Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

This Supplement Contains:

<u>**Original Protocol: Beta-Blockers for the Prevention of Acute Exacerbations of COPD**</u>

<u>**Background and Significance**</u>
Chronic obstructive pulmonary disease (COPD) recently surpassed stroke as the 3rd leading cause of death in the United States and accounts for more than $40 billion annually in direct and indirect health care costs.(1, 2) COPD affects approximately 6% of civilians and at least 8% of the Veteran population, though the prevalence is increasing in both groups, and when Veterans with respiratory complaints are evaluated with spirometry and questionnaires rates of COPD may be as high as 43%.(3) Veterans with COPD also account for significantly higher all-cause and respiratory-related inpatient and outpatient health care utilization including number of physician encounters, emergency room visits, acute inpatient discharges, total bed days of care, pharmacy costs and total costs than those without COPD. Though existing pharmacotherapy can improve symptoms and quality of life, and modestly reduce the risk of acute exacerbations, no treatments alter the natural history of the disease or improve mortality. The impact of COPD on the military and Veteran populations is emphasized by the recent efforts to develop a joint Veterans Affairs/Department of Defense Clinical Practice Guideline for the disease.(4)

COPD is also associated with an increased risk of a number of major comorbid illnesses, most importantly cardiovascular disease which complicates diagnosis and management(5). Despite clear evidence that beta-blockers markedly reduce cardiovascular risk in patients with and without COPD, concerns regarding their potential adverse respiratory effects have led to their dramatic underuse in those with the disease.(6, 7) This practice pattern persists despite recent observational data suggesting that beta-blockers may actually improve respiratory outcomes in COPD patients.(8-11) These data require validation and thus the proposed clinical trial of beta-blockers to prevent exacerbations of COPD addresses the most important chronic lower respiratory tract illness in the United States, will test the efficacy of a novel approach to prevent its most morbid and costly consequences, and will provide critical information needed to shape guideline recommendations regarding the management of patients with comorbid cardiovascular disease.

The majority of COPD-related morbidity and health-care costs are due to acute exacerbations, particularly those requiring hospitalization.(12, 13) Multiple treatment strategies have been employed to reduce the rate of exacerbations, including drugs administered via inhalation such as corticosteroids and bronchodilators as well as systemically delivered drugs such as prednisone, azithromycin and roflumilast.(14) Though each of these drugs reduces the rate of exacerbations by approximately 20 percent, little additional benefit is observed when they are used in combination and a substantial number of patients suffer frequent events despite ongoing maintenance therapy.(15) There are a number of possible explanations for the failure of available treatments to adequately control the disease including the fact that many exacerbations are triggered or made more severe by underlying cardiovascular disease. COPD is associated with up to a 5-fold increase in atherosclerosis and cardiovascular disease independent of shared risk factors,(16) and cardiovascular disease is an independent risk factor for hospitalization for COPD exacerbations,(17) in-hospital mortality,(18, 19) and long-term survival.(20-23) COPD is also associated with systolic and diastolic congestive heart failure as well as an increased risk for arrhythmias which are also associated with COPD exacerbations.(16)

It is well established that beta-blockers reduce mortality in patients with cardiovascular disease most notably after myocardial infarction (MI) (7), in the presence of congestive heart failure (24), and in the perioperative setting.(25) However, patients with COPD are often denied these medications because of concerns about possible adverse effects of beta-blockade on airway function.(6, 7, 26, 27) This is despite the fact that cardioselective beta-blockers have no demonstrable effect on lung function regardless of the severity of airflow limitation or the presence of absence of bronchodilator reversibility.(26, 27) The current American Heart Association/American College of Cardiology guidelines for secondary prevention of coronary disease include

beta-blockers as a class I intervention in patients with prior MI or acute coronary syndrome or with heart failure (28-30) and the Centers for Medicare and Medicaid include beta-blocker use after discharge following MI as a hospital performance measure. COPD has been cited as the primary reason for withholding beta-blockade in up to 33% of these patients.(6)
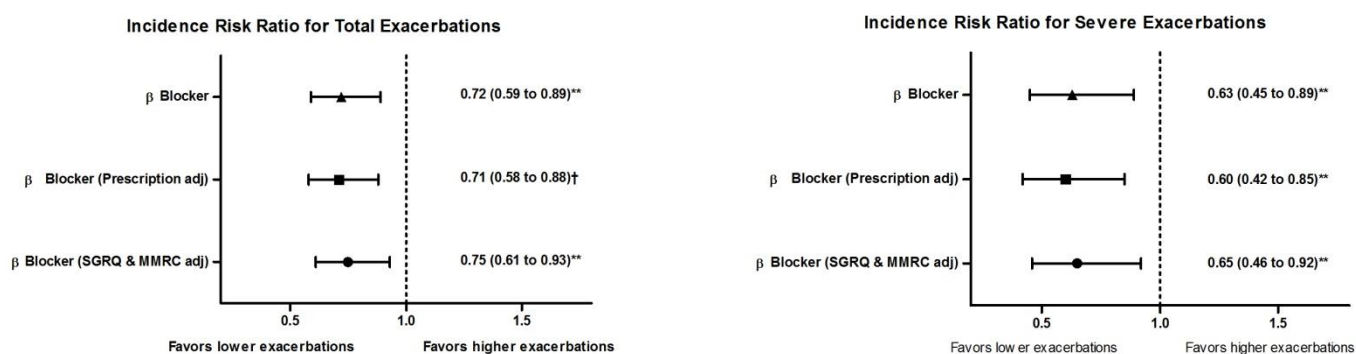
Multiple observational and retrospective studies have indicated that beta-blockers impact outcomes favorably in patients with COPD and underlying cardiovascular disease. Gottlieb et al. reviewed the medical records of all Medicare patients discharged after acute MI over an 18-month period (n = 210,752) and evaluated survival with Social Security records.(7) Of those with COPD, only 22% were given beta-blockers, compared to 34% of the population as a whole, but receipt of the drugs was associated with a 40% reduction in mortality, an effect similar to that seen in the entire population. A second study examined the effect of beta-blockers as compared to other antihypertensive agents on all-cause two-year mortality in patients with COPD and found that the drugs were associated with a reduced risk of death (hazard ratio=0.57).(31) Similarly, Quint et al. analyzed data from the General Practice Research Database in the United Kingdom and found that initiating beta-blockers prior to or after an acute MI in patients with COPD was associated with similarly improved survival over 3 years of follow-up.(22)

More recent data suggest that the benefits of beta-blockers may in fact extend to COPD patients without known cardiac disease and may also reduce the risk of acute exacerbations.(8, 9, 11, 32-35) Mancini demonstrated that COPD patients at high risk for coronary events who had an MI, were hospitalized for COPD, or died during the study period were less likely to be taking beta-blockers than those who did not suffer these events (17.1% vs. 24.0%, p<0.0001).(9) COPD patients at low risk for cardiovascular events who suffered these events were also less likely to be taking beta-blockers (7.5% vs. 9.3%, p<0.0001).(9) In an analysis of 825 patients admitted to the University of Alabama Hospital with acute exacerbations of COPD, beta-blocker use was an independent predictor of survival to hospital discharge (OR=0.39, 95%CI 0.14-0.99) after adjustment for a variety of factors including the presence of cardiovascular disease.(8) Rutten et al. also reported that the use of beta-blockers was associated with a reduced risk of death (OR=0.68, 0.56-0.83) and of acute exacerbation (OR=0.71, 0.60-0.83).(10) Subgroup analyses demonstrated similar benefits in patients with versus without overt cardiovascular disease. A recent meta-analyses of nine retrospective cohort studies found that the pooled relative risk of COPD related mortality secondary to beta-blocker use was 0.69 (95% CI: 0.62-0.78).(11) Collectively, these data argue strongly that a prospective trial verifying that beta-blockers are both safe in COPD and efficacious to prevent exacerbations could have a major impact on mortality in both the civilian and Veteran populations.

The mechanisms by which beta-blockers may reduce exacerbations remain uncertain though several explanations are biologically plausible including both respiratory and cardiovascular effects. First, chronic blockade of beta-receptors may up-regulate receptor density in the lungs leading to improved bronchodilation with beta-agonists.(36) Second, murine data suggests that beta-blockers may reduce airway hyper-reactivity, inflammation and mucous secretion which may also be of benefit in the COPD airway.(37, 38) Third, beta-blockers may blunt the resting tachycardia in COPD (which occurs in up to 40% of patients) and thus improve cardiac performance and exercise tolerance leading to reduced symptoms.(39) Fourth, as we recently reported, P wave dispersion, a surrogate for atrial arrhythmias, is greater in patients with more frequent exacerbations, suggesting a causative role for arrhythmias (40) and raising the possibility that beta blockade may be beneficial in prevention.(41) Lastly, and perhaps most importantly, up to a third or more of acute exacerbations occur in the absence of pulmonary inflammation and are very likely caused by cardiac events including both clinically apparent and subclinical coronary ischemia for which beta-blockers have clear benefits.(5)

The positive results of these observational studies should be tempered by the fact that they were all retrospective and hence subject to bias. Indeed, another recent large prospective study suggested that beta-blockers increased mortality in oxygen dependent COPD patients (HR 1.19; 95% CI, 1.04-1.37; p = 0.01).(42) In contrast however, we analyzed prospectively collected data from the multicenter COPDGene study (43) to determine the relationship between the use of beta-blockers and exacerbation, taking into account the propensity to prescribe beta-blockers based on the presence of coronary artery disease (CAD), congestive heart failure (CHF) and the severity of symptoms and airflow obstruction.(44) After adjustment for this propensity and for a number of other demographic and clinical characteristics, use of beta-blockers was associated with a significantly reduced rate of total and severe exacerbations as shown in Figure 1.

Figure 1. Relationship between beta-blocker use and acute exacerbations.

Shown are adjusted Incidence Risk Ratios (IRR) for total and severe exacerbations occurring during long term follow-up in COPDGene patients who were or were not on beta-blocker therapy at enrolment. Three models are shown including model 1 labeled beta-blocker and adjusted for age, gender, race, smoking burden, body mass index, airflow obstruction, %emphysema on computed tomography, coronary artery calcification, presence of congestive heart failure and coronary artery disease, and long acting respiratory medications; model 2 labeled beta-blocker (Prescription adj) adjusted for these factors and the propensity to be prescribed the drugs; and model 3 labeled beta-blocker (SGRQ and MMRC adj) adjusted further for the severity of dyspnea and impairment in quality of life as assessed by these scales. All values expressed as Odds Ratios (95% Confidence Intervals). SQRQ = St. George's Respiratory Questionnaire. MMRC = Modified Medical Research Council Dyspnea Scale. **p<0.01 †p<0.001

In those with advanced disease and on home oxygen, use of beta-blockers was again associated with a reduction in the rate of total (IRR 0.40, 95%CI 0.24 to 0.67; p=0.001) and severe exacerbations (IRR 0.49, 95%CI 0.25 to 0.98; p=0.045). Similar results from previous studies have been confounded by a lower rate of mortality of in those receiving beta-blockers suggesting residual healthy user bias. However, in our analysis no difference in deaths was observed between the two groups suggesting this is less likely. In addition, we observed no relationship between the use of other cardioprotective medications including angiotensin converting enzyme inhibitors and calcium channel blockers and exacerbations suggesting our observations are class specific.

In summary, despite multiple non-randomized studies suggesting a potential benefit of beta blockade in COPD patients including those without overt cardiovascular disease, the data are not definitive and the drugs continue to be underutilized in this population due to persistent safety concerns. This conundrum cannot be solved

without a prospective randomized controlled trial. Therefore, we propose a safety and efficacy study of once-daily metoprolol succinate versus placebo in COPD patients at risk for acute exacerbation to determine the effect of beta-blockade on lung function, dyspnea, quality of life, exercise tolerance and exacerbation risk.

Research Design and Methods

Overview
This is a multicenter, prospective, randomized, double-blind, placebo-controlled trial that will enroll 1028 patients with at least moderately severe COPD over a three year period and follow them at regular intervals for one year. The primary endpoint is time to first acute exacerbation. Secondary endpoints include rates and severity of COPD exacerbations, cardiovascular events, all-cause mortality, lung function, dyspnea, quality of life and metoprolol-related side effects.

Hypothesis
The primary hypothesis is that metoprolol succinate will reduce the risk of COPD exacerbations as compared to placebo. The secondary hypothesis is that metoprolol succinate will not adversely impact lung function, exercise tolerance, dyspnea or quality of life as compared to placebo.

Specific Aims:
Primary: To determine the effect of once daily metoprolol succinate compared with placebo on the time to first exacerbation in moderate to severe COPD patients who are prone to exacerbations and who do not have absolute indications for beta-blocker therapy.

Secondary: To estimate the effect of metoprolol succinate compared with placebo on:

1) The rate and severity of COPD exacerbations over 12 months
2) Incidence and severity of metoprolol-related side effects including those that require cessation of drug
3) Lung function as assessed by spirometry, dyspnea as assessed by the Modified Medical Research Council Scale (MMRC)(45) and San Diego Shortness of Breath Questionnaire (46, 47), exercise tolerance as measured by six minute walk test (6MWD)(48), and quality of life as assessed by the Short Form 36 (49), St. Georges Respiratory Questionnaire (SGRQ)(50) and COPD Assessment Test (CAT)(51) and Personal HEART Score (52).
4) Hospitalizations
5) The rate of major adverse cardiovascular events (MACE) (defined by cardiovascular death, hospitalization for myocardial infarction, heart failure, or stroke), percutaneous coronary intervention or coronary artery bypass grafting
6) All-cause mortality

Eligibility Criteria
Inclusion Criteria
1. Male and female subjects, ≥ 40 and less than 85 years of age
2. Clinical diagnosis of at least moderate COPD as defined by the Global Initiative for Obstructive Lung Disease (GOLD) criteria (53):
   a. Post bronchodilator $FEV_1/FVC < 70\%$,
   b. Post bronchodilator $FEV_1 < 80\%$ predicted, with or without chronic symptoms (i.e., cough, sputum production).
3. Cigarette consumption of 10 pack-years or more. Patients may or may not be active smokers.

4. To enrich the population for patients who are more likely to have acute exacerbations (54), each subject must meet one or more of the following 4 conditions:
    a. Have a history of receiving a course of systemic corticosteroids for respiratory problems in the past year,
    b. Visiting an Emergency Department for a COPD exacerbation within the past year, or
    c. Being hospitalized for a COPD exacerbation within the past year
    d. Be using supplemental oxygen for 12 or more hours per day
5. Willingness to make return visits and availability by telephone for duration of study.

Exclusion Criteria
1. A diagnosis of asthma established by each study investigator on the basis of the recent American Thoracic Society/European Respiratory Society and National Institute for Health and Care Excellence guidelines (55, 56) (Table 1).

Table 1: Clinical Features Differentiating COPD & Asthma

History	COPD	Asthma
Smoker or ex-smoker	Nearly all	Possibly
Symptom onset < 35 yrs	Rare	Common
Chronic productive cough	Common	Uncommon
Breathlessness	Persistent and progressive	Variable
Nighttime waking with breathlessness and wheeze	Uncommon	Common
Significant diurnal or day-to-day variation of symptoms	Uncommon	Common

If, after applying the above criteria, investigators are still unsure about the distinction in a specific patient bronchodilator testing with inhaled albuterol will be performed and patients with changes in FEV1 > 400 mL will be excluded.
2. The presence of a diagnosis other than COPD that results in the patient being either medically unstable, or having a predicted life expectancy < 2 years.
3. Women who are at risk of becoming pregnant during the study (pre-menopausal) and who refuse to use acceptable birth control (hormone-based oral or barrier contraceptive) for the duration of the study.
4. Current tachy or brady arrhythmias requiring treatment
5. Presence of a pacemaker and/or internal cardioverter/defibrillator
6. Patients with a history of second or third degree (complete) heart block, or sick sinus syndrome
7. Baseline EKG revealing left bundle branch block, bifascicular block, ventricular tachyarrhythmia, atrial fibrillation, atrial flutter, supraventricular tachycardia (other than sinus tachycardia and multifocal atrial tachycardia), or heart block (2nd degree or complete)
8. Resting heart rate less than 70 beats per minute, or sustained resting tachycardia defined as heart rate greater than 120 beats per minute.
9. Resting systolic blood pressure of less than 100mm Hg.
10. Subjects with absolute (Class 1) indications for beta-blocker treatment as defined by the combined American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons Guidelines which include myocardial infarction, acute coronary syndrome, percutaneous

coronary intervention or coronary artery bypass surgery within the prior 3 years and patients with known congestive heart failure defined as left ventricular ejection fraction <40%.(29, 30)

11. Critical ischemia related to peripheral arterial disease.

12. Other diseases that are known to be triggered by beta-blockers or beta-blocker withdrawal including myasthenia gravis, periodic hypokalemic paralysis, pheochromocytoma, and thyrotoxicosis

13. Patients on other cardiac medications known to cause atrioventricular (AV) node conduction delays such as amiodarone, digoxin, and calcium channel blockers including verapamil and diltiazem as well as patients taking clonidine.

14. Hospitalization for uncontrolled diabetes mellitus or hypoglycemia within the last 12 months.

15. Patients with cirrhosis

16. A clinical diagnosis of bronchiectasis defined as production of > one-half cup of purulent sputum/day.

17. Patients otherwise meeting the inclusion criteria will not be enrolled until they are a minimum of four weeks from their most recent acute exacerbation (i.e., they will not have received a course of systemic corticosteroids, an increased dose of chronically administered systemic corticosteroids, and/or antibiotics for an acute exacerbation for a minimum of four weeks).

Outcome Measures

The primary endpoint of this study is the time to first occurrence of an acute COPD exacerbation during the one-year treatment period.

Acute exacerbations are defined as a "complex of respiratory symptoms (increase or new onset) of more than one of the following: cough, sputum, wheezing, dyspnea, or chest tightness *requiring treatment with antibiotics and/or systemic steroids* for at least three days ".(54)

Acute exacerbations will be graded according to the following scale:

1. Mild (home management, with or without contacting a health care provider)
2. Moderate (requiring a visit to an Emergency Department)
3. Severe (requiring hospitalization with or without use of non-invasive positive pressure ventilation)
4. Very severe (requiring intubation and mechanical ventilation)

When patients report that they have severe or very severe exacerbation, the hospital records of that encounter will be obtained and reviewed.

The end of an exacerbation is when the patient has returned to their clinical baseline and has completed their course of antibiotic, oral steroids or combination of oral steroids and antibiotics to treat the exacerbation as defined by Anthonisen.(57) Since some patients may be on chronic steroid therapy or have varying steroid taper regimes used to treat an acute exacerbation by their primary physicians, a return to the baseline chronic steroid prescription level or end of the corticosteroid taper course will be considered the end of steroid therapy for an acute exacerbation. A relapse of a previous exacerbation will be defined as the complex of respiratory symptoms of more than one of the following: cough, sputum, wheezing, dyspnea, or chest tightness with a duration of at least three days *that recurs and requires re- treatment with antibiotics and/or systemic steroids without a return to baseline and within 2 weeks of the start date of a prior treated event*.

Secondary endpoints include:

1) The number of acute exacerbations occurring within 12 months of randomization

2) The number of ED visits resulting from acute exacerbations

3) The number of hospital admissions resulting from acute exacerbations

4) The number of hospital days resulting from acute exacerbations

5) The rate of major adverse cardiovascular events (MACE) (defined by cardiovascular death, hospitalization for myocardial infarction, heart failure, or stroke), percutaneous coronary intervention or coronary artery bypass grafting

6) All-cause mortality

7) The incidence of presumed metoprolol-related side-effects including new or worsened (Neural: depression, headache, syncope, seizures, somnolence, memory loss, loss of sexual desire or erectile dysfunction, and fatigue; Hypersensitivity: rash, pruritus, tongue or facial swelling; Gastrointestinal: diarrhea, vomiting, nausea or constipation; Cardiovascular: bradycardia and hypotension as discussed below; Respiratory: bronchospasm and changes in lung function as discussed below). Presumed metoprolol-related side effects will be specifically queried for and the severity recorded daily by participants during the dose titration period described below and at each clinic and phone visit. The rate of discontinuation of study drug due to presumed metoprolol related side effects will also be collected.

8) Quality of life (SF-36, SGRQ and CAT). The SF-36 is a generic tool to assess overall health status and allows comparison between different diseases. SF-36 scores range from 0 to 100 with higher scores representing better health status and a Minimal Clinically Important Difference (MCID) that can be appreciated by patients of 4(49). The SGRQ is a respiratory specific health status questionnaire with scores ranging from 0 to 100.(50) A lower score indicates a better health status and the MCID of the SGRQ total score is 4. The CAT is a simple, eight item, health status instrument for patients with COPD which is highly practical, has robust psychometric properties, and has been shown to be responsive to pulmonary rehabilitation and recovery from exacerbation.(51) Lower scores denote better health status and the MCID for the CAT is 2 points.

9) Dyspnea (MMRC and San Diego Shortness of Breath Questionnaire. The MMRC scale is a five-point scale originally published in 1959 that considers certain activities, such as walking or climbing stairs, which provoke breathlessness.(45, 58) The MMRC scale is not optimal as an evaluative instrument to measure changes in dyspnea as its broad grades are generally unresponsive responsive to interventions but does sub-classify patients well at baseline and has been used to assess dyspnea due to cardiovascular disease. A one point worsening (increase) in the scale would denote a marked worsening of dyspnea. The San Diego Shortness of Breath Questionnaire (SOBQ), a 24-item measure that assesses self-reported shortness of breath while performing a variety of activities of daily living.(47) The MCID for this questionnaire is 5.(46, 58).

10) Lung function (FEV1) as assessed by spirometry. Spirometry is the key pulmonary function parameter used for the monitoring of COPD severity. The MCID for changes in FEV1 is approximately 100 mL.(58)

11) Exercise capacity as assessed by the 6 minute walk distance (6MWD). The 6MWD has been used as a simple tool to assess overall exercise tolerance in patients with chronic cardiopulmonary disease including COPD. The MCID for the 6MWD in COPD is approximately 54 meters.(58)

12) Markers of cardiac stretch, injury and systemic inflammation (troponin-I, pro-NT Brain Natriuretic Peptide, high sensitivity C-reactive protein, and fibrinogen). These parameters will be assessed at screening/randomization and at conclusion of the study to determine if beta-blockade impacts volume status and cardiac performance as well as levels of systemic inflammation that portend overall cardiac risk.

<u>Description of the Investigational Product, Safety and Dosing Considerations</u>
The clinical trial will utilize metoprolol succinate extended release tablets (50 mg) and matching placebo manufactured by Temple School of Pharmacy. Drug and matching placebo will be labeled using blinded coding and distributed to the study sites as needed to support enrolment and retention over the 42 months of human subject participation. The planned starting dose for metoprolol succinate extended release is one 50mg tablet taken orally daily though patients will undergo a dose titration procedure as outlined below which will result in a final dose of 25mg (1/2 of one tablet daily), 50 mg, or 100 mg (two tablets daily). Matching placebo manufactured at Temple University will be administered similarly. Following completion of the 12 month dosing period patients will be weaned off study drug over the following 4 weeks in order to avoid possible rebound myocardial ischemia. The same approach will be used for patients assigned to blinded placebo. There is no plan to seek an indication for metoprolol's specific use in patients with COPD and the trial will be conducted with an FDA IND waiver.

Metoprolol Safety: Prior Studies of Beta-blockers and Effects on Lung Function and Exercise
A number of studies have examined the safety of a number of beta blockers in patients with COPD though there have been no dose ranging studies to specifically determine the optimal dose for the prevention of exacerbations. Typical doses in trials of patients with coronary artery disease, congestive heart failure and hypertension range from 12.5 mg to 200 mg (see package insert) and doses in this range are well tolerated by patients with COPD including those with moderate to severe disease(59). The dose titration procedure is modeled after the approach used in a pivotal trial of metoprolol succinate in patients with heart failure (60). In that study, in which daily doses of up to 200 mg (mean dose 159 mg once-daily) were used, 10.3% of 1990 patients assigned to metoprolol succinate extended-release tablets patients discontinued for adverse reactions vs. 12.2% of placebo patients. Adverse events that occurred at an incidence of ≥ 1% in the metoprolol succinate extended-release tablets group and greater than placebo by more than 0.5% (and regardless of causality) included dizziness/vertigo (1.8% vs. 1.0%), bradycardia (1.5% vs. 0.4%) and accident and/or injury (1.4% vs. 0.8%). The planned median daily dose of metoprolol in the proposed trial will fall between 50mg and 100mg and these as well as a number of other possible drug related side effects will be specifically sought and recorded.

Multiple studies demonstrate that in general the effect of cardioselective beta-blockers on lung function is minimal whether administered as a single dose or with continued treatment. A Cochrane analysis revealed that cardioselective beta-blockers produced no significant change in FEV1 or respiratory symptoms compared to placebo, given as a single dose (-2.05% [95% CI, -6.05% to 1.96%]) or for longer duration (-2.55% [CI, -5.94% to 0.84]), and did not significantly affect the FEV1 treatment response to beta2-agonists.(27, 59) Subgroup analyses revealed no significant change in results for those participants with severe chronic airways obstruction or for those with a reversible obstructive component. The trials of metoprolol tested single and multiple dosing of the drug at doses between 50mg and 200mg daily.

A more recent study of bisoprolol (a cardioselective beta-blocker) titrated to the maximally tolerated dose and given for four months in patients with coexistent congestive heart failure and severe COPD did demonstrate a modest reduction in FEV1 (70mL, p=0.01 vs. placebo and lower than accepted MCID) but reversibility was not

impacted and all measures of health status exhibited a consistent non-significant improvement, including the Short Form 36 physical and mental component scores (2.6 vs. 0.5 and 0.8 vs. -0.3, respectively), Minnesota Living with Heart Failure Questionnaire (-2.5 vs. 3.5) and Chronic Respiratory Questionnaire (0.07 vs. -0.24).(61)

Two studies have examined the relationship between bisoprolol use and exercise time in patients with COPD and though in one dynamic hyperinflation was worsened slightly there was no impact on peak oxygen consumption or exercise time.(62, 63)

Selection of Metoprolol Dose and Dose Titration Procedures
The initial dose of metoprolol and subsequent titration procedures are adapted from the landmark Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) trial which definitively demonstrated the safety and efficacy of beta blockade in patients with symptomatic heart failure, a disease that similar to COPD had been considered a contraindication to beta-blocker treatment. That trial demonstrated that as compared to placebo, metoprolol CR/XL not only improved survival and reduced the need for hospitalization due to worsening heart failure but improved New York Heart Association functional class and had beneficial effects on patient well-being.(60) At the randomization visit, patients were allocated to treatment with metoprolol CR/XL or placebo administered once daily. The starting dosage was one 25-mg tablet once per day (half of a 25-mg tablet was recommended for patients with NYHA functional class III or IV). It was recommended to double the dosage after each 2-week period to reach the target dosage level of 200 mg/d of metoprolol CR/XL or placebo. This regimen could be modified according to the judgment of the investigator which was done successfully without compromising the blinding of study drug. If a patient did not tolerate the increased dosage of study drug, reduction in dosage was advocated. In a post hoc analysis, there was no difference in the benefit on mortality between patients who ultimately were titrated to a high dose of metoprolol (median 192 mg) and those titrated to a lower dose (median 76 mg). These data suggest that individualized dosing based on patient tolerability was appropriate but and titration to a dose above 100 mg may not be necessary to derive clinical benefits.(64) The initial starting dose of metoprolol is based on prior studies in patients with COPD suggesting tolerance both with single and continued dosing at comparable doses of the drug and other cardioselective beta-blockers.(27, 59, 65-67) It is anticipated that many patients will tolerate titration to the maximal dose of 100mg while some will require a dose reduction to remain on study medication. This approach was used in the previous CCRN trial of azithromycin to prevent exacerbations in which dosing was changed to every other day in patients with persistent diarrhea as well as the prior simvastatin trial in which three times per week dosing was used in the event of mild muscle discomfort or cramps.   Although guidelines and performance measures for the care of post-MI patients clearly indicate that virtually all such patients should be treated with beta-blocker therapy, the guidelines do not provide guidance on dosing and thus cannot be used to select the optimum dose for the proposed trial. There are a number of reasons for this uncertainty including the fact that the recommendations are derived from evidence accumulated from multiple clinical trials using a number of different drugs and with different regimens and that dose-response studies for long term outcomes have not been performed.(68, 69)

Study Flow
Patients will be screened and then randomized over a 2 week period and will then undergo a dose titration period for the following six weeks. Thereafter patients will be followed for 42 additional weeks on their target dose of metoprolol or placebo followed by a 4 week washout period. The schedule of study events is shown in Table 2.

Table 2. Schedule of Study Interventions

Assessment	Screening (Day -14 to -1)	Randomization (Day 0)	Dose Titration (Days 14 and 28)	Dose Finalization (Day 42)	Clinic Visit (Day 112)	Clinic Visit (Day 224)	Wean IP Clinic Visit (Day 336)	Stop IP Clinic Visit (Day 350)	Close-out Clinic Visit (Day 364)
Informed Consent	X								
Medical History	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X@	X	X	X
Safety Laboratory Assessments*	X								
Questionnaires**	X				X		X		
Troponin	X								
Pro-NT BNP/CRP/fibrinogen		X					X		
Urine pregnancy	X								
Spirometry#	X		X	X	X		X		
EKG	X		X	X	X		X	X	X
6 Minute Walk		X			X		X		
Randomization		X							
Drug Dispensing		X	X	X	X	X	X		
Adverse Event Assessment		X	X	X	X	X	X	X	X
Drug Return and Accountability			X	X	X	X	X	X	

Phone Calls Day 2, 3, 15,16, 56, 168, 280, 343, 357, 378 for adverse event assessment

Visit windows +/- 3 days until dose finalization visit then +/- 14 days until Wean IP visit then +/- 3 days until close-out visit

Unscheduled Visits will include medical history, adverse event assessment, EKG, and spirometry

*Complete blood count, comprehensive metabolic profile including magnesium, AST, ALT, ALP

**Modified Medical Research Council Dyspnea Scale, COPD Assessment Test, St. George Respiratory Questionnaire, SF-36, San Diego Shortness of Breath Questionnaire; Personal HEART Score at screening only

#Pre- & Post-bronchodilator Spirometry at screening, otherwise post- bronchodilator only

@ Heart rate and blood pressure only

Visit 1: Day -14 to -1: Clinic Visit for Screening:

1.   Informed consent prior to any study procedures.

2.   Demographics (including age, gender, smoking history, oxygen use), information regarding where the patient might be seen in an emergency department (ED) and/or hospitalized, should this be required during the course of the study, primary care physician name and contact information.

3.   A medical history and physical examination that includes recording a list of all medications including cardiac and respiratory medications, allergies, menopausal status (women), whether the patient has received influenza and/or pneumococcal pneumonia vaccination and if so, when, a list of all comorbidities, whether they have chronic bronchitis (defined in American Thoracic Society, 1986), previous COPD-related emergency room visits and hospitalizations (including whether they have previously required invasive or non-invasive mechanical ventilation), a body mass index (BMI) determination, and a resting oxygen saturation on the prescribed amount of supplemental O_2 being given, if any, or on air, and resting heart rate and resting blood pressure measurements.

4.   Spirometry will be performed before and 15-30 min after inhalation of two puffs of albuterol (Ferguson, 2000; Hankinson, 2003), and post bronchodilator FEV1 and FVC will be recorded.

5.   A 12 lead surface EKG in the resting state.

6.   Quality of life and dyspnea assessment as described above.

7.   Laboratory studies to include:
     a.   Complete blood count with differential
     b.   Comprehensive metabolic panel including blood urea nitrogen, creatinine, AST, ALT, ALP, and magnesium levels.
     c.   Serum Troponin-I. Patients with troponin levels above the upper limit of normal suggesting recent ischemia will not be eligible for further screening and referred to their primary physician or the emergency department for evaluation.
     d.   HCG (urine or blood) for pre-menopausal women.

Visit 2: Clinic Visit for Randomization at Day 0:

1. Interim medical history, physical exam and adverse event assessment.

2. Basic education about COPD, its treatment and how to recognize acute exacerbations. Patients will also be given a diary to collect the daily occurrence of potential metoprolol-related side effects (see Table of side effects above) and with recalling acute exacerbations including those that are treated at home, without contact with a health care provider.

3. A wallet card indicating that they are participating in the study and stating "This person may be taking the beta-blocker: Extended release Metoprolol succinate. Please carefully consider potential drug interactions and contact research staff with any questions". The patients will be instructed to contact the clinic coordinator if they are given any new medications.

4. Assessment of functional capacity and exercise tolerance will be made by asking patients to perform a six minute walk test according to standard ATS guidelines.

5. Venipuncture for collection of markers of cardiac stretch and systemic inflammation (pro-NT Brain Natriuretic Peptide, hs-C-reactive protein, fibrinogen). These parameters will be reassessed at the conclusion of the study to determine if beta-blockade impacts volume status and cardiac performance as well as levels of systemic inflammation that portend overall cardiac risk.(70)

6. Only those with resting HR greater than or equal to 70 and SBP greater than or equal to 100 will be randomized.

7. Subject will be randomized to extended release metoprolol succinate or placebo (see details of randomization process below). A dose of 50 mg will be used as starting dose to be followed by dose titration protocol as described below (Table 3).

Visits 3 and 4: Phone Calls on Day 2 and 3:

Assessment of potential adverse respiratory events including symptomatic dyspnea, wheezing, chest tightness as well as other potential metoprolol-related side effects. Patients reporting symptoms concerning for significant intolerance of study drug will be seen at an unscheduled protocol visit as indicated in table 2 above. The investigator will determine whether study drug should be discontinued or the dose lowered.

Visits 5: Clinic Visit for dose adjustment at 14 days

1. Respiratory symptoms, concomitant medications, and whether any acute exacerbations occurred since the randomization visit will be assessed and recorded.

2. Possible metoprolol-related side effects will be assessed and recorded. If the patient is not tolerating the medication based on clinically significant symptoms as judged by the investigator, they will be discontinued from study medication or the dose lowered. If patients are not able to tolerate 25mg of study drug it will be discontinued.

3. The patient's self-assessment of compliance with study drug will be recorded, as will a pill count.

4. A repeat 12 lead EKG will be obtained.

5. Pre-menopausal women will be queried about their contraceptive use and pregnancy status. Those not using acceptable birth control will be discontinued from study medication.

6. Spirometry will be performed. If a patient has a significant decline in FEV1 (defined as drop in post-bronchodilator of greater than 15% or 200 ml from baseline) study drug will be discontinued.

7. For those tolerating medication well, dose adjustments of metoprolol or equivalent placebo will be made by a blinded investigator based on tolerability according to the dose adjustment protocol (Table 3):

Table 3. Dose adjustment protocol.

Visit	HR (beats/min)	SBP (mmHg)	Instruction
Enrollment/Randomization	>=70	>=100	Randomize
Dose adjustment Visit at 14 days	>=70	>=100	↑ dose to 100 mg
		90-99	↔ maintain same dose
		<90	↓ dose to 25 mg or stop
	50-69	>= 90	↔ maintain same dose
		<90	↓ dose to 25 mg or stop
	<50	Any	Stop study drug
Dose adjustment Visit at 28 days	>=70	>=90	↔ maintain same dose
		<90	↓ dose by 1/2 or stop
	50-69	>=90	↔ maintain same dose
		<90	↓ dose by 1/2 or stop
	<50	Any	Stop study drug
Dose Finalization Visit at 42 days	>=70	>=90	↔ maintain same dose
		<90	Stop study drug
	50-69	>=90	↔ maintain same dose
		<90	Stop study drug
	<50	Any	Stop study drug

Visit 6 and 7: Phone calls on Day 15 and 16:

Assessment of potential adverse respiratory events including symptomatic dyspnea, wheezing, chest tightness as well as other potential metoprolol-related side effects. Patients reporting symptoms concerning for significant intolerance of study drug will be seen at an unscheduled protocol visit as indicated in table 2 above. The investigator will determine whether study drug should be discontinued or the dose lowered. If patients are not able to tolerate 25mg of study drug it will be discontinued.

Visits 8: Clinic Visit for dose adjustment at 28 days:

1. Respiratory symptoms, concomitant medications, and whether any acute exacerbations occurred since the randomization visit will be assessed and recorded.

2. Possible metoprolol-related side effects will be assessed and recorded. If the patient is not tolerating the medication based on clinically significant symptoms as judged by the investigator, they will be discontinued from study medication or the dose lowered. If patients are not able to tolerate 25mg of study drug it will be discontinued.

3. The patient's self-assessment of compliance with study drug will be recorded, as will a pill count.

4. A repeat 12 lead EKG will be obtained.

5. Pre-menopausal women will be queried about their contraceptive use and pregnancy status. Those not using acceptable birth control will be discontinued from study medication.

6. Spirometry will be performed. If a patient has a significant decline in FEV1 (defined as drop in post-bronchodilator of greater than 15% or 200 ml from baseline) study drug will be discontinued.

7. For those tolerating medication well, dose adjustments of metoprolol or equivalent placebo will be made by a blinded investigator based on tolerability according to the dose adjustment protocol (Table 3).

Visit 9: Clinic Visit for dose confirmation/finalization at 42 days:

Spirometry and EKG will be obtained in addition to obtaining an interim history, adverse events, and concomitant medications. During this visit, it will be confirmed that the subject is on the same dose as at last visit and is tolerating medication well. If not, study drug will be stopped. Drug will be accounted for and dispensed.

Visits 10, 12, 14: Phone Call at Day 56, 168 and 280:

Patients will be contacted by regular phone calls between clinic visits and queried about adverse events including:

1. Whether any acute exacerbations occurred within the previous month/after last contact

2. Whether the patient has any possible metoprolol-related side effects (see above)

3. Patients with any of these side effects will be assessed for severity, specifically with regard to whether the medication should be discontinued.

Visit 11: Clinic Visit at Day 112:

Interim history and adverse events will be collected. A complete history and physical will be obtained at this visit. Questionnaires will be administered again and spirometry, 6MWT and EKG will be performed. Drug will be accounted for and dispensed.

Visit 13: Clinic Visit at Day 224:

Interim history, heart rate, blood pressure and adverse events will be collected. Drug will be accounted for and dispensed.

Visit 15: Study End and Dose Wean Clinic Visit at Day 336:

Interim history and adverse events will be collected. A complete history and physical will be obtained at this visit. Questionnaires will be administered again and spirometry, 6MWT and EKG will be performed. Blood will be drawn for hsCRP, fibrinogen and pro-NT BNP. Dose of study drug will be halved at this visit and dispensed.

Visit 16 and 18: Phone calls at Day 343 and 357:

This call will ascertain any symptoms of beta-blocker withdrawal including palpitations, chest pain, light headedness and new or worsening shortness of breath. Patients reporting significant symptoms will be seen at an unscheduled protocol visit as indicated in table 2 above.

Visit 17: Clinic Visit to stop medication at Day 350:

Interim history and adverse events will be collected. A complete history and physical will be obtained to investigate any symptoms or signs of beta-blocker withdrawal. An EKG will be obtained.

Visit 19: In office closeout Clinic Visit at Day 364:

Interim history and adverse events will be collected. A complete history and physical will be obtained to investigate any symptoms or signs of beta-blocker withdrawal such as palpitations, arrhythmias, angina or myocardial infarction. An EKG will be obtained.

Visit 20: Phone call closeout Phone call at Day 378: Confirm vital status and collect interim history 4 weeks after last dose of study drug.
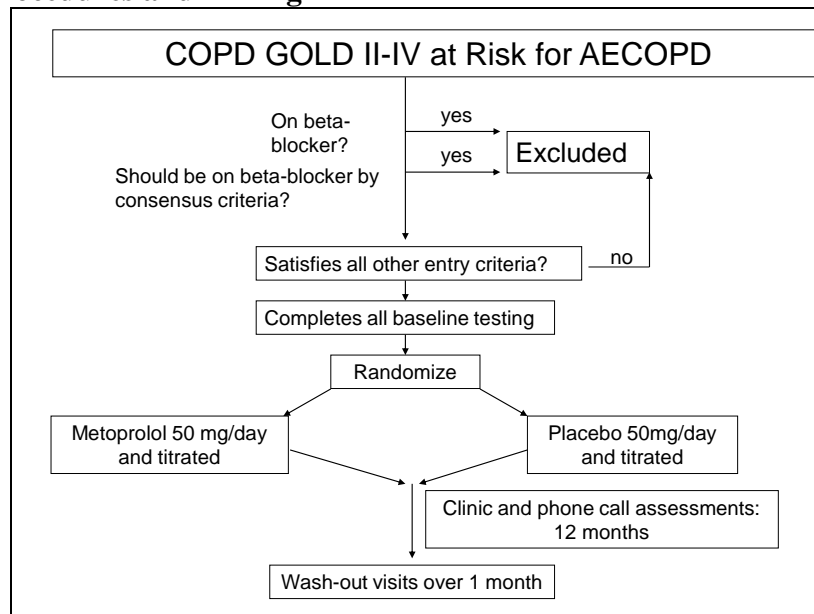
Additional Design Considerations

Recruitment and consent

Recruitment for the proposed trial will follow the well established procedures at the participating CCRN centers. Patients at these sites are recruited from the daily clinical practice of the CCRN investigators and their colleagues as well as from HIPAA compliant recruitment databases maintained at the majority of the facilities. As referral centers for COPD both within and outside the VA system, the CCRN sites care for a large number of patients with moderate to severe disease who are likely to meet inclusion and exclusion criteria. Based on our review of the prior azithromycin and simvastatin trials we are confident we have access to adequate numbers of patients to complete recruitment within the proposed three year time frame. Study records from these trials indicate that only 15% of enrolled patients were prescribed beta-blockers and as we will recruit a similar exacerbation-prone population, we anticipate a comparable number of patients will be excluded based on their current prescription for the drugs. This rate of beta-blocker use is similar to the 11.8% we observed in our analysis of patients with moderate to severe COPD enrolled in COPDGene which also supports the feasibility of meeting recruitment goals. We will also exclude patients with absolute indications for beta-blockers including myocardial infarction or acute coronary syndrome within the 3 previous years or significant congestive heart failure even if such patients are not currently receiving the drugs. Published data and our COPDGene analysis suggests that approximately 15-20% of patients with moderate to severe COPD would meet one or more of these criteria and thus would not qualify for participation. This rate of exclusionary baseline beta-blocker use and indication for use is significantly less than the 65-75% rate of prescribed or indicated statin use we observed in our prior clinical trial which successfully recruited more than 850 participants in approximately 42 months. This provides reasonable assurance that a sufficient number of participants should be able to be recruited for this trial and speaks to its clinical and scientific relevance as its conduct will provide important information on the role of beta-blockers in a COPD cohort who currently does not meet indications for treatment.

Potential COPD study participants will have to be screened for the use of beta-blockers or the necessity to use them by established criteria. As we have successfully done previously, medical record review and/or phone interviews will be used to screen potential patients before they are scheduled for on-site clinic visit testing to improve trial efficiency. During in clinic screening, subjects will be interviewed in detail about past medical history and prior records will be requested and reviewed. Absolute indications for beta blockade as established by international guidelines include myocardial infarction, acute coronary syndrome, percutaneous coronary intervention, or coronary artery bypass surgery within the prior 3 years and left ventricular dysfunction (ejection fraction < 40%).(29, 30)

An overview of the timing for screening potential study participants for beta-blocker use or need and the flow of study assessments and tests for study participants are shown in the Figure 2 below:

Figure 2. Screening Procedures and Timing

Before being enrolled, patients must consent to participate after the nature, scope, and possible consequences of the study have been explained in a form understandable to them. After identification of eligible subjects that wish to participate, signed informed consent will be obtained by well-trained Clinical Coordinators or a Study Investigator using an Institutional Review Board (IRB) approved consent document.

Details of the protocol will be discussed with the participant ensuring adequate time for consideration of the protocol (> 24 hours from initial discussion.). These individuals will then be approached with the informed consent form. The risks, benefits and alternatives will be discussed so that the decision to participate in the study will be made independently by the participant.

Any potential participants who cannot consent for themselves will be excluded. This includes anyone who will be, or will have been, in a stressful, painful, or drugged condition before or during the consent process or otherwise lacks the mental capacity to consent for themselves. We will not obtain consent from Legally Authorized Representatives (LARs). We will not enroll minors.

Informed consent is an ongoing process. Participants will be asked regularly by Clinical Coordinators or a Study Investigator if they have questions about the study. Furthermore subjects will be re-consented as determined necessary by each participating site's IRB in conjunctions with protocol amendments, study reports, and any other changes that would affect the participant's decision to stay in the study.

Discontinuation of Study Drug

There are four instances in which the study drug might be discontinued:
1. Development of symptoms that might represent medication-related side effects.

Prior to beginning the study patients are instructed about what might constitute a metoprolol-related side effect and whom they should notify should such symptoms develop. They are also queried at each clinic visit and phone contact about a specific list of possible metoprolol-related side effects. If potential side effects develop, study personnel will assess the severity of the problem and decide whether the study medication should be discontinued or reduced in dose.

2. Development of an absolute indication for beta blocker

This includes myocardial infarction, acute coronary syndrome, percutaneous coronary intervention, coronary artery bypass surgery or new congestive heart failure with ejection fraction <40%. In these instances study medication will be stopped and the patient referred for appropriate medical treatment.

3. Intercurrent illness

We anticipate that during the one year treatment period some patients will develop medical and/or surgical problems that are unrelated to COPD or to a possible metoprolol-related side effect but warrant treatment. In these instances the patient's treating physicians will decide whether the specific problem encountered warrants discontinuation of the study medication. Each patient will carry a wallet card for the duration of the study that provides information regarding the study and how unmasking of treatment can be accomplished should the indication merit (see below).

4. New prescription of a contraindicated medication

In instances in which the clinic coordinator/PI become aware that a patient has been prescribed or has started taking a contraindicated medication the study drug will be stopped. The study drug can be restarted if the contraindicated medication is stopped after consultation between the PI and the prescribing physician.

Concomitant Therapy

COPD-related

All concomitant COPD-related medications are permitted in this trial. This includes: inhaled corticosteroids, systemic corticosteroids long acting bronchodilators, short acting bronchodilators, phosphodiesterase inhibitors (roflumilast, theophylline), mucolytics, anti-oxidants, chronic antibiotics, and leukotriene modifiers.

Non-COPD-related

Given the expected age of the patients we will be enrolling many are likely to have one or more medical conditions in addition to COPD. Therapy for these problems will be continued at the direction of each patient's treating physician with the exceptions of the medications listed in the exclusion criteria.

Unmasking

Emergency situations may arise in which it is necessary to discontinue the study drug and unmask treating physicians, Emergency Department personnel, clinic personnel, or the patient to the assigned treatment. Participants will be given a wallet-size card explaining that they are in a research study and that they are

assigned to take either metoprolol or a matched placebo. The card will include telephone numbers of their site's pharmacy, the responsible investigator and the DCC. Patients will be instructed to carry the card at all times.

Situations that require unmasking are expected to be rare. In most emergency situations it will be sufficient to have the participant discontinue taking either the drug or the placebo until the event is resolved. It is possible however, that emergency personnel or treating physicians might feel it is necessary to know the medication the participant was taking to decide upon a rational course of treatment, or to ensure that other medications are not given that might adversely interact with metoprolol. In such cases the treating medical personnel should call the clinic pharmacy (first choice) or the DCC to obtain the treatment assignment.

Adverse events or hypersensitivity reactions may occur which are believed to be definitely or probably associated with the use of metoprolol, and which result in discontinuation of the use of the assigned medication by the participant. In such cases, the participant should be informed of the study drug prescription. The reason for this is to provide information to the participant regarding their use of metoprolol in the future. If the study drug is metoprolol, then the participant should be told that there have been indications that he/she is hypersensitive or reactive to this drug and use of it in the future should be avoided. The participant should also be informed if the study drug is placebo, so that his/her use of metoprolol in the future will not be restricted.

Such events must be thoroughly and carefully documented, and an Unmasking Report for the event must be completed and transmitted promptly to the DCC. Such events must be reported to the DSMC on at least a quarterly basis.

Inclusion of Women and Minorities

The prevalence of at least moderate COPD (defined by spirometry), the number of COPD-related office visits, and the COPD-related death rate are lower in minority patients than in Whites, but Blacks have a higher prevalence of ED visits and hospitalization. There are now more COPD deaths in women than men in the United States. The large male predominance in the armed services results in the fact that patients in any study that has Veteran's hospitals as enrollment sites will be disproportionately male unless special enrollment strategies are employed to assure a more equal gender distribution. Accordingly, strategies specifically targeting enrollment of women from the other sites will be will be needed for this study. Demographics vary by study site but all efforts will be made to recruit subjects of all genders and ethnicity.

Statistics

Sample size and power considerations for this clinical trial are based on the assumption that the primary endpoint will be the time to first exacerbation. The risk of exacerbation and estimated time to first exacerbation in the placebo group is based on observations in the control groups of the prior CCRN trials of azithromycin and simvastatin of similar design.(71, 72) The percent of patients suffering an exacerbation in the placebo arm of the azithromycin trial was 69% compared with 57% in those receiving azithromycin. In the simvastatin trial the probability of patients in the placebo arm suffering an exacerbation was 65% while the probability in those taking simvastatin was not statistically different (68%). The inclusion and exclusion criteria for the proposed trial are very similar to these prior studies and thus we anticipate a comparable exacerbation rate. Prior observational studies suggest that beta-blockers may reduce the risk of exacerbation by as much as 30% though it is probable that this overestimates the potential benefit due to residual confounding. We believe a 15% relative reduction (65% vs. 55%) in the one year probability of exacerbation is clinically significant and plausible and have thus selected that as our hypothesized effect size.

Assumptions:

The basic study design: two groups (metoprolol, placebo), recruitment over a 3-year period, each participant on study for 1 year, plus:

1. Two-sided alpha = 0 .05
2. Power = 90%
3. Primary Outcome = time to exacerbation (days)
4. Probability of exacerbation in the placebo group over 1 year: 65%
5. Probability of exacerbation in the metoprolol group over 1 year: 55%
6. Equal probability of assignment to either the placebo or beta-blocker group

These assumptions yield a predicted sample size requirement of 912 patients. Assuming 12% drop out yields a final sample size of 1028 patients.

Principal Analysis of the Primary Outcome Measure

All randomized patients will be followed until the end of the study (whether or not they continue to take study medications) and 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. Baseline characteristics in the two treatment arms will be compared using univariate descriptive statistics.   The analyses of the time to first COPD exacerbation (and all-cause mortality) will be performed using survival analysis. Kaplan-Meier survival curves will be used to describe the probability of remaining outcome-free in the two treatment arms as a function of time from randomization into the study. The curves will be compared using the log-rank test statistic.

Principal analysis of the secondary outcome measures

Secondary outcome measures will be assessed at baseline, 4 and 12 months. COPD exacerbation rates will be calculated as events/person-year and compared using a rate ratio. Independence of individual exacerbation events will be assured by considering patients to have experienced a new COPD exacerbation if they had been off of oral steroids and antibiotics for at least 14 days following their previous exacerbation.(57)   Exacerbation rates for each group, and the resultant rate ratio, will be analyzed using negative binomial regression modeling. The model will employ time-weighted intention-to-treat analyses with adjustments of the confidence intervals for between-subject variation (overdispersion).(73, 74) This methodology, which implicitly includes a random effect for the individual, has been established as the 'state of the art' for analysis of COPD exacerbation rates and is less subject to bias than other approaches. Continuous outcome measures, including absolute and percent changes in FEV_1 and FVC, 6 minute walk distance, dyspnea, and quality of life scores will be analyzed using multivariate repeated measures analysis of variance using the SAS Proc Mixed program.

Interim Analysis, Stopping Guidelines, Monitoring Boundaries

Participants will be randomized into this study over an estimated period of 3 years. Each participant will be randomized to one year of treatment and thus operationally the study will take 4 years to complete. A Data and Safety Monitoring Committee (DSMC) will meet approximately every 6 months to review recruitment, follow-up rates, and compliance, safety and efficacy results. Reviews of endpoint data at such meetings involve the problem of multiple statistical testing performed on a set of accumulating data. As a solution to the problem of repeated tests, we propose to adopt a group sequential method related to that proposed in the 1970s by O'Brien

and Fleming.(75) Such procedures typically require large critical values (or boundaries) early in the trial, but these decrease as the trial progresses. Because of the conservatism early in the trial, the critical value in the final analysis is close to the "nominal" critical value. The specific method we propose is a general approach to group sequential testing developed by Lan and DeMets for which neither the number of looks nor the increments between looks need to be pre-specified.(76) Rather, the Lan-DeMets approach requires only specification of the rate at which Type I error (which here will be chosen to be *alpha* = 0.05) will be "spent". This procedure allows "spending" a little of *alpha* at each interim analysis in such a way that at the end of the study, the total Type I error does not exceed 0.05.

We propose to carry out interim formal testing at the following time points: 12 months and 24 months, and 36 months after initiating the study. That is, analyses of efficacy will be presented to the DSMC beginning 12 months after the first patients are randomized and continuing at 12-month intervals thereafter until all patients have completed follow-up. A final analysis will be conducted at 48 months. Two-sided tests of significance will be assumed.

Use of the alpha-spending function approach to sequential monitoring has the advantage that, if necessary, additional looks at the data can be accommodated without affecting the overall probability of Type I error (alpha). Thus if recruitment into the trial takes longer than expected, analyses of the data for DSMC meetings may occur at information times which are different from those above.

Judgment concerning the continuation or termination of the study will involve not only the level of statistical significance observed at the interim analysis, but also the likelihood of achieving significance should enrollment continue to the original projected sample size. As an aid in this assessment, the Data Coordinating Center will supplement the group sequential analysis outlined above with calculations of conditional power based on the method of stochastic curtailment (also known as futility analysis).(77). This procedure evaluates the conditional probability that a particular statistical comparison will be significant (or not significant) at the end of the trial at the *alpha* level used in the design, given the hypothesized treatment difference and the endpoint data accumulated to date. Conditional power for the primary endpoint will be computed and provided to the DSMC as part of the interim study reports, and will include calculations based on the originally hypothesized treatment difference as well as the observed treatment difference up to that point in the trial.

Planned Subgroup Analyses: Using the approach outlined for primary and secondary analyses, we will perform two subgroup analyses for: 1) cardiovascular risk based on Personal HEART Score and 2) age greater versus less than 65. These analyses will primarily be hypothesis generating in nature.

Randomization

Randomization will be carried out by linking to the Data Coordinating Center through a website, (http://www.copdcrn.org) using a required COPD Clinical Research Network (CCRN) User ID and password. Randomization will be halted if required data are missing or if eligibility criteria are not met. The treatment assignment will not be issued until all criteria are met.

Each participant may receive only one randomization assignment. Randomization is stratified by each designated site in each clinical center. As an example, the Minneapolis clinical center has three sites: the VA Hospital in Minneapolis, Health Partners, and the Mayo Clinic. Separate schedules are created for each.

If all eligibility criteria are met the randomization program will issue a treatment assignment number such as '113'. This number matches a schedule that is retained in each site's clinical pharmacy, where separate supplies

of active drug and the placebo are also kept. The only persons knowing this schedule will be the pharmacist and DCC staff. The actual assignment will only be revealed in cases of emergencies where caregivers need to know what drugs the person was taking to provide treatment, or to avoid prescribing other medications that might adversely interact with the study drug. Each randomization code number will be associated with either metoprolol or placebo.

Active-drug and placebo will be identical in appearance. Clinic staff will make no attempt to determine the treatment assignment except in cases of emergency. It will be clearly explained to each study participant that they will be assigned to use either active drug or placebo, that the treatment assignment is random (i.e., cannot be predicted in advance, like the outcome of a coin-flip), and that they should not attempt to discover the treatment assignment.

Each time the participant returns for a renewed supply of study drug, the clinic coordinator must request that the pharmacist distribute pills for that specific participant's treatment assignment number, referring to the schedule in the pharmacy. If the participant's treatment assignment number is lost or forgotten, the information can be obtained by contacting the pharmacy or the DCC.

Study Confidentiality and Privacy

Study participants are identified by a unique number with a check digit for data integrity and an enrollment code consisting of the first letter of the participant's last name and the last two digits of their birth year. No PHI will be collected on study case report forms (CRF) or transmitted to the Data Coordinating Center (DCC). Any identifying information that could be classified as PHI will be kept separate from the participant CRFs in a secure environment at the clinical center accessible only to study staff allowed access to PHI. Documents which contain PHI requested by the DCC will be properly de-identified prior to transmission so that no PHI can be obtained from the records. Abnormal and clinically important screening test results including laboratory findings (serum chemistries, blood count values, cardiac markers) as well as clinically relevant EKG findings will be shared with the participant if he/she agrees shared with their primary care provider. Recommendations for referrals to specialist care will also be provided as necessary.

Data Security

The web-based data submission software is Oracle Application Server 10g Release 1, which uses the FIPS 140-2 compliant RSA 2048 bit algorithm to encrypt all data transmitted from the clinical sites to the DCC and from the DCC to the clinical sites. The website is secured by individual usernames and strong passwords.

Non-secure ports of all servers are located behind the DCC network firewall and accessible only under the following conditions: 1) a workstation physically present in the building and physically connected to the network 2) granted system access to the database server 3) a user name and password for that database server 4) a second username and password for database software 5) granted database access to data items.
All non-essential ports of the database server and web servers are closed. Only one secure (HTTPS) port on the website server is open outside of the firewall; this port displays the login link to the secured website.
Clinical site staff may access individual data items for a given participant (only those in their own clinic) for review, but they are unable to download any participant data, aggregate it, or cross reference an individual's data in any way via the website.

DCC staff will be trained and instructed not to export data to a standalone file, whether to laptops, hard drives, thumb drives, CDs, or any other media.

All servers are physically located in a secured room which is accessible only by a key card; currently, only two system administrators, one financial administrator, and the Database Administrator have access to this room. In addition, the secured room is located in a secured suite which is also accessible only by key cards given to current University of Minnesota employees located in the suite. The building is locked and accessible only by University of Minnesota employees located in the building after business hours and on weekends.

The security administrator for Oracle RDBMS and Oracle Application Server is the Database Administrator. A network system administrator regularly monitors for occurrences of attempted access to the network by unauthorized users. Only the Database Administrator has access to sensitive software passwords.

On-site backup of study data is performed nightly; off-site backups are taken twice weekly and stored at a secure University of Minnesota location, in a locked office in a secure suite. Additional redundancy is accomplished by storing duplicate database data files and control files on a separate server for disaster mitigation.

Clinical center staff will have access to participant CRFs and identifying information. DCC staff who will have access only to de-identified data which does not contain PHI include the senior statistician, masters level statisticians, the Database Administrator, and the Data Quality Control Specialist. Representatives of the Department of Defense who are allowed to have access to PHI are eligible to review study records.

Clinical Monitoring Plan:

Clinical trial monitoring to ensure the trial is conducted in compliance with Good Clinical Practices and ICH E6 will be multifaceted including real time oversight by the local PIs, regular and real time monitoring of entered clinical data by staff at DCC, as well as by an independent Data and Safety Monitoring Committee (DSMC) which will meet at 6-month intervals by teleconference or in person. The DSMC will be made up of a lead Medical Monitor, at least one cardiologist, one pulmonologist and a statistician.

The DCC will prepare all materials for the DSMC and will schedule meetings and prepare draft agendas. At each of its meetings the DSMC will review:
- Progress in recruiting
- By-clinic data on follow-up rates, forms completion, data entry, and adherence to protocol
- Efficacy: Survival-analyses of time to first exacerbation; rates of exacerbations per person-year as specified in the statistical plan for interim analyses
- Serious adverse events
- Other data (e.g., changes in lung function, adherence to assigned drug, other drug use)

The DCC will report on Serious Adverse Events (SAEs), with masking of the treatment assignment, to the clinical center PIs (to be forwarded to their IRBs), to the DOD Project Office, and to the DSMC.

The DCC will monitor the study to ensure that the:
- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The DCC will conduct monthly teleconferences throughout the study to review study enrolment and retention, procedures, adherence to protocol, timeliness of data entry, and adverse events including those that may warrant protocol changes.

Limitations

As with any clinical trial a major consideration is recruitment which often proves challenging. Based on our prior experience with the azithromycin and simvastatin clinical trials, we anticipate that our targets are readily achievable based on a number of factors. First, allowing three years for recruitment of the full population is in line with these two prior studies. Second, we believe that recruitment for the proposed trial will in fact be significantly easier than for the simvastatin trial, which excluded patients with even modest cardiovascular risk who should already be prescribed a statin. By only excluding patients with an absolute indication for beta-blockers (recent myocardial infarction, coronary artery bypass surgery, percutaneous coronary intervention, and congestive heart failure) many patients not eligible for the simvastatin trial will be eligible for the current study. Third, each participating center has a history of recruiting well not only for the CCRN trials but for other interventional studies in COPD.

There is a possibility that patients will not tolerate metoprolol, forcing drug to be discontinued. Though we anticipate that the inclusion of a protocol for dose reduction will minimize this possibility, this could reduce the number of patients continuing on study drug and compromise the probability of detecting a beneficial effect of beta-blockers on exacerbations. We have estimated this drop out to be 12% which is higher than expected based on the previously conducted safety studies of beta-blockers in COPD.

Clinical Impact and Future Directions

The results of this trial will definitively answer two questions of major public health importance. First, the study will settle the ongoing debate regarding the safety of beta-blockers in patients with COPD. If proven safe, these data will have immediate clinical impact and lead to significant modification of existing guidelines for the use of beta-blockers in patients with COPD and coexisting cardiovascular disease. This could lead to a major increase in the prescription of beta-blockers in this population which should in turn improve outcomes. Second, demonstrating the efficacy of beta-blockers in reducing the risk of acute exacerbations would establish an entirely new treatment approach for the prevention of these highly morbid and costly events. It would also allow future investigation of the possible role of beta-blockers in the acute treatment of hospitalized patients with COPD exacerbations in whom cardiac ischemia and arrhythmias are very common.

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Final Protocol: Beta-Blockers for the Prevention of Acute Exacerbations of COPD

βLOCK-COPD

Revised Protocol Version 04
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Revision History	
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-	**27 July 2015**
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Table of Contents

Beta-Blockers for the Prevention of Acute Exacerbations of COPD

Background and Significance
Chronic obstructive pulmonary disease (COPD) recently surpassed stroke as the 3rd leading cause of death in the United States and accounts for more than $40 billion annually in direct and indirect health care costs.(1, 2) COPD affects approximately 6% of civilians and at least 8% of the Veteran population, though the prevalence is increasing in both groups, and when Veterans with respiratory complaints are evaluated with spirometry and questionnaires rates of COPD may be as high as 43%.(3) Veterans with COPD also account for significantly higher all-cause and respiratory-related inpatient and outpatient health care utilization including number of physician encounters, emergency room visits, acute inpatient discharges, total bed days of care, pharmacy costs and total costs than those without COPD. Though existing pharmacotherapy can improve symptoms and quality of life, and modestly reduce the risk of acute exacerbations, no treatments alter the natural history of the disease or improve mortality. The impact of COPD on the military and Veteran populations is emphasized by the recent efforts to develop a joint Veterans Affairs/Department of Defense Clinical Practice Guideline for the disease.(4)

COPD is also associated with an increased risk of a number of major comorbid illnesses, most importantly cardiovascular disease which complicates diagnosis and management(5). Despite clear evidence that beta-blockers markedly reduce cardiovascular risk in patients with and without COPD concerns regarding their potential adverse respiratory effects have led to their dramatic underuse in those with the disease.(6, 7) This practice pattern persists despite recent observational data suggesting that beta-blockers may actually improve respiratory outcomes in COPD patients.(8-11) These data require validation and thus the proposed clinical trial of beta-blockers to prevent exacerbations of COPD addresses the most important chronic lower respiratory tract illness in the United States, will test the efficacy of a novel approach to prevent its most morbid and costly consequences, and will provide critical information needed to shape guideline recommendations regarding the management of patients with comorbid cardiovascular disease.

The majority of COPD-related morbidity and health-care costs are due to acute exacerbations, particularly those requiring hospitalization.(12, 13) Multiple treatment strategies have been employed to reduce the rate of exacerbations, including drugs administered via inhalation such as corticosteroids and bronchodilators as well as systemically delivered drugs such as prednisone, azithromycin and roflumilast.(14) Though each of these drugs reduces the rate of exacerbations by approximately 20 percent, little additional benefit is observed when they are used in combination and a substantial number of patients suffer frequent events despite ongoing maintenance therapy.(15) There are a number of possible explanations for the failure of available treatments to adequately control the disease including the fact that many exacerbations are triggered or made more severe by underlying cardiovascular disease. COPD is associated with up to a 5-fold increase in atherosclerosis and cardiovascular disease independent of shared risk factors,(16) and cardiovascular disease is an independent risk factor for hospitalization for COPD exacerbations,(17) in-hospital mortality,(18, 19) and long-term survival.(20-23) COPD is also associated with systolic and diastolic congestive heart failure as well as an increased risk for arrhythmias which are also associated with COPD exacerbations.(16)

It is well established that beta-blockers reduce mortality in patients with cardiovascular disease most notably after myocardial infarction (MI) (7), in the presence of congestive heart failure (24), and in the perioperative setting.(25) However, patients with COPD are often denied these medications because of concerns about possible adverse effects of beta-blockade on airway function.(6, 7, 26, 27) This is despite the fact that

cardioselective beta-blockers have no demonstrable effect on lung function regardless of the severity of airflow limitation or the presence of absence of bronchodilator reversibility.(26, 27) The current American Heart Association/American College of Cardiology guidelines for secondary prevention of coronary disease include beta-blockers as a class I intervention in patients with prior MI or acute coronary syndrome or with heart failure (28-30) and the Centers for Medicare and Medicaid include beta-blocker use after discharge following MI as a hospital performance measure. COPD has been cited as the primary reason for withholding beta-blockade in up to 33% of these patients.(6)

Multiple observational and retrospective studies have indicated that beta-blockers impact outcomes favorably in patients with COPD and underlying cardiovascular disease. Gottlieb et al. reviewed the medical records of all Medicare patients discharged after acute MI over an 18-month period (n = 210,752) and evaluated survival with Social Security records.(7) Of those with COPD, only 22% were given beta-blockers, compared to 34% of the population as a whole, but receipt of the drugs was associated with a 40% reduction in mortality, an effect similar to that seen in the entire population.   A second study examined the effect of beta-blockers as compared to other antihypertensive agents on all-cause two-year mortality in patients with COPD and found that the drugs were associated with a reduced risk of death (hazard ratio=0.57).(31) Similarly, Quint et al. analyzed data from the General Practice Research Database in the United Kingdom and found that initiating beta-blockers prior to or after an acute MI in patients with COPD was associated with similarly improved survival over 3 years of follow-up.(22)
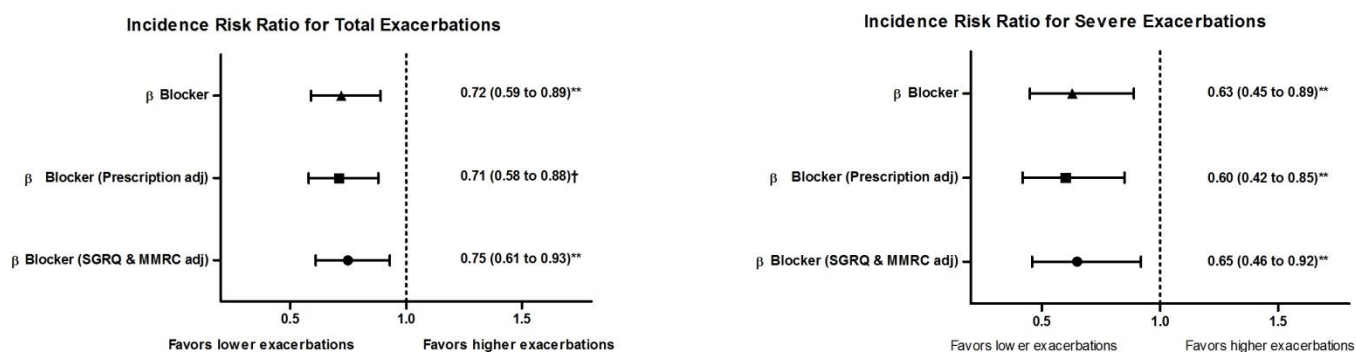
More recent data suggest that the benefits of beta-blockers may in fact extend to COPD patients without known cardiac disease and may also reduce the risk of acute exacerbations.(8, 9, 11, 32-35) Mancini demonstrated that COPD patients at high risk for coronary events who had an MI, were hospitalized for COPD, or died during the study period were less likely to be taking beta-blockers than those who did not suffer these events (17.1% vs. 24.0%, p<0.0001).(9) COPD patients at low risk for cardiovascular events who suffered these events were also less likely to be taking beta-blockers (7.5% vs. 9.3%, p<0.0001).(9) In an analysis of 825 patients admitted to the University of Alabama Hospital with acute exacerbations of COPD, beta-blocker use was an independent predictor of survival to hospital discharge (OR=0.39, 95%CI 0.14-0.99) after adjustment for a variety of factors including the presence of cardiovascular disease.(8) Rutten et al. also reported that the use of beta-blockers was associated with a reduced risk of death (OR=0.68, 0.56-0.83) and of acute exacerbation (OR=0.71, 0.60-0.83).(10)   Subgroup analyses demonstrated similar benefits in patients with versus without overt cardiovascular disease. A recent meta-analyses of nine retrospective cohort studies found that the pooled relative risk of COPD related mortality secondary to beta-blocker use was 0.69 (95% CI: 0.62-0.78).(11) Collectively, these data argue strongly that a prospective trial verifying that beta-blockers are both safe in COPD and efficacious to prevent exacerbations could have a major impact on mortality in both the civilian and Veteran populations.

The mechanisms by which beta-blockers may reduce exacerbations remain uncertain though several explanations are biologically plausible including both respiratory and cardiovascular effects. First, chronic blockade of beta-receptors may up-regulate receptor density in the lungs leading to improved bronchodilation with beta-agonists.(36) Second, murine data suggests that beta-blockers may reduce airway hyper-reactivity, inflammation and mucous secretion which may also be of benefit in the COPD airway.(37, 38) Third, beta-blockers may blunt the resting tachycardia in COPD (which occurs in up to 40% of patients) and thus improve cardiac performance and exercise tolerance leading to reduced symptoms.(39) Fourth, as we recently reported, P wave dispersion, a surrogate for atrial arrhythmias, is greater in patients with more frequent exacerbations, suggesting a causative role for arrhythmias (40) and raising the possibility that beta blockade may be beneficial in prevention.(41) Lastly, and perhaps most importantly, up to a third or more of acute exacerbations occur in

the absence of pulmonary inflammation and are very likely caused by cardiac events including both clinically apparent and subclinical coronary ischemia for which beta-blockers have clear benefits.(5)

The positive results of these observational studies should be tempered by the fact that they were all retrospective and hence subject to bias. Indeed, another recent large prospective study suggested that beta-blockers increased mortality in oxygen dependent COPD patients (HR 1.19; 95% CI, 1.04-1.37; p = 0.01).(42) In contrast however, we analyzed prospectively collected data from the multicenter COPDGene study (43) to determine the relationship between the use of beta-blockers and exacerbation, taking into account the propensity to prescribe beta-blockers based on the presence of coronary artery disease (CAD), congestive heart failure (CHF) and the severity of symptoms and airflow obstruction.(44) After adjustment for this propensity and for a number of other demographic and clinical characteristics, use of beta-blockers was associated with a significantly reduced rate of total and severe exacerbations as shown in Figure 1.

Figure 1. Relationship between beta-blocker use and acute exacerbations.

Shown are adjusted Incidence Risk Ratios (IRR) for total and severe exacerbations occurring during long term follow-up in COPDGene patients who were or were not on beta-blocker therapy at enrolment. Three models are shown including model 1 labeled beta-blocker and adjusted for age, gender, race, smoking burden, body mass index, airflow obstruction, %emphysema on computed tomography, coronary artery calcification, presence of congestive heart failure and coronary artery disease, and long acting respiratory medications; model 2 labeled beta-blocker (Prescription adj) adjusted for these factors and the propensity to be prescribed the drugs; and model 3 labeled beta-blocker (SGRQ and MMRC adj) adjusted further for the severity of dyspnea and impairment in quality of life as assessed by these scales. All values expressed as Odds Ratios (95% Confidence Intervals). SQRQ = St. George's Respiratory Questionnaire. MMRC = Modified Medical Research Council Dyspnea Scale. **p<0.01   †p<0.001

In those with advanced disease and on home oxygen, use of beta-blockers was again associated with a reduction in the rate of total (IRR 0.40, 95%CI 0.24 to 0.67; p=0.001) and severe exacerbations (IRR 0.49, 95%CI 0.25 to 0.98; p=0.045). Similar results from previous studies have been confounded by a lower rate of mortality of in those receiving beta-blockers suggesting residual healthy user bias. However, in our analysis no difference in deaths was observed between the two groups suggesting this is less likely. In addition, we observed no relationship between the use of other cardioprotective medications including angiotensin converting enzyme inhibitors and calcium channel blockers and exacerbations suggesting our observations are class specific.

In summary, despite multiple non-randomized studies suggesting a potential benefit of beta blockade in COPD patients including those without overt cardiovascular disease, the data are not definitive and the drugs continue to be underutilized in this population due to persistent safety concerns. This conundrum cannot be solved without a prospective randomized controlled trial. Therefore, we propose a safety and efficacy study of once-daily metoprolol succinate versus placebo in COPD patients at risk for acute exacerbation to determine the effect of beta-blockade on lung function, dyspnea, quality of life, exercise tolerance and exacerbation risk.

Research Design and Methods

Overview
This is a multicenter, prospective, randomized, double-blind, placebo-controlled trial that will enroll 1028 patients with at least moderately severe COPD over a three year period and follow them at regular intervals for one year. The primary endpoint is time to first acute exacerbation. Secondary endpoints include rates and severity of COPD exacerbations, cardiovascular events, all-cause mortality, lung function, dyspnea, quality of life and metoprolol-related side effects.

Hypothesis
The primary hypothesis is that metoprolol succinate will reduce the risk of COPD exacerbations as compared to placebo. The secondary hypothesis is that metoprolol succinate will not adversely impact lung function, exercise tolerance, dyspnea or quality of life as compared to placebo.

Specific Aims:
Primary: To determine the effect of once daily metoprolol succinate compared with placebo on the time to first exacerbation in moderate to severe COPD patients who are prone to exacerbations and who do not have absolute indications for beta-blocker therapy.

Secondary: To estimate the effect of metoprolol succinate compared with placebo on:

7) The rate and severity of COPD exacerbations over 12 months
8) Incidence and severity of metoprolol-related side effects including those that require cessation of drug
9) Lung function as assessed by spirometry, dyspnea as assessed by the Modified Medical Research Council Scale (MMRC)(45) and San Diego Shortness of Breath Questionnaire (46, 47), exercise tolerance as measured by six minute walk test (6MWD)(48), and quality of life as assessed by the Short Form 36 (49), St. Georges Respiratory Questionnaire (SGRQ)(50) and COPD Assessment Test (CAT)(51) and Personal HEART Score (52).
10) Hospitalizations
11) The rate of major adverse cardiovascular events (MACE) (defined by cardiovascular death, hospitalization for myocardial infarction, heart failure, or stroke), percutaneous coronary intervention or coronary artery bypass grafting
12) Combined rate of acute exacerbations and MACE
13) All-cause mortality

Eligibility Criteria
Inclusion Criteria
2. Male and female subjects, ≥ 40 and less than 85 years of age
2. Clinical diagnosis of at least moderate COPD as defined by the Global Initiative for Obstructive Lung Disease (GOLD) criteria (53):

      a. Post bronchodilator $FEV_1/FVC < 70\%$,

      b. Post bronchodilator $FEV_1 < 80\%$ predicted, with or without chronic symptoms (i.e., cough, sputum production).

5. Cigarette consumption of 10 pack-years or more. Patients may or may not be active smokers.
6. To enrich the population for patients who are more likely to have acute exacerbations (54), each subject must meet one or more of the following 4 conditions:

      e. Have a history of receiving a course of systemic corticosteroids or antibiotics for respiratory problems in the past year, or

      f. Visiting an Emergency Department for a COPD exacerbation within the past year, or

      g. Being hospitalized for a COPD exacerbation within the past year, or

      h. Be using or be prescribed supplemental oxygen for 12 or more hours per day

5. Willingness to make return visits and availability by telephone for duration of study.

Exclusion Criteria

18. A diagnosis of asthma as the primary cause of respiratory symptoms as established by each study investigator on the basis of the recent American Thoracic Society/European Respiratory Society and National Institute for Health and Care Excellence guidelines (55, 56) (Table 1).

Table 1: Clinical Features Differentiating COPD & Asthma

History	COPD	Asthma
Smoker or ex-smoker	Nearly all	Possibly
Symptom onset < 35 yrs	Rare	Common
Chronic productive cough	Common	Uncommon
Breathlessness	Persistent and progressive	Variable
Nighttime waking with breathlessness and wheeze	Uncommon	Common
Significant diurnal or day-to-day variation of symptoms	Uncommon	Common

If, after applying the above criteria, investigators are still unsure about the distinction in a specific patient bronchodilator testing with inhaled albuterol will be performed and patients with changes in FEV1 > 400 mL will be excluded.

19. The presence of a diagnosis other than COPD that results in the patient being either medically unstable, or having a predicted life expectancy < 2 years.
20. Women who are at risk of becoming pregnant during the study (pre-menopausal) and who refuse to use acceptable birth control (hormone-based oral or barrier contraceptive) for the duration of the study.
21. Current tachy or brady arrhythmias requiring treatment
22. Presence of a pacemaker and/or internal cardioverter/defibrillator
23. Patients with a history of second or third degree (complete) heart block, or sick sinus syndrome
24. Baseline EKG revealing left bundle branch block, bifascicular block, ventricular tachyarrhythmia, atrial fibrillation, atrial flutter, supraventricular tachycardia (other than sinus tachycardia and multifocal atrial tachycardia), or heart block (2nd degree or complete)
25. Resting heart rate less than 65 beats per minute, or sustained resting tachycardia defined as heart rate greater than 120 beats per minute.
26. Resting systolic blood pressure of less than 100mm Hg.

27. Subjects with absolute (Class 1) indications for beta-blocker treatment as defined by the combined American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons Guidelines which include myocardial infarction, acute coronary syndrome, percutaneous coronary intervention or coronary artery bypass surgery within the prior 3 years and patients with known congestive heart failure defined as left ventricular ejection fraction <40%.(29, 30)

28. Critical ischemia related to peripheral arterial disease.

29. Other diseases that are known to be triggered by beta-blockers or beta-blocker withdrawal including myasthenia gravis, periodic hypokalemic paralysis, pheochromocytoma, and thyrotoxicosis

30. Patients on other cardiac medications known to cause atrioventricular (AV) node conduction delays such as amiodarone, digoxin, and calcium channel blockers including verapamil and diltiazem as well as patients taking clonidine. Patients currently on beta blockers including beta blocker eye drops are also excluded.

31. Hospitalization for uncontrolled diabetes mellitus or hypoglycemia within the last 12 months.

32. Patients with cirrhosis

33. A clinical diagnosis of bronchiectasis defined as production of > one-half cup of purulent sputum/day.

34. Patients otherwise meeting the inclusion criteria will not be enrolled until they are a minimum of four weeks from their most recent acute exacerbation (i.e., they will not have received a course of systemic corticosteroids, an increased dose of chronically administered systemic corticosteroids, and/or antibiotics for an acute exacerbation for a minimum of four weeks).

Outcome Measures
The primary endpoint of this study is the time to first occurrence of an acute COPD exacerbation during the one-year treatment period.

Acute exacerbations are defined as a "complex of respiratory symptoms (increase or new onset) of more than one of the following: cough, sputum, wheezing, dyspnea, or chest tightness *requiring treatment with antibiotics and/or systemic steroids* for at least three days ".(54)

Acute exacerbations will be graded according to the following scale:

1. Mild (home management, with or without contacting a health care provider)
2. Moderate (requiring a visit to an Emergency Department)
3. Severe (requiring hospitalization with or without use of non-invasive positive pressure ventilation)
4. Very severe (requiring intubation and mechanical ventilation)

When patients report that they have severe or very severe exacerbation, the hospital records of that encounter will be obtained and reviewed.

The end of an exacerbation is when the patient has returned to their clinical baseline and has completed their course of antibiotic, oral steroids or combination of oral steroids and antibiotics to treat the exacerbation as defined by Anthonisen.(57) Since some patients may be on chronic steroid therapy or have varying steroid taper regimes used to treat an acute exacerbation by their primary physicians, a return to the baseline chronic steroid prescription level or end of the corticosteroid taper course will be considered the end of steroid therapy for an acute exacerbation. A relapse of a previous exacerbation will be defined as the complex of respiratory symptoms of more than one of the following: cough, sputum, wheezing, dyspnea, or chest tightness with a duration of at least three days *that recurs and requires re- treatment with antibiotics and/or systemic steroids without a return to baseline and within 2 weeks of the start date of a prior treated event*.

Secondary endpoints include:

13) The number of acute exacerbations occurring within 12 months of randomization

14) The number of ED visits resulting from acute exacerbations

15) The number of hospital admissions resulting from acute exacerbations

16) The number of hospital days resulting from acute exacerbations

17) The rate of major adverse cardiovascular events (MACE) (defined by cardiovascular death, hospitalization for myocardial infarction, heart failure, or stroke), percutaneous coronary intervention or coronary artery bypass grafting

18) Combined rate of acute exacerbations and MACE

19) All-cause mortality

20) The incidence of presumed metoprolol-related side-effects including new or worsened (Neural: depression, headache, syncope, seizures, somnolence, memory loss, loss of sexual desire or erectile dysfunction, and fatigue; Hypersensitivity: rash, pruritus, tongue or facial swelling; Gastrointestinal: diarrhea, vomiting, nausea or constipation; Cardiovascular: bradycardia and hypotension as discussed below; Respiratory: bronchospasm and changes in lung function as discussed below). Presumed metoprolol-related side effects will be specifically queried for and the severity recorded daily by participants during the dose titration period described below and at each clinic and phone visit. The rate of discontinuation of study drug due to presumed metoprolol related side effects will also be collected.

21) Quality of life (SF-36, SGRQ and CAT). The SF-36 is a generic tool to assess overall health status and allows comparison between different diseases. SF-36 scores range from 0 to 100 with higher scores representing better health status and a Minimal Clinically Important Difference (MCID) that can be appreciated by patients of 4(49). The SGRQ is a respiratory specific health status questionnaire with scores ranging from 0 to 100.(50) A lower score indicates a better health status and the MCID of the SGRQ total score is 4. The CAT is a simple, eight item, health status instrument for patients with COPD which is highly practical, has robust psychometric properties, and has been shown to be responsive to pulmonary rehabilitation and recovery from exacerbation.(51) Lower scores denote better health status and the MCID for the CAT is 2 points.

22) Dyspnea (MMRC and San Diego Shortness of Breath Questionnaire. The MMRC scale is a five-point scale originally published in 1959 that considers certain activities, such as walking or climbing stairs, which provoke breathlessness.(45, 58) The MMRC scale is not optimal as an evaluative instrument to measure changes in dyspnea as its broad grades are generally unresponsive responsive to interventions but does sub-classify patients well at baseline and has been used to assess dyspnea due to cardiovascular disease. A one point worsening (increase) in the scale would denote a marked worsening of dyspnea. The San Diego Shortness of Breath Questionnaire (SOBQ), a 24-item measure that assesses self-reported shortness of breath while performing a variety of activities of daily living.(47) The MCID for this questionnaire is 5.(46, 58).

23) Lung function (FEV1) as assessed by spirometry. Spirometry is the key pulmonary function parameter used for the monitoring of COPD severity. The MCID for changes in FEV1 is approximately 100 mL.(58)

24) Exercise capacity as assessed by the 6 minute walk distance (6MWD). The 6MWD has been used as a simple tool to assess overall exercise tolerance in patients with chronic cardiopulmonary disease including COPD. The MCID for the 6MWD in COPD is approximately 54 meters.(58)

25) Markers of cardiac stretch and systemic inflammation (NT-pro BNP N-terminal prohormone of brain natriuretic peptide, high sensitivity C-reactive protein, and fibrinogen). These parameters will be assessed at screening/randomization and at conclusion of the study to determine if beta-blockade impacts volume status and cardiac performance as well as levels of systemic inflammation that portend overall cardiac risk.

Description of the Investigational Product, Safety and Dosing Considerations

The clinical trial will utilize metoprolol succinate extended release tablets (50 mg) and matching placebo manufactured by Temple School of Pharmacy. Drug and matching placebo will be labeled using blinded coding and distributed to the study sites as needed to support enrolment and retention over the 42 months of human subject participation. The planned starting dose for metoprolol succinate extended release is one 50mg tablet taken orally daily though patients will undergo a dose titration procedure as outlined below which will result in a final dose of 25mg (1/2 of one tablet daily), 50 mg, or 100 mg (two tablets daily). Matching placebo manufactured at Temple University will be administered similarly. Following completion of the 12 month dosing period patients will be weaned off study drug over the following 4 weeks in order to avoid possible rebound myocardial ischemia. The same approach will be used for patients assigned to blinded placebo. There is no plan to seek an indication for metoprolol's specific use in patients with COPD and the trial will be conducted with an FDA IND waiver.

Metoprolol Safety: Prior Studies of Beta-blockers and Effects on Lung Function and Exercise

A number of studies have examined the safety of a number of beta blockers in patients with COPD though there have been no dose ranging studies to specifically determine the optimal dose for the prevention of exacerbations. Typical doses in trials of patients with coronary artery disease, congestive heart failure and hypertension range from 12.5 mg to 200 mg (see package insert) and doses in this range are well tolerated by patients with COPD including those with moderate to severe disease(59). The dose titration procedure is modeled after the approach used in a pivotal trial of metoprolol succinate in patients with heart failure (60). In that study, in which daily doses of up to 200 mg (mean dose 159 mg once-daily) were used, 10.3% of 1990 patients assigned to metoprolol succinate extended-release tablets patients discontinued for adverse reactions vs. 12.2% of placebo patients. Adverse events that occurred at an incidence of $\geq 1\%$ in the metoprolol succinate extended-release tablets group and greater than placebo by more than 0.5% (and regardless of causality) included dizziness/vertigo (1.8% vs. 1.0%), bradycardia (1.5% vs. 0.4%) and accident and/or injury (1.4% vs. 0.8%). The planned median daily dose of metoprolol in the proposed trial will fall between 50mg and 100mg and these as well as a number of other possible drug related side effects will be specifically sought and recorded.

Multiple studies demonstrate that in general the effect of cardioselective beta-blockers on lung function is minimal whether administered as a single dose or with continued treatment. A Cochrane analysis revealed that cardioselective beta-blockers produced no significant change in FEV1 or respiratory symptoms compared to placebo, given as a single dose (-2.05% [95% CI, -6.05% to 1.96%]) or for longer duration (-2.55% [CI, -5.94% to 0.84]), and did not significantly affect the FEV1 treatment response to beta2-agonists.(27, 59) Subgroup

analyses revealed no significant change in results for those participants with severe chronic airways obstruction or for those with a reversible obstructive component.   The trials of metoprolol tested single and multiple dosing of the drug at doses between 50mg and 200mg daily.

A more recent study of bisoprolol (a cardioselective beta-blocker) titrated to the maximally tolerated dose and given for four months in patients with coexistent congestive heart failure and severe COPD did demonstrate a modest reduction in FEV1 (70mL, p=0.01 vs. placebo and lower than accepted MCID) but reversibility was not impacted and all measures of health status exhibited a consistent non-significant improvement, including the Short Form 36 physical and mental component scores (2.6 vs. 0.5 and 0.8 vs. -0.3, respectively), Minnesota Living with Heart Failure Questionnaire (-2.5 vs. 3.5) and Chronic Respiratory Questionnaire (0.07 vs. -0.24).(61)

Two studies have examined the relationship between bisoprolol use and exercise time in patients with COPD and though in one dynamic hyperinflation was worsened slightly there was no impact on peak oxygen consumption or exercise time.(62, 63)

Selection of Metoprolol Dose and Dose Titration Procedures
The initial dose of metoprolol and subsequent titration procedures are adapted from the landmark Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) trial which definitively demonstrated the safety and efficacy of beta blockade in patients with symptomatic heart failure, a disease that similar to COPD had been considered a contraindication to beta-blocker treatment. That trial demonstrated that as compared to placebo, metoprolol CR/XL not only improved survival and reduced the need for hospitalization due to worsening heart failure but improved New York Heart Association functional class and had beneficial effects on patient well-being.(60) At the randomization visit, patients were allocated to treatment with metoprolol CR/XL or placebo administered once daily. The starting dosage was one 25-mg tablet once per day (half of a 25-mg tablet was recommended for patients with NYHA functional class III or IV). It was recommended to double the dosage after each 2-week period to reach the target dosage level of 200 mg/d of metoprolol CR/XL or placebo. This regimen could be modified according to the judgment of the investigator which was done successfully without compromising the blinding of study drug. If a patient did not tolerate the increased dosage of study drug, reduction in dosage was advocated. In a post hoc analysis, there was no difference in the benefit on mortality between patients who ultimately were titrated to a high dose of metoprolol (median 192 mg) and those titrated to a lower dose (median 76 mg). These data suggest that individualized dosing based on patient tolerability was appropriate but and titration to a dose above 100 mg may not be necessary to derive clinical benefits.(64) The initial starting dose of metoprolol is based on prior studies in patients with COPD suggesting tolerance both with single and continued dosing at comparable doses of the drug and other cardioselective beta-blockers.(27, 59, 65-67) It is anticipated that many patients will tolerate titration to the maximal dose of 100mg while some will require a dose reduction to remain on study medication. This approach was used in the previous CCRN trial of azithromycin to prevent exacerbations in which dosing was changed to every other day in patients with persistent diarrhea as well as the prior simvastatin trial in which three times per week dosing was used in the event of mild muscle discomfort or cramps.   Although guidelines and performance measures for the care of post-MI patients clearly indicate that virtually all such patients should be treated with beta-blocker therapy, the guidelines do not provide guidance on dosing and thus cannot be used to select the optimum dose for the proposed trial. There are a number of reasons for this uncertainty including the fact that the recommendations are derived from evidence accumulated from multiple clinical trials using a number of different drugs and with different regimens and that dose-response studies for long term outcomes have not been performed.(68, 69)

Study Flow

Patients will be screened and then randomized over a 2 week period and will then undergo a dose titration period for the following six weeks. Thereafter patients will be followed for 42 additional weeks on their target dose of metoprolol or placebo followed by a 4 week washout period. The schedule of study events is shown in Table 2.

(Note: screening and randomization visits can be combined as long as all procedures are conducted and eligibility can be confirmed.)

Table 2. Schedule of Study Interventions

Assessment	Screening+ (Day -14 to -1)	Randomization+ (Day 0)	Dose Titration (Days 14 and 28)	Dose Finalization (Day 42)	Clinic Visit (Day 112)	Clinic Visit (Day 224)	Wean IP Clinic Visit (Day 336)	Stop IP Clinic Visit (Day 350)	Close-out Clinic Visit (Day 364)
Informed Consent	X								
Medical History	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Physical Examination	X@	X	X	X	X@	X	X@	X	X
Safety Laboratory Assessments*	X								
Questionnaires**	X				X		X		
Troponin	X								
NT-pro BNP/CRP/fibrinogen		X					X		
Urine pregnancy	X								
Spirometry#	X		X	X	X		X		
EKG	X		X	X	X		X	X	X
6 Minute Walk		X			X		X		
Randomization		X							
Drug Dispensing		X	X	X	X	X	X		
Adverse Event Assessment		X	X	X	X	X	X	X	X
Drug Return and Accountability			X	X	X	X	X	X	

Phone Calls Day 2, 3, 15,16, 56, 168, 280, 343, 357, 378 for adverse event assessment

Visit windows +/- 3 days until dose finalization visit then +/- 14 days until Wean IP visit then +/- 3 days until close-out visit

Unscheduled Visits will include medical history, adverse event assessment, and both EKG and spirometry if during titration period until day 42; after day 42, the EKG and spirometry are at PI discretion

*Complete blood count, comprehensive metabolic profile including magnesium, AST, ALT, ALP

**Modified Medical Research Council Dyspnea Scale, COPD Assessment Test, St. George Respiratory Questionnaire, SF-36, San Diego Shortness of Breath Questionnaire; Personal HEART Score at screening only

#Pre- & Post-bronchodilator Spirometry at screening, otherwise post- bronchodilator only; not done at day 112 and 336 if patient has had an acute exacerbation in the two weeks prior

@ Full physical by physician; other visits may be brief and do not require physician

+   Screening and randomization visits may occur on the same day as long as all procedures are conducted and eligibility can be confirmed.

Visit 1: Day -14 to -1: Clinic Visit for Screening:

8. Informed consent prior to any study procedures.

9. Demographics (including age, gender, smoking history, oxygen use), information regarding where the patient might be seen in an emergency department (ED) and/or hospitalized, should this be required during the course of the study, primary care physician name and contact information.

10. A medical history and physical examination that includes recording a list of all medications including cardiac and respiratory medications, allergies, menopausal status (women), whether the patient has received influenza and/or pneumococcal pneumonia vaccination and if so, when, a list of all comorbidities, whether they have chronic bronchitis (defined in American Thoracic Society, 1986), previous COPD-related emergency room visits and hospitalizations (including whether they have previously required invasive or non-invasive mechanical ventilation), a body mass index (BMI) determination, and a resting oxygen saturation on the prescribed amount of supplemental O_2 being given, if any, or on air, and resting heart rate and resting blood pressure measurements.

11. Spirometry will be performed before and 15-30 min after inhalation of two puffs of albuterol (Ferguson, 2000; Hankinson, 2003), and post bronchodilator FEV1 and FVC will be recorded.

12. A 12 lead surface EKG in the resting state.

13. Quality of life and dyspnea assessment as described above.

14. Laboratory studies to include:
    a. Complete blood count with differential
    e. Comprehensive metabolic panel including blood urea nitrogen, creatinine, AST, ALT, ALP, and magnesium levels.
    f. Serum Troponin-I. Patients with troponin levels above the upper limit of normal suggesting recent ischemia will not be eligible for further screening and referred to their primary physician or the emergency department for evaluation.
    g. HCG (urine or blood) for pre-menopausal women.

Visit 2: Clinic Visit for Randomization at Day 0:

8. Interim medical history, physical exam and adverse event assessment.

9. Basic education about COPD, its treatment and how to recognize acute exacerbations. Patients will also be given a diary to collect the daily occurrence of potential metoprolol-related side effects (see Table of side effects above) and with recalling acute exacerbations including those that are treated at home, without contact with a health care provider.

10.   A wallet card indicating that they are participating in the study and stating "This person may be taking the beta-blocker: Extended release Metoprolol succinate. Please carefully consider potential drug interactions and contact research staff with any questions". The patients will be instructed to contact the clinic coordinator if they are given any new medications.

11. Assessment of functional capacity and exercise tolerance will be made by asking patients to perform a six minute walk test according to standard ATS guidelines.

12. Venipuncture for collection of markers of cardiac stretch and systemic inflammation (NT-pro Brain Natriuretic Peptide, hs-C-reactive protein, fibrinogen). These parameters will be reassessed at the conclusion of the study to determine if beta-blockade impacts volume status and cardiac performance as well as levels of systemic inflammation that portend overall cardiac risk.(70)

13. Only those with resting HR greater than or equal to 65 and SBP greater than or equal to 100 will be randomized.

14. Subject will be randomized to extended release metoprolol succinate or placebo (see details of randomization process below). A dose of 50 mg will be used as starting dose to be followed by dose titration protocol as described below (Table 3).

Visits 3 and 4: Phone Calls on Day 2 and 3:

Assessment of potential adverse respiratory events including symptomatic dyspnea, wheezing, chest tightness as well as other potential metoprolol-related side effects. Patients reporting symptoms concerning for significant intolerance of study drug may be seen at an unscheduled protocol visit as indicated in table 2 above. The investigator will determine whether study drug should be discontinued or the dose lowered.

Visits 5: Clinic Visit for dose adjustment at 14 days

8. Respiratory symptoms, concomitant medications, and whether any acute exacerbations occurred since the randomization visit will be assessed and recorded.

9. Possible metoprolol-related side effects will be assessed and recorded. If the patient is not tolerating the medication based on clinically significant symptoms as judged by the investigator, they will be discontinued from study medication or the dose lowered. If patients are not able to tolerate 25mg of study drug it will be discontinued.

10. The patient's self-assessment of compliance with study drug will be recorded, as will a pill count.

11. A repeat 12 lead EKG will be obtained.

12. Pre-menopausal women will be queried about their contraceptive use and pregnancy status. Those not using acceptable birth control will be discontinued from study medication.

13. Spirometry will be performed. If a patient has a significant decline in FEV1 (defined as drop in post-bronchodilator of greater than 15% or 200 ml from the baseline pre-bronchodilator value) and the PI believes that it is unsafe to continue study drug then it will be discontinued.

14. For those tolerating medication well, dose adjustments of metoprolol or equivalent placebo will be made by a blinded investigator based on assessment of symptoms and tolerability according to the dose adjustment protocol (Table 3). The investigator may modify the dose titration based on his/her clinical judgment and after consideration of vital signs, pulmonary function tests, and possible drug side effects.

Table 3. Dose adjustment protocol.

Visit	HR (beats/min)*	SBP (mmHg)	Instruction
Enrollment/Randomization	>=65	>=100	Randomize
Dose adjustment Visit at 14 days	>=70	>=100	↑ dose to 100 mg
		90-99	↔ maintain same dose
		<90	↓ dose to 25 mg or stop
	50-69	>= 90	↔ maintain same dose
		<90	↓ dose to 25 mg or stop
	<50	Any	Stop study drug
Dose adjustment Visit at 28 days	>=70	>=90	↔ maintain same dose
		<90	↓ dose by 1/2 or stop
	50-69	>=90	↔ maintain same dose
		<90	↓ dose by 1/2 or stop
	<50	Any	Stop study drug
Dose Finalization Visit at 42 days	>=70	>=90	↔ maintain same dose
		<90	Stop study drug
	50-69	>=90	↔ maintain same dose
		<90	Stop study drug
	<50	Any	Stop study drug

*Heart rate from vital signs (not EKG) will be used.

Visit 6 and 7: Phone calls on Day 15 and 16:

Assessment of potential adverse respiratory events including symptomatic dyspnea, wheezing, chest tightness as well as other potential metoprolol-related side effects. Patients reporting symptoms concerning for significant intolerance of study drug may be seen at an unscheduled protocol visit as indicated in table 2 above. The investigator will determine whether study drug should be discontinued or the dose lowered. If patients are not able to tolerate 25mg of study drug it will be discontinued.

Visits 8: Clinic Visit for dose adjustment at 28 days:

8. Respiratory symptoms, concomitant medications, and whether any acute exacerbations occurred since the randomization visit will be assessed and recorded.

9. Possible metoprolol-related side effects will be assessed and recorded. If the patient is not tolerating the medication based on clinically significant symptoms as judged by the investigator, they will be discontinued from study medication or the dose lowered. If patients are not able to tolerate 25mg of study drug it will be discontinued.

10. The patient's self-assessment of compliance with study drug will be recorded, as will a pill count.

11. A repeat 12 lead EKG will be obtained.

12. Pre-menopausal women will be queried about their contraceptive use and pregnancy status. Those not using acceptable birth control will be discontinued from study medication.

13. Spirometry will be performed. If a patient has a significant decline in FEV1 (defined as drop in post-bronchodilator of greater than 15% or 200 ml from the baseline pre-bronchodilator value) and the PI believes that it is unsafe to continue study drug then it will be discontinued.

14. For those tolerating medication well, dose adjustments of metoprolol or equivalent placebo will be made by a blinded investigator based on assessment of symptoms and tolerability according to the dose adjustment protocol (Table 3). The investigator may modify the dose titration based on his/her clinical judgment and after consideration of vital signs, pulmonary function tests, and possible drug side effects. :

Visit 9: Clinic Visit for dose confirmation/finalization at 42 days:

Spirometry and EKG will be obtained in addition to obtaining an interim history, adverse events, and concomitant medications. During this visit, it will be confirmed that the subject is on the same dose as at last visit and is tolerating medication well. If not, study drug will be stopped. Drug will be accounted for and dispensed.

Visits 10, 12, 14: Phone Call at Day 56, 168 and 280:

Patients will be contacted by regular phone calls between clinic visits and queried about adverse events including:

1. Whether any acute exacerbations occurred within the previous month/after last contact

2. Whether the patient has any possible metoprolol-related side effects (see above)

3. Patients with any of these side effects will be assessed for severity, specifically with regard to whether the medication should be discontinued and whether an unscheduled visit is needed.

The same issues will be addressed if participants contact the clinical center by phone on their own.

Visit 11: Clinic Visit at Day 112:

Interim history and adverse events will be collected. A complete history and physical will be obtained at this visit. Questionnaires will be administered again and spirometry, 6MWT and EKG will be performed. Drug will be accounted for and dispensed.

Visit 13: Clinic Visit at Day 224:

Interim history, heart rate, blood pressure and adverse events will be collected. Drug will be accounted for and dispensed.

Visit 15: Study End and Dose Wean Clinic Visit at Day 336:

Interim history and adverse events will be collected. A complete history and physical will be obtained at this visit. Questionnaires will be administered again and spirometry, 6MWT and EKG will be performed. Blood will be drawn for hsCRP, fibrinogen and NT-pro BNP. Dose of study drug will be halved at this visit and dispensed.

Visit 16 and 18: Phone calls at Day 343 and 357:

This call will ascertain any symptoms of beta-blocker withdrawal including palpitations, chest pain, light headedness and new or worsening shortness of breath. Patients reporting significant symptoms will be unblinded and may be seen at an unscheduled protocol visit as indicated in table 2 above.

Visit 17: Clinic Visit to stop medication at Day 350:

Interim history and adverse events will be collected. A complete history and physical will be obtained to investigate any symptoms or signs of beta-blocker withdrawal. An EKG will be obtained. Patients with signs or symptoms of withdrawal will be unblinded.

Visit 19: In office closeout Clinic Visit at Day 364:

Interim history and adverse events will be collected. A complete history and physical will be obtained to investigate any symptoms or signs of beta-blocker withdrawal such as palpitations, arrhythmias, angina or myocardial infarction. An EKG will be obtained. Patients with signs or symptoms of withdrawal will be unblinded.

Visit 20: Phone call closeout Phone call at Day 378: Confirm vital status and collect interim history 4 weeks after last dose of study drug.
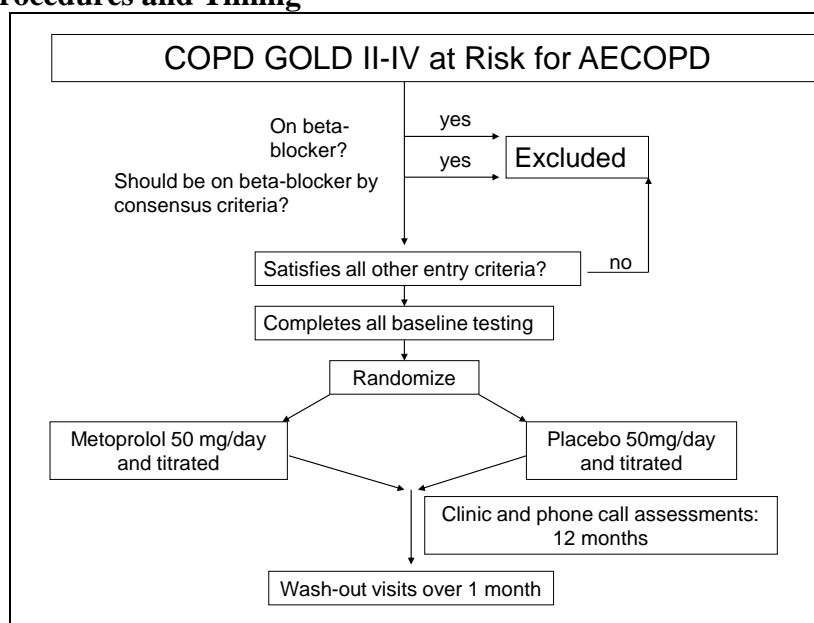
Additional Design Considerations

Recruitment and consent

Recruitment for the proposed trial will follow the well established procedures at the participating CCRN centers. Patients at these sites are recruited from the daily clinical practice of the CCRN investigators and their colleagues as well as from HIPAA compliant recruitment databases maintained at the majority of the facilities. As referral centers for COPD both within and outside the VA system, the CCRN sites care for a large number of patients with moderate to severe disease who are likely to meet inclusion and exclusion criteria. Based on our review of the prior azithromycin and simvastatin trials we are confident we have access to adequate numbers of patients to complete recruitment within the proposed three year time frame. Study records from these trials indicate that only 15% of enrolled patients were prescribed beta-blockers and as we will recruit a similar exacerbation-prone population, we anticipate a comparable number of patients will be excluded based on their current prescription for the drugs. This rate of beta-blocker use is similar to the 11.8% we observed in our analysis of patients with moderate to severe COPD enrolled in COPDGene which also supports the feasibility of meeting recruitment goals. We will also exclude patients with absolute indications for beta-blockers including myocardial infarction or acute coronary syndrome within the 3 previous years or significant congestive heart failure even if such patients are not currently receiving the drugs. Published data and our COPDGene analysis suggests that approximately 15-20% of patients with moderate to severe COPD would meet one or more of these criteria and thus would not qualify for participation. This rate of exclusionary baseline beta-blocker use and indication for use is significantly less than the 65-75% rate of prescribed or indicated statin use we observed in our prior clinical trial which successfully recruited more than 850 participants in approximately 42 months. This provides reasonable assurance that a sufficient number of participants should be able to be recruited for this trial and speaks to its clinical and scientific relevance as its conduct will provide important information on the role of beta-blockers in a COPD cohort who currently does not meet indications for treatment.

Potential COPD study participants will have to be screened for the use of beta-blockers or the necessity to use them by established criteria. As we have successfully done previously, medical record review and/or phone interviews will be used to screen potential patients before they are scheduled for on-site clinic visit testing to improve trial efficiency. During in clinic screening, subjects will be interviewed in detail about past medical history and prior records may be requested and reviewed. While medical records are not necessary to document exacerbation history, they may be requested and reviewed to help determine other eligibility criteria. Absolute indications for beta blockade as established by international guidelines include myocardial infarction, acute coronary syndrome, percutaneous coronary intervention, or coronary artery bypass surgery within the prior 3 years and left ventricular dysfunction (ejection fraction < 40%).(29, 30)

An overview of the timing for screening potential study participants for beta-blocker use or need and the flow of study assessments and tests for study participants are shown in the Figure 2 below:

Figure 2. Screening Procedures and Timing

Before being enrolled, patients must consent to participate after the nature, scope, and possible consequences of the study have been explained in a form understandable to them. After identification of eligible subjects that wish to participate, signed informed consent will be obtained by well-trained Clinical Coordinators or a Study Investigator using an Institutional Review Board (IRB) approved consent document.

Details of the protocol will be discussed with the participant ensuring adequate time for consideration of the protocol (> 24 hours from initial discussion.). These individuals will then be approached with the informed consent form. The risks, benefits and alternatives will be discussed so that the decision to participate in the study will be made independently by the participant.

Any potential participants who cannot consent for themselves will be excluded. This includes anyone who will be, or will have been, in a stressful, painful, or drugged condition before or during the consent process or otherwise lacks the mental capacity to consent for themselves. We will not obtain consent from Legally Authorized Representatives (LARs). We will not enroll minors.

Informed consent is an ongoing process. Participants will be asked regularly by Clinical Coordinators or a Study Investigator if they have questions about the study. Furthermore subjects will be re-consented as determined necessary by each participating site's IRB in conjunctions with protocol amendments, study reports, and any other changes that would affect the participant's decision to stay in the study.

Discontinuation of Study Drug

There are four instances in which the study drug might be discontinued:
5. Development of symptoms that might represent medication-related side effects.

Prior to beginning the study patients are instructed about what might constitute a metoprolol-related side effect and whom they should notify should such symptoms develop. They are also queried at each clinic visit and phone contact about a specific list of possible metoprolol-related side effects. If potential side effects develop, study personnel will assess the severity of the problem and decide whether the study medication should be discontinued or reduced in dose.

6. Development of an absolute indication for beta blocker

This includes myocardial infarction, acute coronary syndrome, percutaneous coronary intervention, coronary artery bypass surgery or new congestive heart failure with ejection fraction <40%. In these instances study medication will be stopped and the patient referred for appropriate medical treatment.

7. Intercurrent illness

We anticipate that during the one year treatment period some patients will develop medical and/or surgical problems that are unrelated to COPD or to a possible metoprolol-related side effect but warrant treatment. In these instances the patient's treating physicians will decide whether the specific problem encountered warrants discontinuation of the study medication. Each patient will carry a wallet card for the duration of the study that provides information regarding the study and how unmasking of treatment can be accomplished should the indication merit (see below).

8. New prescription of a contraindicated medication

In instances in which the clinic coordinator/PI becomes aware that a patient has been prescribed or has started taking a contraindicated medication the study drug will be stopped. The study drug can be restarted if the contraindicated medication is stopped after consultation between the PI and the prescribing physician.

Concomitant Therapy

COPD-related

All concomitant COPD-related medications are permitted in this trial. This includes: inhaled corticosteroids, systemic corticosteroids long acting bronchodilators, short acting bronchodilators, phosphodiesterase inhibitors (roflumilast, theophylline), mucolytics, anti-oxidants, chronic antibiotics, and leukotriene modifiers.

Non-COPD-related

Given the expected age of the patients we will be enrolling many are likely to have one or more medical conditions in addition to COPD. Therapy for these problems will be continued at the direction of each patient's treating physician with the exceptions of the medications listed in the exclusion criteria.

Unmasking

Emergency situations may arise in which it is necessary to discontinue the study drug and unmask treating physicians, Emergency Department personnel, clinic personnel, or the patient to the assigned treatment. Participants will be given a wallet-size card explaining that they are in a research study and that they are assigned to take either metoprolol or a matched placebo. The card will include telephone numbers of their site's pharmacy and/or the responsible investigator. Patients will be instructed to carry the card at all times.

Situations that require unmasking are expected to be rare. In most emergency situations it will be sufficient to have the participant discontinue taking either the drug or the placebo until the event is resolved. It is possible however, that emergency personnel or treating physicians might feel it is necessary to know the medication the participant was taking to decide upon a rational course of treatment, or to ensure that other medications are not given that might adversely interact with metoprolol. In such cases the treating medical personnel should call the clinic pharmacy and/or responsible investigator.

Adverse events or hypersensitivity reactions may occur which are believed to be definitely or probably associated with the use of metoprolol, and which result in discontinuation of the use of the assigned medication by the participant. In such cases, the participant should be informed of the study drug prescription. The reason for this is to provide information to the participant regarding their use of metoprolol in the future. If the study drug is metoprolol, then the participant should be told that there have been indications that he/she is hypersensitive or reactive to this drug and use of it in the future should be avoided. The participant should also be informed if the study drug is placebo, so that his/her use of metoprolol in the future will not be restricted.

Such events must be thoroughly and carefully documented, and an Unmasking Report for the event must be completed and transmitted promptly to the DCC. Such events must be reported to the DSMC on at least a quarterly basis.

Inclusion of Women and Minorities

The prevalence of at least moderate COPD (defined by spirometry), the number of COPD-related office visits, and the COPD-related death rate are lower in minority patients than in Whites, but Blacks have a higher prevalence of ED visits and hospitalization. There are now more COPD deaths in women than men in the United States. The large male predominance in the armed services results in the fact that patients in any study that has Veteran's hospitals as enrollment sites will be disproportionately male unless special enrollment strategies are employed to assure a more equal gender distribution. Accordingly, strategies specifically targeting enrollment of women from the other sites will be will be needed for this study. Demographics vary by study site but all efforts will be made to recruit subjects of all genders and ethnicity.

Statistics

Sample size and power considerations for this clinical trial are based on the assumption that the primary endpoint will be the time to first exacerbation. The risk of exacerbation and estimated time to first exacerbation in the placebo group is based on observations in the control groups of the prior CCRN trials of azithromycin and simvastatin of similar design.(71, 72) The percent of patients suffering an exacerbation in the placebo arm

of the azithromycin trial was 69% compared with 57% in those receiving azithromycin. In the simvastatin trial the probability of patients in the placebo arm suffering an exacerbation was 65% while the probability in those taking simvastatin was not statistically different (68%). The inclusion and exclusion criteria for the proposed trial are very similar to these prior studies and thus we anticipate a comparable exacerbation rate. Prior observational studies suggest that beta-blockers may reduce the risk of exacerbation by as much as 30% though it is probable that this overestimates the potential benefit due to residual confounding. We believe a 15% relative reduction (65% vs. 55%) in the one year probability of exacerbation is clinically significant and plausible and have thus selected that as our hypothesized effect size.

Assumptions:

The basic study design: two groups (metoprolol, placebo), recruitment over a 3-year period, each participant on study for 1 year, plus:

7. Two-sided alpha = 0 .05
8. Power = 90%
9. Primary Outcome = time to exacerbation (days)
10. Probability of exacerbation in the placebo group over 1 year: 65%
11. Probability of exacerbation in the metoprolol group over 1 year: 55%
12. Equal probability of assignment to either the placebo or beta-blocker group

These assumptions yield a predicted sample size requirement of 912 patients. Assuming 12% drop out yields a final sample size of 1028 patients.

Principal Analysis of the Primary Outcome Measure

All randomized patients will be followed until the end of the study (whether or not they continue to take study medications) and 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. Baseline characteristics in the two treatment arms will be compared using univariate descriptive statistics. The analyses of the time to first COPD exacerbation (and all-cause mortality) will be performed using survival analysis. Kaplan-Meier survival curves will be used to describe the probability of remaining outcome-free in the two treatment arms as a function of time from randomization into the study. The curves will be compared using the log-rank test statistic.

Principal analysis of the secondary outcome measures

Secondary outcome measures will be assessed at baseline, 4 and 12 months. COPD exacerbation rates will be calculated as events/person-year and compared using a rate ratio. Independence of individual exacerbation events will be assured by considering patients to have experienced a new COPD exacerbation if they had been off of oral steroids and antibiotics for at least 14 days following their previous exacerbation.(57) Exacerbation rates for each group, and the resultant rate ratio, will be analyzed using negative binomial regression modeling. The model will employ time-weighted intention-to-treat analyses with adjustments of the confidence intervals for between-subject variation (overdispersion).(73, 74) This methodology, which implicitly includes a random effect for the individual, has been established as the 'state of the art' for analysis of COPD exacerbation rates and is less subject to bias than other approaches. Continuous outcome measures, including absolute and percent changes in FEV_1 and FVC, 6 minute walk distance, dyspnea, and quality of life scores will be analyzed using multivariate repeated measures analysis of variance using the SAS Proc Mixed program.

Interim Analysis, Stopping Guidelines, Monitoring Boundaries

Participants will be randomized into this study over an estimated period of 3 years. Each participant will be randomized to one year of treatment and thus operationally the study will take 4 years to complete. A Data and Safety Monitoring Committee (DSMC) will meet approximately every 6 months to review recruitment, follow-up rates, and compliance, safety and efficacy results. Reviews of endpoint data at such meetings involve the problem of multiple statistical testing performed on a set of accumulating data. As a solution to the problem of repeated tests, we propose to adopt a group sequential method related to that proposed in the 1970s by O'Brien and Fleming.(75) Such procedures typically require large critical values (or boundaries) early in the trial, but these decrease as the trial progresses. Because of the conservatism early in the trial, the critical value in the final analysis is close to the "nominal" critical value. The specific method we propose is a general approach to group sequential testing developed by Lan and DeMets for which neither the number of looks nor the increments between looks need to be pre-specified.(76) Rather, the Lan-DeMets approach requires only specification of the rate at which Type I error (which here will be chosen to be *alpha* = 0.05) will be "spent". This procedure allows "spending" a little of *alpha* at each interim analysis in such a way that at the end of the study, the total Type I error does not exceed 0.05.

We propose to carry out interim formal testing for efficacy at two interim time points when approximately one third and two thirds of the expected primary outcome events (first exacerbation) in the placebo group have occurred. However, exacerbations will be included in the safety analyses presented to the DSMC beginning twelve months after the first patient is randomized and continuing at twelve month intervals until all patients have completed follow-up. A final analysis will be conducted at study completion. Two-sided tests of significance will be assumed.

Use of the alpha-spending function approach to sequential monitoring has the advantage that, if necessary, additional looks at the data can be accommodated without affecting the overall probability of Type I error (alpha). Thus if recruitment into the trial takes longer than expected, analyses of the data for DSMC meetings may occur at information times which are different from those above.

Judgment concerning the continuation or termination of the study will involve not only the level of statistical significance observed at the interim analysis, but also the likelihood of achieving significance should enrollment continue to the original projected sample size. As an aid in this assessment, the Data Coordinating Center will supplement the group sequential analysis outlined above with calculations of conditional power based on the method of stochastic curtailment (also known as futility analysis).(77). This procedure evaluates the conditional probability that a particular statistical comparison will be significant (or not significant) at the end of the trial at the *alpha* level used in the design, given the hypothesized treatment difference and the endpoint data accumulated to date. Conditional power for the primary endpoint will be computed and provided to the DSMC as part of the interim study reports, and will include calculations based on the originally hypothesized treatment difference as well as the observed treatment difference up to that point in the trial.

Planned Subgroup Analyses: Using the approach outlined for primary and secondary analyses, we will perform two subgroup analyses for: 1) cardiovascular risk based on Personal HEART Score and 2) age greater versus less than 65. These analyses will primarily be hypothesis generating in nature.

Randomization

Randomization will be carried out by linking to the Data Coordinating Center through a website, (https://beta.umn.edu or https://betablocker.umn.edu) using a required COPD Clinical Research Network (CCRN) User ID and password.
Randomization cannot occur if required data are missing or if eligibility criteria are not met. The treatment assignment will not be issued until all criteria are met.

Each participant may receive only one randomization assignment. Randomization is stratified by each designated site in each clinical center. As an example, the Minneapolis clinical center has three sites: the VA Hospital in Minneapolis, Health Partners, and the Mayo Clinic. Separate schedules are created for each.

If all eligibility criteria are met the randomization program will issue a treatment assignment number such as '113'. This number matches a schedule that is retained in each site's clinical pharmacy, where separate supplies of active drug and the placebo are also kept. The only persons knowing this schedule will be the pharmacist and DCC staff. The actual assignment will only be revealed in cases of emergencies where caregivers need to know what drugs the person was taking to provide treatment, or to avoid prescribing other medications that might adversely interact with the study drug. Each randomization code number will be associated with either metoprolol or placebo.

Active-drug and placebo will be identical in appearance. Clinic staff will make no attempt to determine the treatment assignment except in cases of emergency. It will be clearly explained to each study participant that they will be assigned to use either active drug or placebo, that the treatment assignment is random (i.e., cannot be predicted in advance, like the outcome of a coin-flip), and that they should not attempt to discover the treatment assignment.

Each time the participant returns for a renewed supply of study drug, the clinic coordinator must request that the pharmacist distribute pills for that specific participant's treatment assignment number, referring to the schedule in the pharmacy. If the participant's treatment assignment number is lost or forgotten, the information can be obtained by contacting the pharmacy or the DCC.

Study Confidentiality and Privacy

Study participants are identified by a unique number with a check digit for data integrity and an enrollment code consisting of the first letter of the participant's last name and the last two digits of their birth year. No PHI will be collected on study case report forms (CRF) or transmitted to the Data Coordinating Center (DCC). Any identifying information that could be classified as PHI will be kept separate from the participant CRFs in a secure environment at the clinical center accessible only to study staff allowed access to PHI. Documents which contain PHI requested by the DCC will be properly de-identified prior to transmission so that no PHI can be obtained from the records. Abnormal and clinically important screening test results including laboratory findings (serum chemistries, blood count values, cardiac markers) as well as clinically relevant EKG findings will be shared with the participant if he/she agrees shared with their primary care provider. Recommendations for referrals to specialist care will also be provided as necessary.

Data Security

The web-based data submission software is Oracle Application Server 11g Release 1. All data transmitted from the clinical sites to the DCC and from the DCC to the clinical sites is SSL encrypted. The cryptographic

libraries used for SSL are designed to meet FIPS 140-2 Level 2 certification. The website is secured by individual usernames and strong passwords.

Non-secure ports of all servers are located behind the DCC network firewall and accessible only under the following conditions: 1) a workstation physically present in the building and physically connected to the network 2) granted system access to the database server 3) a user name and strong password for that database server 4) a second username and strong password for database software 5) granted database access to data items.

All non-essential ports of the database server and web servers are closed. Only one secure (HTTPS) port on the website server is open outside of the firewall; this port displays the login link to the secured website.
Clinical site staff may access individual data items for a given participant (only those in their own clinic) for review, but they are unable to download any participant data, aggregate it, cross reference an individual's data, or view participant data from another clinical site via the website.

DCC staff will be trained and instructed not to export data to a standalone file, whether to laptops, hard drives, thumb drives, CDs, or any other media.

All servers are physically located in a secured room which is accessible only by a key card; currently, only two system administrators, one financial administrator, and the Database Administrator have access to this room. In addition, the secured room is located in a secured suite which is also accessible only by key cards given to current University of Minnesota employees located in the suite. The building is locked and accessible only by University of Minnesota employees located in the building after business hours and on weekends.
The security administrator for Oracle RDBMS and Oracle Application Server is the Database Administrator. A network system administrator regularly monitors for occurrences of attempted access to the network by unauthorized users. Only the Database Administrator has access to sensitive software passwords.
On-site backup of study data is performed nightly; off-site backups are taken twice weekly and stored at a secure University of Minnesota location, in a locked office in a secure suite. Additional redundancy is accomplished by storing duplicate database data files and control files on a separate server for disaster mitigation.

Clinical center staff will have access to participant CRFs and identifying information. DCC staff who will have access only to de-identified data which does not contain PHI include the senior statistician, masters level statisticians, the Database Administrator, and the Data Quality Control Specialist. Representatives of the Department of Defense who are allowed to have access to PHI are eligible to review study records.

Clinical Monitoring Plan:

Clinical trial monitoring to ensure the trial is conducted in compliance with Good Clinical Practices and ICH E6 will be multifaceted including real time oversight by the local PIs, regular and real time monitoring of entered clinical data by staff at DCC, as well as by an independent Data and Safety Monitoring Committee (DSMC) which will meet at 6-month intervals by teleconference or in person. The DSMC will be made up of a lead Research Monitor, at least one cardiologist, one pulmonologist and a statistician.

The Research Monitor, Nadia Hansel, MD, MPH is responsible to oversee the safety of the research and report observations/findings to the IRB or a designated institutional official. The Research Monitor will review all unanticipated problems involving risks to subjects or others associated with the protocol and provide an independent report of the event to the IRB. The Research Monitor may discuss the research protocol with the

investigators; shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; and shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

The DCC will prepare all materials for the DSMC and will schedule meetings and prepare draft agendas. At each of its meetings the DSMC will review:
- Progress in recruiting
- By-clinic data on follow-up rates, forms completion, data entry, and adherence to protocol
- Efficacy: Survival-analyses of time to first exacerbation; rates of exacerbations per person-year as specified in the statistical plan for interim analyses
- Serious adverse events
- Other data (e.g., changes in lung function, adherence to assigned drug, other drug use)

The DCC will report on Serious Adverse Events (SAEs), with masking of the treatment assignment, to the clinical center PIs (to be forwarded to their IRBs), to the DOD Project Office, and to the DSMC.

The DCC will monitor the study to ensure that the:
- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The DCC will conduct monthly teleconferences throughout the study to review study enrolment and retention, procedures, adherence to protocol, timeliness of data entry, and adverse events including those that may warrant protocol changes.

Limitations

As with any clinical trial a major consideration is recruitment which often proves challenging. Based on our prior experience with the azithromycin and simvastatin clinical trials, we anticipate that our targets are readily achievable based on a number of factors. First, allowing three years for recruitment of the full population is in line with these two prior studies. Second, we believe that recruitment for the proposed trial will in fact be significantly easier than for the simvastatin trial, which excluded patients with even modest cardiovascular risk who should already be prescribed a statin. By only excluding patients with an absolute indication for beta-blockers (recent myocardial infarction, coronary artery bypass surgery, percutaneous coronary intervention, and congestive heart failure) many patients not eligible for the simvastatin trial will be eligible for the current study. Third, each participating center has a history of recruiting well not only for the CCRN trials but for other interventional studies in COPD.

There is a possibility that patients will not tolerate metoprolol, forcing drug to be discontinued. Though we anticipate that the inclusion of a protocol for dose reduction will minimize this possibility, this could reduce the number of patients continuing on study drug and compromise the probability of detecting a beneficial effect of beta-blockers on exacerbations. We have estimated this drop out to be 12% which is higher than expected based on the previously conducted safety studies of beta-blockers in COPD.

Clinical Impact and Future Directions

The results of this trial will definitively answer two questions of major public health importance. First, the study will settle the ongoing debate regarding the safety of beta-blockers in patients with COPD. If proven safe, these data will have immediate clinical impact and lead to significant modification of existing guidelines for the use of beta-blockers in patients with COPD and coexisting cardiovascular disease. This could lead to a major increase in the prescription of beta-blockers in this population which should in turn improve outcomes. Second, demonstrating the efficacy of beta-blockers in reducing the risk of acute exacerbations would establish an entirely new treatment approach for the prevention of these highly morbid and costly events. It would also allow future investigation of the possible role of beta-blockers in the acute treatment of hospitalized patients with COPD exacerbations in whom cardiac ischemia and arrhythmias are very common.

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Summary of Beta-Blockers for the Prevention of Acute Exacerbations of COPD (Block-COPD) Protocol and SAP Amendments:

27 JULY 2015
Original protocol

21 SEPT 2015 First revision
Per the request of the DOD Human Subjects Protection Scientist at the HRPO the protocol has been revised to more clearly explain the role of the Research Monitor. The following information has been added to page 22 of the protocol under the Clinical Monitoring Plan, second paragraph:

"The Research Monitor, Nadia, MD, MPH is responsible to oversee the safety of the research and report observations/findings to the IRB or a designated institutional official. The Research Monitor will review all unanticipated problems involving risks to subjects or others associated with the protocol and provide an independent report of the event to the IRB. The Research Monitor may discuss the research protocol with the investigators; shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; and shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO."

20 MAR 2016 v.01
Page 6- Secondary Aims, 'Combined rate of acute exacerbations and MACE" (major adverse cardiovascular events) has been added.
Page 7 – eligibility criteria – inclusion - has been clarified to add a history of receiving antibiotics in addition to steroids and to add clarifying language about use or prescriptions for supplemental oxygen.
Page 7- eligibility criteria –exclusion- asthma exclusion has been clarify by adding "…as the primary cause of respiratory symptoms …"
Page 8 – exclusion – "Patients currently on beta blockers including beta blocker eye drops are also excluded" has been added.
Page 9- "Combined rate of acute exacerbations and MACE" has been added to secondary endpoints
Page 10 - secondary end points #13 – for consistency troponin has been deleted from list of lab tests and the word injury has been removed.
Page 13 Clarifications about the physical exam, spirometry and EKG have been added to the schedule of study interventions
Pages 16-18- Clarifying language has been added regarding scheduling unscheduled visits and un-blinding.

Typos have been corrected throughout and the protocol has been revised to include a title page, a table of contents, and a clear version date on each page and revision history.

26 AUG 2017 v.02
Page 12- Study Flow has been revised to include, "Note: screening and randomization visits can be combined as long as all procedures are conducted and eligibility can be confirmed." to clarify that these visits may be conducted on the same day.

Page 13 - <u>Table 2 - Schedule of Study Interventions</u> has been revised to include "Screening and randomization visits may occur on the same day as long as all procedures are conducted and eligibility can be confirmed." to clarify that these visits may be conducted on the same day.

Page15 – *Visits 5: Clinic Visit for dose adjustment at 14 day,* item number six has been revised with the following clarifying language, " … and the PI believes that it is unsafe to continue study drug then it will be discontinued."

Page 16 "Heart rate from vital signs (not EKG) will be used." has been added to <u>Table 3 - Dose adjustment</u> to clarify the source of heart rate.

Page17 – *Visits 8: Clinic Visit for dose adjustment at 28 days,* item number six has been revised with the following clarifying language, " … and the PI believes that it is unsafe to continue study drug then it will be discontinued."

Page 19- *Recruitment and consent information* has been revised to clarify that while medical records are not necessary to document exacerbation history, they may be requested and reviewed to help determine other eligibility criteria.

Page 21 – *Unmasking* information has been revised to clarify information the wallet card will contain and who may be contacted, specifically reference to the DCC has been removed.

Pages 24 - <u>Randomization</u> information has been revised to add updated website information and to clarify that randomization cannot occur if data is missing.

Page 24-25 - <u>Data Security</u> information has been updated to include updated software and password information.

Typos have been corrected throughout. The Table of Contents has been revised to reflect updated page numbers. The protocol version has been updated to v 02 and dated August 26, 2016.

24 FEB 2017 v.03
When we started the study we wanted to be conservative about enrolling patients at risk for bradycardia and thus chose a baseline heart rate of 70 as the lowest allowed for eligibility. We have not encountered any significant issues with bradycardia with this threshold and no patients have been taken off study drug for this reason. However, we have excluded a number of otherwise eligible patients and would therefore like to lower the baseline heart rate requirement from 70 to 65. The Independent Research Monitor and members of the DSMC, including the cardiologist have review this change and are in agreement that this change is reasonable and raises no additional concerns from their perspective. We would also like to revise the protocol to make clarifications regarding dose adjustment. Investigators will be handling dose titration based on his/her clinical judgment and after consideration of vital signs, pulmonary function tests, and possible drug side effects along with the dose titration table.
Summary of protocol revisions:
Page 7 – Exclusion criteria #8 revised, "resting heart rate less than 70 beats per minute…" to "resting heart rate less than *65* beats per minute…"

Page 15 – Clinic Visit 2 Randomization #6 revised, "Only those with resting HR greater than or equal to 70…" to "only those with resting HR greater than or equal to *65…"*

Page 15 – Clinic Visit 5 - #7 revised to, "For those tolerating medication well, dose adjustments of metoprolol or equivalent placebo will be made by a blinded investigator based on *assessment of symptoms and* tolerability according to the dose adjustment protocol (Table 3). *The investigator may modify the dose titration based on his/her clinical judgment and after consideration of vital signs, pulmonary function tests, and possible drug side effects.*

Page 16 – Dose Adjustment Protocol Table, Enrollment/Randomization HR has been lowered to >= *65*.

Page 17- clinic visit 8 revised to, "For those tolerating medication well, dose adjustments of metoprolol or equivalent placebo will be made by a blinded investigator based on *assessment of symptoms and* tolerability according to the dose adjustment protocol (Table 3). *The investigator may modify the dose titration based on his/her clinical judgment and after consideration of vital signs, pulmonary function tests, and possible drug side effects.*

Typos have been corrected throughout.

12 DEC 2017 v.04
During the December 1, 2017 DSMC meeting the DSMC approved revising the interim analysis plan from the 12 and 24 month time points to one third and two thirds of the expected primary outcomes events in the placebo group have occurred.

Protocol page 23:

Interim analysis plan has been revised from:
We propose to carry out interim formal testing at the following time points: 12 months and 24 months, and 36 months after initiating the study. That is, analyses of efficacy will be presented to the DSMC beginning 12 months after the first patients are randomized and continuing at 12-month intervals thereafter until all patients have completed follow-up. A final analysis will be conducted at 48 months. Two-sided tests of significance will be assumed.

to:
We propose to carry out interim formal testing for efficacy at two interim time points when approximately one third and two thirds of the expected primary outcome events (first exacerbation) in the placebo group have occurred. However, exacerbations will be included in the safety analyses presented to the DSMC beginning twelve months after the first patient is randomized and continuing at twelve month intervals until all patients have completed follow-up. A final analysis will be conducted at study completion. Two-sided tests of significance will be assumed.