/_____/_____
year mo. day

Results of last PFT done before today's visit:

Post-bronchodilator:

FEV_1	% Predicted	FVC	FEV_1 / FVC
_____	_____	_____	_____

VISIT 1

EMERGENCY ROOM SPIROMETRY (done by Emerg. Personnel when patient came to Emergency Department)

Pre-bronchodilator

FEV_1	% Predicted	FVC	FEV_1/FVC
____	_____	____	_____

Bronchodilator used : 400 µg salbutamol + 80 µg ipratropium _____

or

5 mg nebulized salbutamol + 500 µg nebulized ipratropium bromide _____

Post-bronchodilator

FEV_1	% Predicted	FVC	FEV_1/FVC
____	_____	____	_____

EMERGENCY DEPARTMENT PULSE OXIMETRY

SaO_2 : _____ FiO_2: _____ or _____litres/minute

EMERGENCY DEPARTMENT ARTERIAL BLOOD GAS (if done)

pH _____ pCO_2____ pO_2_____ HCO_3_____

VISIT 1- Emergency Department

STUDY ASSESSMENTS

SPIROMETRY (to be done by yourself once patient has consented and has been randomized into the study)

FEV_1	% Predicted	FVC	FEV_1/FVC
____	_____	_____	_____

PULSE OXIMETRY **(to be done by yourself once patient has consented and has been randomized into the study)**

-do test on room air, unless the patient is on home oxygen, in which case measure saturations on the patient's usual oxygen flow rate.

SaO_2 : _____% FiO_2 :_____ or _____ litres/minute

Patient Initials: ..... **Study Number.....**

100

VISIT 1- Emergency Department

DYSPNEA ASSESSMENT

Administer the Mahler baseline dyspnea index (see handout):

	Yes	No
Has the baseline dyspnea index been administered ?	____	____

Results:

a) Functional impairment grade = _____ (range 0-4)

b) Magnitude of task grade = _____ (range 0-4)

c) Magnitude of effort grade = _____ (range 0-4)

Total score = a + b + c = _____ range (0- 12)

Patient Initials: ..... **Study Number.....**

VISIT 1

QUALITY OF LIFE QUESTIONNAIRE

	Yes	No
Has the Chronic Respiratory Questionnaire been completed ?	____	____

RESULTS:

Question #:	Score (range 1-7):	Question #:	Score (range 1-7):
4A	____	10	____
4B	____	11	____
4C	____	12	____
4D	____	13	____
4E	____	14	____
5	____	15	____
6	____	16	____
7	____	17	____
8	____	18	____
9	____	19	____

VISIT 1

CHECKLIST (For you, the study employee to check through before the patient goes home)

1. Informed consent obtained. ____

2. Study medication issued to patient. ____

3. **Is the patient allergic to sulfa or septra ?** Yes____ No____

   If yes, substitute doxycline for septra in the patient's medication bag. Done ____

4. Antibiotics (Septra or doxycycline) have been issued. ____

5. Salbutamol (2 puffs four times daily)and ipratropium bromide 3 puffs four times daily) MDIs issued. ____

6. Spacer devices issued and proper inhalation technique verified. ____

7. Inhaled corticosteroids and/or theophylline preparations in use prior to entering the trial should be continued. ____

8. Patient given a copy of the consent form, a Patient Information sheet and A Physician Information sheet. ____

9. Patient reminded to contact study personnel in case of relapse. ____

10. Patient reminded to bring medication containers (even if empty) with him to 10 day followup appointment. ____

11. Patient's primary care physician to be informed of the study. ____

DAY 3 RELAPSE ASSESSMENT
(Telephone Contact)

Date of telephone contact with patient : ____/____/____
yy mm dd

	Yes	No
Is the patient taking his study medications as prescribed?	____	____

	Yes	No
Does the patient report a worsening of breathlessness since Visit 1?	____	____

	Yes	No
A) Was there an unscheduled visit to the primary care physician because of worsening breathlessness?	____	____

If yes, what was the date : ____/____/____
yy mm dd

	Yes	No
B) Was there an unscheduled visit to the Emergency Department because of worsening breathlessness ?	____	____

If yes, what was the date of the ED visit : ____/____/____
yy mm dd

If questions A or B are checked yes, the patient must be withdrawn from the study. Day 10 study assessments must be completed.

Date of withdrawal, if applicable : ____/____/____
yy mm dd

VISIT 2
FOLLLOWUP ASSESSMENT (TO BE DONE ON DAY TEN, OR ON DAY OF PATIENT WITHDRAWAL DUE TO UNSCHEDULED PHYSICIAN VISIT)

Visit date: ____/____/____
yy mm dd

	Yes	No
Is the patient taking his study medications as prescribed?	____	____

	Yes	No
Were the study meds. and pill containers returned?	____	____

How many pills remain in the study medication container? _____

How many pills remain in the antibiotic container? _____

	Yes	No
Does the patient report a worsening of breathlessness since day 1?	____	____

	Yes	No
Was there an unscheduled visit to the primary care physician because of worsening breathlessness?	____	____

If yes, what was the date : ____/____/____
yy mm dd

	Yes	No
Was there an unscheduled visit to the Emergency Department because of worsening breathlessness ?	____	____

If yes, what was the date of the ED visit : ____/____/____
yy mm dd

VISIT 2

DAY TEN SPIROMETRY (TO BE DONE ON DAY TEN, OR ON DAY OF PATIENT WITHDRAWAL DUE TO UNSCHEDULED PHYSICIAN VISIT)

Spirometer used for day 10 testing: _____

Research Associate performing assessment: _____

Date of testing: ____/____/____
yy mm dd

How long before your pre-bronchodilator spirometry did the patient last use bronchodilators?

Hours	Minutes
_____	_____

Pre-bronchodilator spirometry results

FEV_1	% Predicted	FVC	FEV_1/FVC
____	_____	____	_____

Bronchodilator used: 200 µg (2 puffs) salbutamol
+ 40 µg (2 puffs) Ipratropium bromide _____

Other (specify): _____

Post-bronchodilator spirometry results (do 15 minutes after bronchodilators given)

FEV_1	% Predicted	FVC	FEV_1/FVC
____	_____	____	_____

VISIT 2

DAY TEN PULSE OXIMETRY (TO BE DONE ON DAY TEN, OR ON DAY OF PATIENT WITHDRAWAL DUE TO UNSCHEDULED PHYSICIAN VISIT)

-do test on room air, unless the patient is on home oxygen, in which case measure saturations on the patient's usual oxygen flow rate.

SaO_2 : _____% FiO_2 : _____or_____litres/minute

DAY TEN DYSPNEA ASSESSMENT

Administer the Mahler Transition Dyspnea Index (see handout):

RESULTS (Transition dyspnea index):

a) Change in Functional Impairment grade = _____ (range is from –3 to +3)

b) Change in Magnitude of Task grade = _____ (range is from –3 to +3)

c) Change in Magnitude of Effort grade = _____ (range is from –3 to +3)

Total Score = a + b + c = _____ (range is from –9 to +9)

VISIT 2

QUALITY OF LIFE QUESTIONNAIRE

	Yes	No
Has the Follow-up Chronic Respiratory Questionnaire been completed ?	____	____

RESULTS:

Question #:	Score (range 1-7):	Question #:	Score (range 1-7):
4A	____	10	_____
4B	____	11	_____
4C	____	12	_____
4D	____	13	_____
4E	____	14	_____
5	____	15	_____
6	____	16	_____
7	____	17	_____
8	____	18	_____
9	____	19	_____

VISIT 2

ADVERSE EVENTS

Has the patient reported any of the following adverse events since starting the study medication?

Check those adverse events reported by the patient:

Skin rash _____

Increase in appetite _____

Decrease in appetite _____

Weight gain _____

Weight loss _____

Hyperglycemia _____

Insomnia _____

Mood change _____

Depression _____

Anxiety _____

Nausea _____

Vomiting _____

Abdominal pain _____

Edema (swelling) _____

Others (list) _____

DAY 30 RELAPSE ASSESSMENT
(Telephone contact)

Date of telephone contact with patient : ____/____/____
yy mm dd

	Yes	No
Does the patient report a worsening of dyspnea since the last contact?	____	____

	Yes	No
Was there an unscheduled visit to the primary care physician because of worsening dyspnea?	____	____

If yes, what was the date : ____/____/____
yy mm dd

	Yes	No
Was there an unscheduled visit to the Emergency Department because of worsening dyspnea ?	____	____

If yes, what was the date of the ED visit : ____/____/____
yy mm dd

DAY 30 RELAPSE ASSESSMENT
(Telephone contact)

Finally, has the patient had spirometry available from the chart or the PFT lab showing chronic airflow obstruction before the study started? (see bottom of page 4 of data sheet)

Y_____ **N**_____

If yes, data collection is finished and the patient is discharged from the study.

If no, please arrange for spirometry to be done within the next several days and record results of post-bronchodilator spirometry below:

Post-bronchodilator spirometry: To be done on, or after, day 30 of the study only if no pre-study spirometry was available from the chart or the PFT labs.

Record date of spirometry: ________________
year mm day

Post – bronchodilator

FEV_1	% Predicted	FVC	FEV_1/ FVC
_____	_____	_____	_____

APPENDIX IV

Baseline and Transitional Dyspnea Indexes

Baseline Dyspnea Index:

Done on study day 1:

Patient's plaque

1. Functional Impairment- Questions:

Have you recently had to completely stop any usual activities because of shortness of breath? (Ex. Have you had to stop doing housework, walking, bathing, carrying groceries, lawnwork or shopping, because of shortness of breath?)
If yes list up to 3 activities recently stopped.

Est-ce que vous avez dû récemment cesser complètement certaines de vos activités habituelles à cause de l'essoufflement?
(P. Ex.: Avez-vous dû cesser de faire le ménage, de marcher, de prendre un bain ou une douche , de porter les provisions, de vous occuper de la pelouse ou de faire vos emplettes, parce que vous étiez trop essoufflé(e)?)
Dans l'affirmative, veuillez nommer au plus 3 activities que vous avez dû cesser dernièrement.

If patient answers no, ask the next question:

Have you recently had to reduce any of your usual activities because of shortness of breath? (Ex. Have you had to reduce your housework, walking, bathing, carrying groceries, lawnwork or shopping, because of shortness of breath?).
If yes list up to 3 activities recently reduced.

Est-ce que vous avez dû réduire dernièrement le niveau de certaines de vos activités habituelles á cause de l'essoufflement?
(P.ex.: Avez-vous dû réduire votre niveau d'activitié pour ce qui esst de faire le ménage, de marcher. De prendre un bain ou une douche, de porter les provisions, de vous occuper de la pelouse ou de faire vos emplettes, parce ce que vous étiez trop essoufflé(e)?)
Dans l'affirmative, veuillez nommer au plus 3 activitiés que vous avez dû réduire dernièrement.

Now ask two more questions related to work activities:

Have you had to stop working because of shortness of breath?
Avez-vous dû cesser de travailler à cause de l'essoufflement?

If you are retired, do you think that you could still work at your last job, or would you be too short of breath to work at your last job?
Si vous êtes à retraite, pensez-vous que vous seriez encore capable de travailler à votre dernier emploi, ou croyez-vous que vous seriez trop essoufflé(e) pour faire ce travail?

Baseline Dyspnea Index

1. Functional Impairment- Grading

Based on the answers to the previous questions grade the patient's functional impairment category as follows:

Grade 4- *No impairment*- Patient is able to carry out his usual activities and occupation without shortness of breath.

Grade 3- *Slight impairment*- No activities have been abandoned but some activities have been reduced.

Grade 2- *Moderate impairment*- Patient has changed jobs *or* has recently stopped at least one usual activity due to shortness of breath.

Grade 1- *Severe impairment*- Patient is unable to work *or* has given up most usual activities due to shortness of breath.

Grade 0- *Very severe impairment*- Patient is unable to work *and* has given up most usual activities due to shortness of breath.

W: Amount Uncertain - Patient is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorized.

X: Unknown - Information unavailable regarding impairment

Y: Impaired for reasons other than shortness of breath - For example muskuloskeletal problems or chest pain.

Baseline Dyspnea Index

2. Magnitude of task- Questions and Grading

Are you currently short of breath sitting, lying down or at rest? *Á l'heure actuelle, ressentez-vous de l'essoufflement quand vous êtes au repos ou en position assise ou couchée*?

If yes- grade 0. If no, then continue and ask next question>

Do you currently become short of breath walking, washing or standing? *Á l'heure actuelle, ressentez -vous de l'essoufflement quand vous marchez, vous lavez ou vous tenez debout?*

If yes - grade 1. If no, then continue and ask next question>

Do you currently become short of breath walking uphill, climbing less than 3 flights of stairs, or carrying a light load on level ground? *Á l'heure actuelle, ressentez-vous de l'essoufflement quand vous montez une côte ou moins de 3 escaliers ou quand vous transportez de légers fardeaux sur un terrain plat?*

If yes- grade 2. If no, then continue and ask next question>

Do you currently become short of breath walking up a steep hill, climbing more than 3 flights of stairs, or carrying a moderate load on level ground? *Á l'heure actuelle, ressentez-vous de l'essoufflement quand vous montez une pente raide ou plus de 3 escaliers ou quand vous transportez un fardeau moyennement lourd sur un terrain plat?*

If yes- grade 3. If no, then continue and ask next question>

Do you currently become short of breath only when carrying very heavy loads on level ground, running, or carrying a light load uphill? *Á l'heure actuelle, ressentez-vous de l'essoufflement uniquement quand vous transportez un fardeau très lourd sur un terrain plat, quand vous courez ou quand vous transportez un léger fardeau sur un terrain en pente?*

If yes- grade 4.

W: Amount Uncertain - Patient's ability to perform tasks is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorized.

X: Unknown - Information unavailable regarding limitation of magnitude of task

Y: Impaired for reasons other than shortness of breath - For example muskuloskeletal problems or chest pain.

3. Magnitude of effort- Questions and Grading

Magnitude of effort:

Ask the patient the most strenuous task he can perform for at least 5 minutes: *Demander quelle est la tâche la plus fatigante que le (la) patient(e) peut effecteur pendant au moins 5 minutes.*
Write it in here:

_____

Then ask the patient the following questions:

When you _____(insert task here) can you do it *briskly*, without pausing because of shortness of breath and without slowing down to rest? *Quand vous _____(insérer la tâche), pouvez-vous le faire rapidement, sans vous arrêter pour reprendre votre souffle et sans ralinter pour vous reposer?* **If yes- grade 4**, if no, then continue and ask next question>

When you _____(insert task here) can you do it *slowly* but without pausing or stopping to catch your breath? *Quand vous_____ (insérer la tâche), pouvez-vous le faire lentement, mais sans vous arrêter pour reprendre votre souffle?*
If yes- grade 3, if no, then continue and ask next question>

When you _____(insert task here) can you do it *slowly* and do you need to pause once or twice to catch your breath? *Quand vous_____(insérer la tâche), pouvez-vou le faire lentement, en vous arrêtant une ou deux fois pour reprendre votre souffle?*
If yes- grade 2, if no, then continue and ask next question>

When you _____(insert task here) can you do it *slowly* and do you need to pause many times to catch your breath? *Quand vous_____(insérer la tâche), pouvez-vous le faire lentement, en vous arrêtant de nombreuses fois pour reprendre votre souffle?*
If yes- grade 1, if no, then continue and ask next question>

Can you not do any task, ie. Are you short of breath while lying, sitting or standing? *Est-ce que vous ne pouvez faire aucune tâche , c.-à-d. êtes-vous essoufflé(e) quand vous êtes en position couchée, assise ou debout?*

If yes- grade 0

W: Amount Uncertain - Patient exertional ability is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorized.

X: Unknown - Information unavailable regarding limitation of effort
Y: Impaired for reasons other than shortness of breath - For example muskuloskeletal problems or chest pain.

Results:

Baseline Dyspnea Index:

a) Functional Impairment grade (page 2)= _____ (range 0 - 4)

b) Magnitude of Task grade (page 3)= _____ (range 0 - 4)

c) Magnitude of Effort grade (page 4) = _____ (range 0 - 4)

Total = a+b+c = _____ (range 0 - 12)

Signature_____ Date_____

Transition Dyspnea Index

Done on study day 10:

1) Change in Functional Impairment- Questions:

Ask the patient to recall his/her breathlessness at the baseline visit in the Emergency Department and provide him with his previous response from page 1: (ex. 10 days ago you had to reduce your housework load and you had to stop carrying groceries and stop taking baths because of your shortness of breath.)

Questions:

Since the last time we spoke 10 days ago have you noticed an improvement in your activity level?

Y_____ N_____

Depius notre dernière entrevue, il y a 10 jours, avez-vous remarqué une amé lioration pour ce qui est de notre niveau d'activité?

*O*_____ *N*_____

If patient answers yes then ask:

Are there activities you couldn't do 10 days ago that you now can do again?

Y a-t-il des activités que vous étiez incapable de faire il y a 10 jours et que vous pouvez effecteur maintenant?

Are there activities you had to reduce 10 days ago which you now can do again normally?

Y a-t-il des activités que vous aviez dû réduire il y a 10 jours et que vous pouvez faire normalement maintenant?

Have you been able to go back to work since I last spoke with you 10 days ago?

Avez-vous pu retourner au travail depuis notre entrevue il y a 10 jours?

If the patient answers no ask:

Are there activities you have had to stop doing over the last 10 days because of shortness of breath? *Y a-t-il des activités que vous avez dû cesser au cours des 10 derniers jours à cause de l'essoufflement?*

Have you had to reduce doing any activities over the last 10 days because of shortness of breath? *Y a-t-il des activités que vous avez dû réduire au cours des 10 derniers jours à cause de l'essoufflement?*

Have you had to stop working because of shortness of breath since I last spoke with you 10 days ago? *Avez-vous dû cesser de travaillller à cause de l'essoufflement depuis notre entrevue il y a 10 jours?*

1) Change in Functional Impairment- Grading:

Based on the above answers, grade change in functional impairment as:

-3 Major deterioration

Formerly working and has had to stop working and has completely stopped some of usual activities due to shortness of breath.

-2 Moderate deterioration

Formerly working and has had to stop working or has completely stopped some of usual activities due to shortness of breath.

-1 Minor deterioration

Has changed to a lighter job or has reduced activity level due to shortness of breath.

0 No change

No change in activity level.

+1 Minor improvement

Able to resume work at a reduced pace, or has resumed some activities with more vigor than previously due to improvement in shortness of breath.

+2 Moderate improvement

Able to return to work at nearly usual pace or able to return to most activities with moderate restriction only.

+3 Major improvement

Able to return to work at former pace and able to return to full activities with only mild restriction due to improvement of shortness of breath.

Z: Further impairment for reasons other than shortness of breath.	Subject has stopped working, reduced work, or given up or reduced other activities for other reasons. For example, other medical problems, being laid off from work, etc.

2) Change in Magnitude of Task - Questions: 118

Are you currently short of breath sitting, lying down or at rest? *À l'heure actuelle, ressentez-vous de l'essoufflement quand vous êtes au repos ou en position assise ou couchée?*

If yes- grade 0. If no, then continue and ask next question>

Do you currently become short of breath walking, washing or standing? *À l'heure actuelle, ressentez-vous de l'essoufflement quand vous marchez, vous lavez ou vous tenez debout?*

If yes - grade 1. If no, then continue and ask next question>

Do you currently become short of breath walking uphill, climbing less than 3 flights of stairs, or carrying a light load on level ground? *À l'heure actuelle, ressentez-vous de l'essoufflement quand vous montez une côte ou moins de 3 escaliers ou quand vous transportez un léger fardeau sur un terrain plat?*

If yes- grade 2. If no, then continue and ask next question>

Do you currently become short of breath walking up a steep hill, climbing more than 3 flights of stairs, or carrying a moderate load on level ground? *À l'heure actuelle, ressentez-vous de l'essoufflement quand vous montez une pente raide ou plus de 3 escaliers ou quand vous transportez un fardeau moyennement lourd sur un terrain plat?*

If yes- grade 3. If no, then continue and ask next question>

Do you currently become short of breath only when carrying very heavy loads on level ground, running, or carrying a light load uphill? *À l'heure actuelle, ressentez-vous de l'essoufflement uniquement quand vous transportez un fardeau très lourd sur un terrain plat, quand vous courez ou quand vous transportez un léger fardeau sur un terrain en pente?*

If yes- grade 4.

2) Change in Magnitude of Task - Grading:

Now, record the patient's magnitude of task grade from baseline 10 days ago:

Magnitude of task grade at baseline ten days ago = _____ (from page 3)

Magnitude of task grade today = _____

What has been the patient's change in grade from baseline?

-3: Major deterioration:	if he has deteriorated 2 grades or greater from baseline. (ex. If ten days ago he scored a grade 3 on magnitude of task and today he scores grade 1 or 0)
-2: Moderate deterioration:	if he has deteriorated 1 grade from baseline.
-1: Minor deterioration:	if he has deteriorated within grade, but has not changed grades.
0: *No change*	
+1: *Minor improvement:*	Has improved within grade, but has not changed grades.
+2: *Moderate improvement:*	Has improved one grade from baseline.
+3: *Major improvement:*	Has improved two grades or greater from baseline.
Z: Further impairment for reasons other than shortness of breath.	Subject has reduced exertional capacity, but not related to shortness of breath. For example, musculoskeletal problem or chest pain.

3) Change in Magnitude of Effort- Questions: 120

Remind the patient of the most strenuous 5 minute task which he said that he could do ten days ago and remind him of his score ten days ago.

(ex. 10 days ago the most strenuous 5 minute task you said that you could do was _____ and you indicated you could do it slowly and that you would need to pause once or twice to catch your breath.)
(P.ex.: Il y a 10 jours, vous nous dit que _____ était la tâche la plus fatigante que vous pouviez faire pendant 5 minutes, en précisant que vous pouviez le faire lentement, en vous arrêtant une ou deux fois pour reprendre votre souffle.)

Now ask:

Compared to 10 days ago do you think that you would find _____ (insert the task here) to be easier or harder?
Comparativement à 10 jours plus tôt, pensez-vous qu'il serait plus facile ou plus difficile de _____(insérer la tâche)?

Could you do _____ (insert the task here) faster than you could 10 days ago, or would you have to go slower to avoid shortness of breath?
Pourriez-vous _____(insérer la tâche) plus rapidement qu'il y a 10 jours , ou deviez-vous le faire plus lentement pour éviter de devenir essoufflé(e)?

Would you need to take more pauses now compared to ten days ago, or fewer pauses?
Pensez-vous que vous auriez besoin d'arrêter plus souvent ou moins souvent qu'il y a 10 jours?

3) Change in Magnitude of Effort-Grading: 121

Now grade the change in magnitude of effort:

-3: *Major deterioration*	Patient must perform task **much slower** to avoid shortness of breath. Task now take 50 -100% longer to complete than required at baseline.
-2: *Moderate deterioration*	Patient can do task as quickly as before but requires more pauses compared to baseline.
-1: *Minor deterioration*	Does not require more pauses, but does task at a slightly slower pace to avoid shortness of breath.
0: *No change*	No change
+1: *Minor improvement*	Able to carry out task somewhat more rapidly than previously
+2: *Moderate improvement*	Able to carry out task with fewer pauses and somewhat more rapidly without shortness of breath.
+3: *Major improvement*	Task can be performed 50-100% more rapidly than at baseline, few, if any, pauses.
Z: *Further impairment for reasons other than shortness of breath.*	Subject has reduced exertional capacity, but not related to shortness of breath. For example, musculoskeletal problem or chest pain.

Results:

Transition Dyspnea Index:

a) Change in Functional Impairment grade (page 7) =

_____ (range is from -3 to +3)

b) Change in Magnitude of Task grade (page 9)=

_____ (range is from -3 to +3)

c) Change in Magnitude of Effort grade (page 11) =

_____ (range is from -3 to +3)

Total score = a+b+c = _____ (range is from -9 to +9)

Signature _____ Date_____

APPENDIX V

The Chronic Respiratory Questionnaire

CHRONIC RESPIRATORY QUESTIONNAIRE

FIRST ADMINISTRATION, 7 POINT SCALE

INTERVIEWER FORM

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This questionnaire is designed to find out how you have been feeling during the last 10 days . You will be asked about how short of breath you have been, how tired you have been feeling and how your mood has been.

1. I would like you to think of the activities that you have done during the last 10 days that have made you feel short of breath. These should be activities which you do frequently and which are important to your day-to-day life. Please list as many activities as you can that you have done during the last 10 days that have made you feel short of breath.

   [CIRCLE THE NUMBER ON THE ANSWER SHEET ADJACENT TO EACH ACTIVITY MENTIONED. IF AN ACTIVITY MENTIONED IS NOT ON THE LIST, WRITE IT IN, IN THE RESPONDENT'S OWN WORDS, IN THE SPACE PROVIDED.]

   Can you think of any other activities you have done during the last 10 days that have made you feel short of breath?

   [RECORD ADDITIONAL ITEMS]

2. I will now read a list of activities which make some people with lung problems feel short of breath. I will pause after each item long enough for you to tell me if you have felt short of breath doing that activity during the last 10 days . If you haven't done the activity during the last 10 days , just answer "NO". The activities are:

   [READ ITEMS, OMITTING THOSE WHICH RESPONDENT HAS VOLUNTEERED SPONTANEOUSLY. PAUSE AFTER EACH ITEM TO GIVE RESPONDENT A CHANCE TO INDICATE WHETHER S/HE HAS BEEN SHORT OF BREATH WHILE PERFORMING THAT ACTIVITY DURING THE LAST WEEK. CIRCLE THE NUMBER ADJACENT TO APPROPRIATE ITEMS ON ANSWER SHEET.]

1. BEING ANGRY OR UPSET
2. HAVING A BATH OR SHOWER
3. BENDING
4. CARRYING, SUCH AS CARRYING GROCERIES
5. DRESSING
6. EATING
7. GOING FOR A WALK
8. DOING YOUR HOUSEWORK
9. HURRYING
10. MAKING A BED
11. MOPPING OR SCRUBBING THE FLOOR
12. MOVING FURNITURE
13. PLAYING WITH CHILDREN OR GRANDCHILDREN
14. PLAYING SPORTS
15. REACHING OVER YOUR HEAD
16. RUNNING, SUCH AS FOR A BUS
17. SHOPPING
18. WHILE TRYING TO SLEEP
19. TALKING
20. VACUUMING
21. WALKING AROUND YOUR OWN HOME
22. WALKING UPHILL
23. WALKING UPSTAIRS
24. WALKING WITH OTHERS ON LEVEL GROUND
25. PREPARING MEALS

A) Of the items which you have listed, which is the most important to you in your day-to-day life? I will read through the items, and when I am finished, I would like you to tell me which is the most important.

[READ THROUGH ALL ITEMS SPONTANEOUSLY VOLUNTEERED AND THOSE FROM THE LIST WHICH PATIENT MENTIONED]

Which of these items is most important to you in your day-to-day life?

[LIST ITEMS ON RESPONSE SHEET]

B) Of the remaining items, which is the most important to you in your day-to-day life? I will read through the items, and when I am finished, I would like you to tell me which is the most important.

[READ THROUGH REMAINING ITEMS]

Which of these items is most important to you in your day-to-day life?

[LIST ITEMS ON RESPONSE SHEET]

C) Of the remaining items, which is most important to you in your day-to-day life?

[LIST ITEMS ON RESPONSE SHEET]

D) Of the remaining items, which is the most important to you in your day-to-day life?

[LIST ITEMS ON RESPONSE SHEET]

E) Of the remaining items, which is the most important to you in your day-to-day life?

[LIST ITEMS ON RESPONSE SHEET]

[FOR ALL SUBSEQUENT QUESTIONS, ENSURE RESPONDENT HAS APPROPRIATE RESPONSE CARD IN FRONT OF THEM BEFORE STARTING QUESTION]

4. I would now like you to describe how much shortness of breath you have experienced during the last 10 days while doing the five most important activities you have selected.

A) Please indicate how much shortness of breath you have had during the last 10 days: while **[INTERVIEWER: INSERT ACTIVITY LISTED IN 3A]** by choosing one of the following options from the card in front of you:
[GREEN CARD]

1 EXTREMELY SHORT OF BREATH
2 VERY SHORT OF BREATH
3 QUITE A BIT SHORT OF BREATH
4 MODERATE SHORTNESS OF BREATH
5 SOME SHORTNESS OF BREATH
6 A LITTLE SHORTNESS OF BREATH
7 NOT AT ALL SHORT OF BREATH

B) Please indicate how much shortness of breath you have had during the last 10 days while **[INTERVIEWER: INSERT ACTIVITY LISTED IN 3B]** by choosing one of the following options from the card in front of you. **[GREEN CARD]**

1 EXTREMELY SHORT OF BREATH
2 VERY SHORT OF BREATH
3 QUITE A BIT SHORT OF BREATH
4 MODERATE SHORTNESS OF BREATH
5 SOME SHORTNESS OF BREATH
6 A LITTLE SHORTNESS OF BREATH
7 NOT AT ALL SHORT OF BREATH

C) Please indicate how much shortness of breath you have had during the last **10 days** while **[INTERVIEWER: INSERT ACTIVITY LISTED IN 3C]** by choosing one of the following options from the card in front of you. **[GREEN CARD]**

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1 **EXTREMELY SHORT OF BREATH**
2 **VERY SHORT OF BREATH**
3 **QUITE A BIT SHORT OF BREATH**
4 **MODERATE SHORTNESS OF BREATH**
5 **SOME SHORTNESS OF BREATH**
6 **A LITTLE SHORTNESS OF BREATH**
7 **NOT AT ALL SHORT OF BREATH**

D) Please indicate how much shortness of breath you have had during the last **10 days** while **[INTERVIEWER: INSERT ACTIVITY LISTED IN 3D]** by choosing one of the following options from the card in front of you. **[GREEN CARD]**

1 **EXTREMELY SHORT OF BREATH**
2 **VERY SHORT OF BREATH**
3 **QUITE A BIT SHORT OF BREATH**
4 **MODERATE SHORTNESS OF BREATH**
5 **SOME SHORTNESS OF BREATH**
6 **A LITTLE SHORTNESS OF BREATH**
7 **NOT AT ALL SHORT OF BREATH**

E) Please indicate how much shortness of breath you have had during the last **10 days** while **[INTERVIEWER: INSERT ACTIVITY LISTED IN 3E]** by choosing one of the following options from the card in front of you. **[GREEN CARD]**

1 **EXTREMELY SHORT OF BREATH**
2 **VERY SHORT OF BREATH**
3 **QUITE A BIT SHORT OF BREATH**
4 **MODERATE SHORTNESS OF BREATH**
5 **SOME SHORTNESS OF BREATH**
6 **A LITTLE SHORTNESS OF BREATH**
7 **NOT AT ALL SHORT OF BREATH**

In general, how much of the time during the last **10 days** have you felt frustrated or impatient? Please indicate how often during the last **10 days** you have felt frustrated or impatient by choosing one of the following options from the card in front of you. **[BLUE CARD]**

1 **ALL OF THE TIME**
2 **MOST OF THE TIME**
3 **A GOOD BIT OF THE TIME**
4 **SOME OF THE TIME**
5 **A LITTLE OF THE TIME**
6 **HARDLY ANY OF THE TIME**
7 **NONE OF THE TIME**

How often during the last **10 days** did you have a feeling of fear or panic when you had difficulty getting your breath? Please indicate how often you had a feeling of fear or panic when you had difficulty getting your breath by choosing one of the following options from the card in front of you. **[BLUE CARD]**

1 **ALL OF THE TIME**
2 **MOST OF THE TIME**
3 **A GOOD BIT OF THE TIME**
4 **SOME OF THE TIME**
5 **A LITTLE OF THE TIME**
6 **HARDLY ANY OF THE TIME**
7 **NONE OF THE TIME**

What about fatigue? How tired have you felt over the last **10 days** ? Please indicate how tired you have felt over the last **10 days** by choosing one of the following options from the card in front of you. **[ORANGE CARD]**

1 **EXTREMELY TIRED**
2 **VERY TIRED**
3 **QUITE A BIT OF TIREDNESS**
4 **MODERATELY TIRED**
5 **SOMEWHAT TIRED**
6 **A LITTLE TIRED**
7 **NOT AT ALL TIRED**

How often during the last **10 days** have you felt embarrassed by your coughing or heavy breathing? Please indicate how much of the time you felt embarrassed by your coughing or heavy breathing by choosing one of the following options from the card in front of you. **[BLUE CARD]**

1 **ALL OF THE TIME**
2 **MOST OF THE TIME**
3 **A GOOD BIT OF THE TIME**
4 **SOME OF THE TIME**
5 **A LITTLE OF THE TIME**
6 **HARDLY ANY OF THE TIME**
7 **NONE OF THE TIME**

In the last **10 days** , how much of the time did you feel very confident and sure that you could deal with your illness? Please indicate how much of the time you felt very confident and sure that you could deal with your illness by choosing one of the following options from the card in front of you. **[YELLOW CARD]**

1 **NONE OF THE TIME**
2 **A LITTLE OF THE TIME**
3 **SOME OF THE TIME**
4 **A GOOD BIT OF THE TIME**
5 **MOST OF THE TIME**
6 **ALMOST ALL OF THE TIME**
7 **ALL OF THE TIME**

How much energy have you had in the last **10 days** ? Please indicate how much energy you have had by choosing one of the following options from the card in front of you. **[PINK CARD]**

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1 **NO ENERGY AT ALL**
2 **A LITTLE ENERGY**
3 **SOME ENERGY**
4 **MODERATELY ENERGETIC**
5 **QUITE A BIT OF ENERGY**
6 **VERY ENERGETIC**
7 **FULL OF ENERGY**

In general, how much of the time did you feel upset, worried, or depressed during the last **10 days**? Please indicate how much of the time you felt upset, worried, or depressed during the past **10 days** by choosing one of the following options from the card in front of you. **[BLUE CARD]**

1 **ALL OF THE TIME**
2 **MOST OF THE TIME**
3 **A GOOD BIT OF THE TIME**
4 **SOME OF THE TIME**
5 **A LITTLE OF THE TIME**
6 **HARDLY ANY OF THE TIME**
7 **NONE OF THE TIME**

How often during the last **10 days** did you feel you had complete control of your breathing problems? Please indicate how often you felt you had complete control of your breathing problems by choosing one of the following options from the card in front of you. **[YELLOW CARD]**

1 **NONE OF THE TIME**
2 **A LITTLE OF THE TIME**
3 **SOME OF THE TIME**
4 **A GOOD BIT OF THE TIME**
5 **MOST OF THE TIME**
6 **ALMOST ALL OF THE TIME**
7 **ALL OF THE TIME**

How much of the time during the last **10 days** did you feel relaxed and free of tension? Please indicate how much of the time you felt relaxed and free of tension by choosing one of the following options from the card in front of you. **[YELLOW CARD]**

1 **NONE OF THE TIME**
2 **A LITTLE OF THE TIME**
3 **SOME OF THE TIME**
4 **A GOOD BIT OF THE TIME**
5 **MOST OF THE TIME**
6 **ALMOST ALL OF THE TIME**
7 **ALL OF THE TIME**

14. How often during the last **10 days** have you felt low in energy? Please indicate how often during the last **10 days** you have felt low in energy by choosing one of the following options form the card in front of you. **[BLUE CARD]**

129

1 **ALL OF THE TIME**
2 **MOST OF THE TIME**
3 **A GOOD BIT OF THE TIME**
4 **SOME OF THE TIME**
5 **A LITTLE OF THE TIME**
6 **HARDLY ANY OF THE TIME**
7 **NONE OF THE TIME**

15. In general, how often during the last **10 days** have you felt discouraged or down in the dumps? Please indicate how often during the last **10 days** you felt discouraged or down in the dumps by choosing one of the following options from the card in front of you. **[BLUE CARD]**

1 **ALL OF THE TIME**
2 **MOST OF THE TIME**
3 **A GOOD BIT OF THE TIME**
4 **SOME OF THE TIME**
5 **A LITTLE OF THE TIME**
6 **HARDLY ANY OF THE TIME**
7 **NONE OF THE TIME**

6. How often during the last **10 days** have you felt worn out or sluggish? Please indicate how much of the time you felt worn out or sluggish by choosing one of the following options form the card in front of you. **[BLUE CARD]**

1 **ALL OF THE TIME**
2 **MOST OF THE TIME**
3 **A GOOD BIT OF THE TIME**
4 **SOME OF THE TIME**
5 **A LITTLE OF THE TIME**
6 **HARDLY ANY OF THE TIME**
7 **NONE OF THE TIME**

7. How happy, satisfied, or pleased have you been with your personal life during the last **10 days**? Please indicate how happy, satisfied or pleased you have been by choosing one of the following options from the card in front of you. **[GREY CARD]**

1 **VERY DISSATISFIED, UNHAPPY MOST OF THE TIME**
2 **GENERALLY DISSATISFIED, UNHAPPY**
3 **SOMEWHAT DISSATISFIED, UNHAPPY**
4 **GENERALLY SATISFIED, PLEASED**
5 **HAPPY MOST OF THE TIME**
6 **VERY HAPPY MOST OF THE TIME**
7 **EXTREMELY HAPPY, COULD NOT BE MORE SATISFIED OR PLEASED**

How often during the last **10 days** did you feel upset or scared when you had difficulty getting your breath? Please indicate how often during the past **10 days** you felt upset or scared when you had difficulty getting your breath by choosing one of the following options from the card in front of you. **[BLUE CARD]**

130

1 **ALL OF THE TIME**
2 **MOST OF THE TIME**
3 **A GOOD BIT OF THE TIME**
4 **SOME OF THE TIME**
5 **A LITTLE OF THE TIME**
6 **HARDLY ANY OF THE TIME**
7 **NONE OF THE TIME**

In general, how often during the last **10 days** have you felt restless, tense, or uptight? Please indicate how often you have felt restless, tense, or uptight by choosing one of the following options from the card in front of you. **[BLUE CARD]**

1 **ALL OF THE TIME**
2 **MOST OF THE TIME**
3 **A GOOD BIT OF THE TIME**
4 **SOME OF THE TIME**
5 **A LITTLE OF THE TIME**
6 **HARDLY ANY OF THE TIME**
7 **NONE OF THE TIME**

CHRONIC RESPIRATORY QUESTIONNAIRE

FOLLOW-UP, 7 POINT SCALE, INFORMED 131

INTERVIEWER FORM

You have previously completed a questionnaire(s) telling us about how you were feeling and how your lung disease was affecting your life. This is a follow-up questionnaire designed to find out how you have been getting along during the last 10 days.

When you are answering the questions this time I will tell you the answer you gave us the last time. I would like you to give your answer today keeping in mind what you said the last time. For example, let's say that last time I asked you how short of breath you were while climbing stairs **[GIVE RESPONDENT GREEN CARD]** and you said "4 Moderate shortness of breath". If you were exactly the same today, you would answer 4 once again. If you were **more** short of breath you would choose 1, 2, or 3 and if you were **less** short of breath you would choose 5, 6, or 7.

[FOR QUESTIONS 4A TO 4E INSERT ACTIVITIES 3A TO 3E FROM FIRST ADMINISTRATION ANSWER SHEET]

4. I would now like you to describe how much shortness of breath you have experienced during the last 10 days while doing each of the five most important activities you have selected.

A) Please indicate how much shortness of breath you have had during the last 10 days while **[INTERVIEWER: INSERT ACTIVITY LISTED IN 3A]** by choosing one of the following options from the card in front of you, keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [GREEN CARD]**

B) Please indicate how much shortness of breath you have had during the last 10 days while **[INTERVIEWER: INSERT ACTIVITY LISTED IN 3B]** by choosing one of the following options from the card in front of you, keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [GREEN CARD]**

C) Please indicate how much shortness of breath you have had during the last 10 days while **[INTERVIEWER: INSERT ACTIVITY LISTED IN 3C]** by choosing one of the following options from the card in front of you, keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [GREEN CARD]**

D) Please indicate how much shortness of breath you have had during the last 10 days while **[INTERVIEWER: INSERT ACTIVITY LISTED IN 3D]** by choosing one of the following options from the card in front of you, keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [GREEN CARD]**

E) Please indicate how much shortness of breath you have had during the last 10 days while **[INTERVIEWER: INSERT ACTIVITY LISTED IN 3E]** by choosing one of the following options from the card in front of you, keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [GREEN CARD]**

5. In general, how much of the time during the last 10 days have you felt frustrated or impatient? Please indicate how often during the last 10 days you have felt frustrated or impatient by choosing one of the following options from the card in front of you, keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [BLUE CARD]**

6. How often during the past 10 days did you have a feeling of fear or panic when you had difficulty getting your breath? Please indicate how often you had a feeling of fear or panic when you had difficulty getting your breath by choosing one of the following options from the card in front of you, keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [BLUE CARD]**

7. What about fatigue? How tired have you felt over the last 10 days? Please indicate how tired you have felt over the last 10 days by choosing one of the following options from the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [ORANGE CARD]**

8. How often during the last 10 days have you felt embarrassed by your coughing or heavy breathing? Please indicate how much of the time you felt embarrassed by your coughing or heavy breathing by choosing one of the following options from the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [BLUE CARD]**

9. In the last 10 days , how much of the time did you feel very confident and sure that you could deal with your illness? Please indicate how much of the time you felt very confident and sure that you could deal with your illness by choosing one of the following options from the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [YELLOW CARD]**

10. How much energy have you had in the last 10 days ? Please indicate how much energy you have had by choosing one of the following options from the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [PINK CARD]**

11. In general, how much of the time did you feel upset, worried, or depressed during the last 10 days? Please indicate how much of the time you felt upset, worried, or depressed during the past 10 days by choosing one of the following options from the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [BLUE CARD]**

12. How often during the last 10 days did you feel you had complete control of your breathing problems? Please indicate how often you felt you had complete control of your breathing problems by choosing one of the following options from the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [YELLOW CARD]**

13. How much of the time during the past **10 days** did you feel relaxed and free of tension? Please indicate how much of the time you felt relaxed and free of tension by choosing one of the following options from the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [YELLOW CARD]**

14 How often during the last **10 days** have you felt low in energy? Please indicate how often during the last **10 days** you have felt low in energy by choosing one of the following options form the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [BLUE CARD]**

15. In general, how often during the last **10 days** have vou felt discouraged or down in the dumps? Please indicate how often during the last **10 days** you felt discouraged or down in the dumps by choosing one of the following options from the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [BLUE CARD]**

16. How often during the last **10 days** have you felt worn out or sluggish? Please indicate how much of the time you felt worn out or sluggish by choosing one of the following options form the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [BLUE CARD]**

17. How happy, satisfied, or pleased have you been with your personal life during the last **10 days** ? Please indicate how happy, satisfied or pleased you have been by choosing one of the following options from the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [GREY CARD]**

18. How often during the last **10 days** did you feel upset or scared when you had difficulty getting your breath? Please indicate how often during the last **10 days** you felt upset or scared when you had difficulty getting your breath by choosing one of the following options from the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [BLUE CARD]**

19. In general, how often during the last **10 days** have you felt restless, tense, or uptight? Please indicate how often you have felt restless, tense, or uptight by choosing one of the following options from the card in front of you keeping in mind that last time you answered the questionnaire you chose **[INSERT PATIENT'S ANSWER FROM PREVIOUS ADMINISTRATION]. [BLUE CARD]**

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