Title: Tadalafil for Pulmonary Hypertension Associated with Chronic Lung Disease

PI: Ronald Goldstein, MD
Boston VA
Co-PI: Sharon Rounds, MD
Providence VA
Site-PIs: Shelley Shapiro, MD
Los Angeles VA
Ruxana Sadikot, MD
Atlanta VA
Edward Dempsey, MD
Denver VA

The Boston site and the PI (Ronald H. Goldstein, M.D.) will serve as the coordinating center for the clinical trial. The primary operation of the coordinating center will be to provide coordination and oversight for the study. The Boston site study coordinator(s) will be responsible for maintaining records, organizing the monthly telephone conference agendas and maintaining minutes for these calls. The coordinating center will also serve as the primary statistical and data management center for the trial. All sites will immediately report all SAE's to the VA CSRD Data Monitoring Committee as well as the Coordinating Center.

Rationale:

Chronic obstructive pulmonary disease (COPD) is a critical contributor to the clinical, social, and economic profile of the VA Healthcare system. In particular, COPD patients with right ventricular (RV) dysfunction due to untreated pulmonary hypertension (PH) constitute a patient subgroup at elevated risk for COPD-associated morbidity and mortality. Classical pharmacotherapeutic treatment strategies to attenuate clinically evident PH in COPD, including supplemental oxygen, are largely ineffective at maintaining normal cardiopulmonary hemodynamics and/or preventing right heart failure. A preponderance of basic science, translational, and clinical data accounts for this observation by demonstrating that i) hypoxia-mediated pulmonary vasoconstriction is not exclusively responsible for the clinical expression of PH in COPD and ii) hypoxia-mediated upregulation of signaling pathways that increase inflammation and/or oxidant stress results in maladaptive histopathophenotypic changes to pulmonary arterioles. In addition, specific oxidant stress and/or inflammation mediated perturbations to NO• dependent signaling pathways in the pulmonary artery endothelial and smooth muscle cells exposed to chronic hypoxia promote pulmonary vascular remodeling. In turn, interventions that aim to restore bioavailable levels of NO• in the pulmonary vasculature, including PDE-5 inhibitors, are associated with improvements in cardiopulmonary hemodynamics and functional capacity in various forms of PH. To date, however, the role of PDE-5 inhibition in improving pulmonary vascular function and exercise tolerance in patients with COPD and clinically evident PH is unresolved

and PDE-5 inhibitors are not currently considered a standard treatment for PH associated with COPD.

Hypothesis:

Pharmacological inhibition of PDE-5 will improve functional capacity in patients with COPD-induced moderate to severe PH.

Specific Aims:

This proposal describes a prospective, double-blind, placebo-controlled randomized clinical trial in 64 subjects to address this hypothesis.

Primary Aim: To study the effect of PDE-5 inhibition with Tadalafil on exercise capacity over 12 months as measured by 6MWT in patients with COPD and moderate or severe PH.

Secondary Aims: To determine the effect of Tadalafil on maximal VO2 at 12 months, and pulmonary vascular resistance (PVR) and mean pulmonary artery pressure (mPAP) will be assessed at 6 months.

We will also assess the effect of Tadalafil therapy on dyspnea, health related quality of life (HRQL), COPD exacerbations and hospital admissions over the 12 month study period.

Relevance to VA:

The functional, social, and economic burden of chronic obstructive lung disease (COPD) on the healthcare system is extraordinary. According to the VA HSR&D Health Economics Resource Center, COPD ranks 5th among the 40 most common chronic clinical conditions in the U.S. Veteran patient population and is responsible for >14,000 VA hospital admission annually. Importantly, COPD is associated with frequent emergency room visitation and/or patient hospitalizations. Pulmonary hypertension (PH) is a common comorbid condition that worsens morbidity and mortality in patients with COPD. This study will examine the potential for Tadalafil, a phosphodiesterase type-5 (PDE-5) inhibitor to improve functional status by decreasing PH. Results from this study are expected to define the potential use of PDE-5 inhibitors in COPD-induced PH. If successful, this treatment option may improve quality of life and outcomes for the large number of veterans afflicted with PH due to COPD.

Study design:

We propose a prospective randomized, double blind, placebo-controlled clinical trial to test our hypothesis that PDE-5 inhibition is an effective treatment strategy in patients with COPD and moderate to severe PH.

Inclusion criteria

1. Male and female U.S. Veteran patients 40-85 years old, with Gold Stage ≥ II COPD by pulmonary function testing (FEV_1/FVC <0.70) performed within 12 months of recruitment.

2. Eligible subjects must have PH defined for this study as a mean pulmonary artery pressure ≥25 mm Hg, pulmonary vascular resistance >2.5 Wood units, and pulmonary artery capillary wedge pressure ≤18 mm Hg at rest on right heart catheterization performed within 6 months of study enrollment.

Exclusion Criteria

1. PH belonging to the following subgroups of the updated Dana Point Clinical Classification: Group 1 (Idiopathic, heritable, drug- or toxin-induced, Associated Pulmonary Arterial Hypertension (APAH) with connective tissue disease, congenital heart disease, or HIV), Group 2 (left atrial hypertension), Group 3 PH not due to COPD, Group 4 (chronic thromboembolic PH) or other forms of PH not associated with primary lung disease.
2. Patients with a history of systemic hypotension in the ambulatory setting (reproducible measurements of systolic blood pressure <89 mmHg) on chart review.
3. Patients with moderate or severe hepatic impairment (Child-Pugh B and C).
4. Patients with severe renal insufficiency (GFR <30 ml/min/1.73 m^2).
5. Severe aortic stenosis (aortic valve area <1.0 cm^2).
6. Patients with any acute or chronic impairment (other than dyspnea), limiting the ability to comply with the study requirements.
7. Patients with current unstable angina, recent myocardial infarction or recent stroke (within 6 months).
8. Patients with untreated hypoxemia (SaO_2 <92%) at rest.
9. Patients with any known coagulopathy.
10. Patients requiring nitrate therapy for any clinical indication.
11. Patients with an active prescription for any PDE-5 inhibitor or any other pulmonary vasodilator medication other than oxygen.
12. Patients with a history of nonarteritic anterior ischemic optic neuropathy.
13. Contraindication to Tadalafil use including allergy to any PDE-5 inhibitor, anatomical deformations of the penis, sickle cell anemia, multiple myeloma, leukemia, bleeding disorders, active peptic ulcer disease, retinitis pigmentosa or other retinal disorders.
14. The use or anticipated use of any of the following drugs: any nitrate, protease inhibitor, anti-fungal agent (oral only), and/or rifampin, or doxazosin.
15. Pregnant or breastfeeding women.
16. Patients with a known 6-minute walk distance of less than 50 meters on prior testing.
17. Patients with veno-occlusive disease.

Source of Participants and Participant Recruitment:

Patient recruitment will occur by 2 mechanisms at the Boston site.

1. Database Search: A population of potential study patients will be generated by looking at the echocardiography patient database (Xcelera). This database provides sufficient information to enable ready identification of patients meeting pulmonary artery systolic pressure for study enrollment.

Subsequently, a chart review will be performed on potential patients to evaluate for inclusion and exclusion criteria including review of available clinical

studies in CPRS to categorize the patient's pulmonary hypertension (such as laboratory data--liver function tests, HIV, renal function; heart catherization; pulmonary function tests; CT scan of the thorax; sleep study; echocardiography and V/Q scan or chest CT angiography).

Potential subjects (name, last 4 digits of SSN) will be temporarily recorded in a password protected "screening spreadsheet" kept in a restricted access folder on a VA secure server which only the PI and research staff have access to. After subjects are identified by screening of our database and chart review, subjects will be recruited by mailings that provide i) information regarding the study, ii) the reason for which patients were contacted, and iii) simple methods by which to declare or decline interest in study participation. Interested subjects will be asked to contact our study staff by telephone and/or the mailing will include a postcard for patients to return indicating an interest or indicating a wish not to be further contacted. If patients return the postcard indicating a wish not to be contacted further, no further contact will take place. Patients who do not respond to the mailing by telephone or returning the postcard will be contacted by telephone approximately 2 weeks after the mailing to be invited to participate. Information of patients who decline participation by mail or after telephone contact will be deleted from the "Screening Spreadsheet". Patients who are interested in participating will be scheduled for a screening visit.

2. In-clinic Referral. Study patients may also be identified during routine clinical practice that involves PH and COPD patients in the Cardiology, PH and Pulmonary medicine longitudinal clinics. Providers in the Pulmonary, Cardiology, and PH clinics will be educated about the study and the inclusion/exclusion criteria. Providers will inform patients about the study, and provide them with contact information for the study coordinator/investigators. Patients who contact the study coordinator/investigators and express interest in the study will have a chart review conducted as above, and will be scheduled for a screening visit if potentially eligible.

Study visits (Total of 8 Study Visits and 8 Telephone Calls)

1. Screening visit.

At the screening visit, the study will be explained to the patient. Inclusion and exclusion criteria will be reviewed. If patients meet eligibility criteria and do not have any exclusion criteria, and are willing to participate in the study, written informed consent will be obtained.

The informed consent process will be undertaken by study investigators who have been trained in human subject protection and are credentialed by the VA to conduct the informed consent process. The investigator will explain the study to the potential participants and answer any questions that they may have regarding the study protocol. The investigator will make it clear that the protocol is research as well as voluntary and that declining participation will in no way affect further evaluation or access to clinical care. Participants will also be informed that they may withdraw their consent at any point throughout the study.

Patients will be given adequate time to read the consent form and discuss its contents with research personnel before signing the consent form. Participants will then be asked to sign an IRB-approved written consent document and health insurance portability and accountability act (HIPAA) agreement, which will allow data pertinent to the study to be collected.

Following the completion of informed consent, the test dose visit will be scheduled.

2. Test dose visit:

At this visit, the subjects will undergo a history and physical exam. Blood will be drawn at the clinical phlebotomy lab for BNP measurement. They will be asked to fill out the Shortness of Breath, St. George's Respiratory and Veterans Rand 36 Item Health Survey (VR-36) questionnaires. A six minute walk test will be performed.

Next, we will randomize the patients:

Randomization: The randomization process will occur by computer generated number assignment. The study investigator, after entering an order for study drug in the CPRS system, will bring the assigned number as well as a copy of the informed consent to the pharmacy. The Boston research pharmacist will then match the number to the appropriate test dose medication (study drug or placebo) based on the randomization, identical aside from number labeling. The Boston research pharmacist will distribute placebo/Tadalafil to all study sites, (Boston, Providence, Los Angeles, Denver and Atlanta).

Any enrolled women of childbearing potential will have to have had a documented negative pregnancy test and must be using adequate contraception prior to receiving test dose.

Test dose protocol: Following at least 10 minutes of quiet rest after the 6 minute walk test, blood pressure will be measured by sphygmomanometer and oxygen level will be assessed by a fingertip probe. Subjects will then receive a test dose of the study medication (Tadalafil 20mg or placebo by mouth) if the baseline systolic blood pressure is greater than 90mmHg AND the oxyhemoglobin saturation is greater than 92% on room air or on the patient's typical flow rate of supplemental oxygen at rest. The subject will be observed and the blood pressure and oxygen level will be re-measured and recorded at baseline, 30 minutes post baseline, 1 hour post baseline and then 2 hours post baseline after the test dose to ensure that the blood pressure and oxygen levels are not adversely affected by the medication. If at any time point in the 2 hours following the test dose a subject develops hypotension (systolic blood pressure < 90mmHg, or a drop in systolic blood pressure of greater than 20mmHg accompanied by symptoms such as dizziness, lightheadedness, or syncope), or if the patient experiences significant hypoxemia (a decrease in oxyhemoglobin saturation to less than 90% on room air or, for subjects on supplemental oxygen, a decrease in

oxyhemoglobin saturation that requires an increase in supplemental oxygen to greater than 4lpm at rest to maintain a oxyhemoglobin saturation of 90%), that subject will not participate further in the study. Subjects experiencing hypotension or worsened hypoxemia as above will receive appropriate monitoring and clinical care, potentially including hospital admission, supplemental oxygen, IV fluids, etc., until their blood pressure and oxygenation improve.

Subjects who tolerate the test dose will be scheduled for a baseline study visit.

In the situation whereby another clinical service intends to start prazosin in a patient already on the study, we propose the administration of the first dose of prazosin in the pulmonary clinic with clinical monitoring and will follow the test dose protocol described above. If hypotension developed as per the protocol the subject will not participate further in the research study.

3. Baseline Visit:

At the baseline visit, a brief interview will be conducted to assess for any recent changes in health status. Echocardiogram and cardiopulmonary exercise testing will be performed. (Patients requiring supplemental oxygen will not have a cardiopulmonary exercise test.) The study medication will be prescribed after these tests at this visit. The research pharmacist will provide the patient with a numbered box containing either placebo or study drug. The patient will be provided with a supply of 20 mg Tadalafil tablets or identical placebo tablets.

Women of childbearing potential will have to have a documented negative pregnancy test and must be using adequate contraception during the study treatment phase and for 9 months afterward. Monthly pregnancy tests will be done, and compliance with contraception use will be documented at the telephone and clinic follow up visits. Should a female become pregnant at any time during the study, the study medication will be discontinued at that time.

The patients will be instructed to take 1 tablet daily for three days beginning the following morning (day 1). After telephone contact with a study team member on day 3, assuming no adverse effects are noted, the patient will be instructed to take two tablets per day. Patients who describe new symptoms, particularly dizziness, lightheadedness, or increased dyspnea, will be evaluated in clinic and blood pressure and peripheral oxygen saturation levels will be assessed before advancing therapy.

Study Drug: Tadalafil is an oral PDE-5 inhibitor that was approved by the Food and Drug Administration (FDA) in 2009 for use in treating pulmonary arterial hypertension (WHO Group I). It is administered as a standard dose of 40 mg (2, 20 mg pills). In WHO group I patients, it has been shown to be effective in improving distance achieved on the 6MWT and time to clinical worsening, as well as mean pulmonary pressure and PVR. The half-life of Tadalafil is 15-35 hours, which enables the proposed dosing strategy. Compliance will be assessed by

monitoring return pills and pill counts with the assistance of the research pharmacist.

Day 3 Telephone Follow-up

Following initiation of therapy, study staff will make telephone contact with each participant at post-randomization day 3 to identify any early problems with treatment adherence and to ascertain any early adverse events. The participant will be asked a series of questions to ensure that the patient remains active and performing normal activities of daily living. If no adverse events or symptoms are reported, the patient will be instructed to increase the dose of study drug or placebo to 2 tablets (40mg) by mouth per day the following morning.

Subsequent monthly follow up phone calls will occur between clinic visits

Follow up visits.

Patients will undergo routine follow up visits as outlined in Table 1 to assess compliance with medication use, changes in symptoms, development of adverse reactions and further data collection. At all study visits, history and physical exam, medication compliance, exacerbation history and 6 minute walk tests will be performed. The patient will also complete the Shortness of Breath, St. George's Respiratory and Veterans Rand 36 Item Health Survey (VR-36) questionnaires. In addition, adverse event monitoring, interim ED visits and hospitalizations will be assessed and recorded. Any exacerbations of COPD, defined as an acute worsening of respiratory symptoms, including dyspnea, cough, sputum production, requiring either ED visit, hospitalization, and/or therapy with antibiotics or corticosteroids, will be recorded. If in follow up, patients develop gastroesophageal reflux symptoms, a known side effect of Tadalafil, then proton pump inhibitor therapy (omeprazole 20 mg per day) will be offered.

Summary of follow up visits is as follows:

4. One month visit: history and physical examination, Shortness of Breath, St. George's Respiratory and Veterans Rand 36 Item Health Survey (VR-36) questionnaires, 6MWT.
5) Three month visit: history and physical examination, Shortness of Breath, St. George's Respiratory and Veterans Rand 36 Item Health Survey (VR-36) questionnaires, 6MWT.
6) Six month visit: history and physical examination, Shortness of Breath, St. George's Respiratory and Veterans Rand 36 Item Health Survey (VR-36) questionnaires, 6MWT, blood sample for BNP drawn in clinic lab, and right heart catheterization will be performed.

7) Nine month visit: history and physical examination, Shortness of Breath, St. George's Respiratory and Veterans Rand 36 Item Health Survey (VR-36) questionnaires, 6MWT.
8) Twelve month visit: history and physical examination, Shortness of Breath, St. George's Respiratory and Veterans Rand 36 Item Health Survey (VR-36) questionnaires, 6MWT, blood sample for BNP, echocardiogram, cardiopulmonary exercise study.

	Randomization/ Test Dose Visit	Baseline Visit	Telephone calls*	Month 1	Month 3	Month 6	Month 9	Month 12
Contact	Clinic	Clinic	Tel	Clinic	Clinic	Clinic	Clinic	Clinic
Medical History/Physical	X			X	X	X	X	X
Assess medication compliance			X	X	X	X	X	X
6-Minute Walk Test	X			X	X	X	X	X
Echocardiogram		X						X
CPET**		X						X
Shortness of Breath , St. George's Respiratory and Veterans Rand 36 Item Health Survey (VR-36) questionnaires	X			X	X	X	X	X
BNP	X					X		X
RHC						X		
Exacerbation History		X	X	X	X	X	X	X
Adverse Event Monitoring	X	X	X	X	X	X	X	X

Table 1. Follow-up Clinic Visits, telephone calls and schedule of studies Tel, telephone contact; CPET, cardiopulmonary exercise stress test; BNP, N-terminal brain natriuretic peptide; RHC, right heart catheterization

*Day 3, Month 2, 4, 5, 7, 8, 10, 11

**Patients requiring supplemental oxygen will not have a CPET

Subjects will receive $50 for each clinic visit for their time and effort.

Study procedures that occur at each study visit are described below.

Specific Study Procedures:

Questionnaires: The Shortness of Breath Questionnaire will be the dyspnea questionnaire used and the St. George's Respiratory Questionnaire will be used to assess quality of life. The Veterans Rand 36 Item Health Survey questions your views about your health.

Echocardiogram: Transthoracic echocardiography is a routine medical procedure using ultrasound waves to assess heart structure and function. Echocardiography will be performed in the semi recumbent position. Measurements to be collected include: left ventricular ejection fraction; left ventricular wall thickness; relative wall thickness (as calculated by 2 x posterior wall thickness in diastole/left ventricular diastolic diameter); left ventricular outflow tract minimum diameter, left ventricular outflow tract Doppler flow, ratio of peak mitral Doppler inflow velocities (E/A ratio); diastolic myocardial relaxation velocity of the lateral mitral annulus (E'); and the ratio of mitral inflow velocity to annular relaxation velocity (E/E'), right ventricular dimensions including maximal minor axis (S1), ejection time, myocardial performance index, and function, tricuspid annular motion, and velocity of the tricuspid regurgitant jet, tricuspid inflow velocity, right ventricular outflow velocity.

Cardiopulmonary exercise test: Cardiopulmonary exercise testing is a test of a subject's maximal exercise capacity. This test will be performed on a bicycle in the presence of a physician. The subject will wear nose clips, and will breathe through a mouthpiece connected to a metabolic machine, which will measure factors including oxygen consumption, CO_2 production, volume of air per breath, and respiratory rate. The patient will also be monitored by EKG leads demonstrating the heart rate and rhythm. The patient will then exercise at increasing levels of resistance (increasing intensity of exercise) according to a protocol until the protocol is completed or the patient can no longer exercise. The maximal value for oxygen consumption (VO_2 max) will be recorded, along with other exercise parameters such as maximal heart rate achieved, the respiratory quotient (ratio of O_2 consumption to CO_2 production), and the dead space to tidal volume ratio. Patients requiring supplemental oxygen will not have a cardiopulmonary exercise test.

Phlebotomy: Phlebotomy is a commonly performed medical procedure in which blood samples are drawn from a vein, typically in the forearm, after venipuncture, and which will be performed by a trained laboratory phlebotomist. Phlebotomy will be performed at the initial study visit and the twelve month follow- up study visit.

Right heart catheterization: Right heart catheterization will be performed according to standard guidelines. The patient is continuously monitored by a registered nurse during the procedure. Technicians are also present to assist in recording of hemodynamics. After sterile preparation and draping, ultrasound guidance is used to identify a vein in the neck, subclavian region, or groin. Local anesthesia is provided to minimize discomfort prior to accessing the appropriate vein. Then, a sheath is placed in the vein. A hemodynamic balloon-tipped flow-guided catheter is then passed through the sheath and into the central veins, right heart chambers, and then into the pulmonary artery. The catheter is advanced until wedged in a small pulmonary artery. Fluoroscopy is used as needed during the procedure for additional guidance. Continuous hemodynamic recordings are

made throughout the procedure, including measurements of blood pressure and cardiac output. A sample of 5ml of blood will be drawn via the catheter from the pulmonary artery. After completion of recording, the catheter is removed. The sheath is then removed from the vein and pressure applied until hemostasis is ensured. Total radiation dose is monitored and documented. A post-procedure chest x-ray is performed to assess for any complications. A bandage is applied to the vein access site. The patient is monitored in the post-procedure unit by nursing staff. When standard parameters are met, the patient is discharged.

Arterial blood gas: An arterial blood gas will be drawn at the time of the right heart catheterization. This test involves puncturing an artery in the arm or leg with a needle and collecting a sample of 2ml blood.

Six minute walk test: Six-minute walk testing will be performed on a measured circuit according to standards published by the American Thoracic Society.

Patient safety:

Human Subjects Research

This Human Subjects Research meets the definition of "Clinical Research". This study is a clinical trial, and will be registered on Clinicaltrials.gov.

Protection of human subjects

Potential risks

Questionnaires and record keeping There is no specific physical risk to completing the dyspnea and quality of life questionnaires. All records will be kept confidential, kept in locked cabinets, and identified by study code only in the working databases.

Phlebotomy Phlebotomy for blood drawing is associated with temporary pain at the site and may result in bruising at the needle insertion site. Risks of the procedure include: vasovagal reaction during needle puncture; bruising at the phlebotomy site; and the possibility of skin or soft tissue infection at the needle puncture site.

Echocardiogram Standard approaches to performing transthoracic echocardiography will be utilized, which may induce transient discomfort as the ultrasound probe is pressed against the upper chest.

Cardiopulmonary exercise testing. The testing may cause shortness of breath, fatigue, muscle discomfort, and very rarely (<1:1,000) may be associated with heart attack or death.

Right heart catheterization This is an invasive procedure. Discomfort may result from the needle stick to provide local anesthesia (i.e., most often 1% lidocaine) for placement of the catheter. The discomfort is generally mild and resolves spontaneously within 30 seconds. More serious complications of this procedure such as, but not limited to, air in the pleural space (pneumothorax), major infection, major bleeding, clotting around the catheter, air embolism, arrhythmia, myocardial infarction (heart attack), stroke, and/or death occur in <1% of all right heart catheterization procedures.

Arterial blood gas This involves a needle puncture of an artery. Discomfort may occur from the needle stick. This is usually mild and resolves within 5 minutes. Complications include hematoma formation, infection and bleeding. Rarely, permanent damage or clot in the artery occurs, which can result in tissue damage to the hand or leg.

Therapeutic risks

Treatment with Tadalafil

Although Tadalafil has been taken by many people, it has not been tested as a treatment for pulmonary hypertension caused by chronic lung disease. Side effects that have been most commonly reported by people who have taken Tadalafil include headache, upset stomach, back pain (sometimes severe), muscle ache, stuffy nose, and flushing. When treatment was needed, most headaches and back and muscle pains were relieved by medicines like Tylenol or ibuprofen. Less common side effects reported include dizziness, vomiting, swollen eyelids, eye pain, blurred vision, and irritated eyes. Side effects that have been very rarely reported include rash, hives, face swelling, serious skin reactions (which may be life threatening), heart attack (including fatal ones), stroke, chest pain, skipped heart beats, fast heart rate, high blood pressure, fainting, abdominal pain, heartburn, sweating, and partial loss of vision.

Risks in Men:

Priapism (prolonged erection) has been reported with medications for erectile dysfunction, including Tadalafil. If priapism is not treated immediately, lasting damage can happen to the penis, including the inability to have erections. Other PDE5 inhibitors should not be taken while participating in this study. Serious health problems could result. In animal studies, dogs were given Tadalafil at doses that exposed them to about the same level of Tadalafil that subjects may be exposed to if taking the highest dose in this study (40 mg). After 6- and 12-months of taking Tadalafil every day, the dogs had some damage to their testicle tissues which made them produce less or no sperm. It is not known if the damage to the dogs' testicles would get better after dosing was stopped. The damage may be permanent. The effect of reduced sperm count may include, but is not be limited to, an inability of a spouse or partner to become pregnant. Similar findings have not been seen in human studies designed to assess this risk, but those studies have not been conducted with doses of Tadalafil as high as those given in the present study.

Risks in Women:

Studies in animals showed that Tadalafil did not affect the reproductive cycles of females or their ability to become pregnant. However, there may be unknown risks for pregnant women taking Tadalafil; for their developing embryo, fetus, or unborn child; or for infants breast-fed by women taking Tadalafil. Tadalafil has not been tested in pregnant women.

Risk of low blood oxygen:

Individuals with chronic lung disease may have low blood oxygen or require oxygen treatment. There are small numbers of reports of patients with chronic lung disease whose blood oxygen decreased when they were given a medication similar to Tadalafil. Subjects will be tested for this effect by giving a test dose. Oxygen prescriptions will be adjusted, if needed.

Adequacy of protection from risk

Protection against risk

Study personnel will be fully trained and credentialed in human subject protection. Study ID numbers will not include PHI. All research data which will be kept in locked cabinets or password protected files on VA servers.

Risks from cardiopulmonary exercise testing will be minimized by supervision of testing by an attending physician which is to be performed by trained technicians at Boston VA with emergency equipment readily available. Patients will be encouraged to exercise to their symptomatic limits, if there are any signs of medical instability; the physician will end the test before the symptomatic endpoint is achieved.

The risks from right heart catheterization will be minimized by performance by trained physicians in a fully equipped angiography suite with readily available emergency equipment and personnel.

Phlebotomy will be performed by trained phlebotomists.

Potential benefits of research to human subjects and others

There may be no direct clinical benefits to the subjects. The medication may increase walking capacity, decrease cardiopulmonary hemodynamic measurements of PH, and/or improve quality of life. If the medication is not successful at modulating these anticipated beneficial responses, then our results will provide evidence to establish that PDE-5 inhibition is not a valid therapy in the large number of patients with COPD and PH.

Importance of knowledge gained

The societal benefits to the study include the generation of pivotal data regarding the treatment of COPD-induced PH. If PDE-5 inhibitor therapy is effective in this patient population, the study provides for the first time complete

evidence to demonstrate this as a novel treatment for COPD-induced PH. If the therapy is ineffective in this patient population, then our results will provide evidence against the systematic and/or empiric use of these medications for this disorder. Depending on our findings, the downstream consequences of the proposed work are to reduce VA healthcare costs by decreasing hospital admissions rates in COPD patients or attenuate the use of PDE-5 inhibitors in clinical practice for this patient population.

Data and safety monitoring

As described above, frequent contact will be maintained with participants throughout their participation in this study, with telephone contact at 3 days and monthly as well as clinic visits at 1, 3, 6, 9 and 12 months after randomization to ascertain dyspnea, hospitalizations, illnesses or other adverse events as outlined in Table 1. The PI and staff will meet on a weekly basis to review study progress and adverse events. The PI will, on a weekly basis, review all data collected to assure that no physiological (e.g., blood pressure) findings warrant immediate intervention. If so, the participant will be contacted and advised of the findings and offered assistance with appropriate referrals. Data from the echocardiogram and cardiopulmonary exercise testing procedures will be reviewed by the investigators and any unusual or adverse findings will be communicated to the participant's primary care physician. Adverse events (classified by severity and unexpected/expected) will be defined and reported to the IRB in accordance with the rules regulating each severity class (expected vs. unexpected, serious vs. other, related vs. unrelated). A DMSB has been established—see below.

Follow up visits. Patients will undergo routine follow up visits as outlined in Table 1 to assess compliance with medication use, changes in symptoms, development of adverse reactions and further data collection.

Monitoring for Adverse Events (AEs)

At the baseline clinic visit and each follow-up contact, subjects are to notify study staff if they experience any change in their medical condition or medications, or have urgent care visits, emergency room visits, or hospitalizations. Study staff will also monitor for interim emergency room visits or hospitalizations through patient notification system in CPRS to ensure timely reporting. The investigator will contact participants if any reported adverse event suggests clinical deterioration warranting immediate medical attention. During the study, if a subject experiences medical problems or hospitalization, the study medication will be continued unless complicated by hypotension or new or worsened hypoxemia. If discontinued, it would be resumed once baseline clinical status is confirmed, assuming the event was not felt to be related to the study medication itself.

Any AE that are immediately life-threatening, cause permanent or lasting harm, or require a hospitalization will receive a "serious" classification. All serious AEs and unanticipated problems will be reported to the IRB and DSMB as soon as possible, but no later than 5 days from notification. If an event is

possibly, probably or definitely related to the intervention, it will be classified as intervention-related.

In the event of an emergency medical situation, the patient's treatment assignment can be unblinded. In such a situation, the treating physician can contact the pharmacy, who will have emergency access to the unblinding information.

We have convened an independent, external Data and Safety Monitoring Board (DSMB) to review recruitment, follow-up rates, and protocol adherence and safety results. They will monitor the rates of AEs and SAEs and unanticipated problems. The DSMB is composed of experienced experts in clinical studies of pulmonary hypertension and includes Dr. Raed Dweik, a Professor of Medicine at the Cleveland Clinic and Director of the Pulmonary Vascular Program, Dr. Nicholas Hill, Chief of Pulmonary and Professor of Medicine at Tufts Medical Center and an expert in PH and Dr. Steven Kawut, Associate Professor of Medicine at University of Pennsylvania and Director of the Pulmonary Vascular Disease Program. They will meet every 6 months, and as needed, by telephone conference.

Data Collected:

Data collection will include demographics, interview and questionnaire data, history and physical exam data, medications, hospitalization and emergency department records, acute outpatient care records during study period, laboratory data (baseline labs from chart including arterial and venous blood gas values, blood chemistries--chem 7/basic metabolic panel, complete blood count, BUN, creatinine, rheumatological serologies, HIV testing, liver function tests, thyroid studies, coagulation studies, c-reactive protein, troponin, as well as BNP levels), pulmonary function data, radiological studies including chest x-rays, chest CT scans, ventilation-perfusion lung scans, echocardiography data, heart catheterization data, cardiopulmonary exercise testing and 6 minute walk data.

Data Analysis Plan

The data will be entered into an Access (Microsoft Corp) database, and SAS 9.2, (SAS Institute; Cary, NC) used for analysis. We will compare baseline characteristics between groups (e.g., age, %-predicted FEV1, including pulmonary hemodynamics, exercise capacity, dyspnea score, and quality of life). We will conduct analyses using available data based on an intention to treat strategy, and we will also assess subjects completing the 12 month trial.

Aim 1: The primary outcome will be the difference in distance performed on a 6MWT between baseline and 12 months [Δ6MWT], which will be assessed using a two-sample t-test for independent samples. We will also assess longitudinal change in the 6 repeated measures of 6MWT using mixed linear models that take into consideration the correlated nature of repeated measurements (PROC MIXED in SAS), and the effects will be adjusted for age and %-predicted FEV1 using the same model.

Secondary Aims: The change in maximal VO2 during exercise between baseline and at 12 months [ΔVO2] will also be assessed using a t-test for

independent samples. For multivariate analyses, we will use general linear models (PROC GLM in SAS) to assess if this difference is influenced by adjustment for age and %-predicted FEV1.

We will calculate the mean difference in PVR and mPAP at 6 months compared to baseline value in each group [ΔPVR and ΔmPAP]. For crude analysis, we will use a t-test for independent samples; we will then compare ΔPVR and ΔmPAP in the two groups. For multivariate analyses, we will use general linear models (PROC GLM in SAS) to assess if this difference is influenced by adjustment for age and %-predicted FEV1.

Additional outcome measures: Differences in cardiac echo derived indices of RV function will be compared similarly as noted for ΔPVR and ΔmPAP. There will also be 6 measures of dyspnea score and quality of life. Assessment of the differences in these measures between groups based on these longitudinal assessments will be performed as was done with Δ6MWT above.

Predictors of acute exacerbations and hospitalizations will be assessed using a generalized linear model (assuming a negative binomial distribution) with the logarithm of observation time as an offset variable (PROC GENMOD in SAS). In addition to assessing each group as a predictor of exacerbations and hospitalizations, we will adjust for %-predicted FEV1, age, and a history of previous exacerbations in the past year.

Data storage and sharing: Data will be acquired by the PI and recorded on a Microsoft Excel™ spreadsheet. All data will be collected using a study code that does not identify the patient. The cross-link matching the patient with the code will be saved in a password-protected file, separate from the rest of the data files and stored on the secure VA server that only the PI and research staff have access to. Consent forms are being stored in a locked cabinet in Dr. Ronald Goldstein's office. Paper data such as data abstraction sheets (without patient identifiers) will be kept in a locked cabinet in the locked office of the investigator. No VA sensitive data will be transmitted outside the VA. Only VA non-sensitive data will be transmitted electronically via internet for discussion during study meetings and collaboration with off-site co-investigator/ collaborators.

Study data will also be collected and managed using REDCap electronic data capture tools hosted at the Department of Veterans Affairs.1 REDCap (Research Electronic Data Capture) is a secure, Web application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources
(URL http://vaww.virec.research.va.gov/REDCap/Overview.htm)

1 Paul A. Harris, Robert Taylor, Robert Thielke, Jonathon Payne, Nathaniel Gonzalez, Jose G. Conde, Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support, J Biomed Inform. 2009 Apr; 42(2):377-81.

Data collected from this study will be used for research purposes. No patient identifiable information will be released or published without written permission unless required to do so by law. Records will be maintained in accordance with the Department of Veterans Affairs Record Control Schedule 10-1. In the event that theft, loss of other unauthorized access of sensitive data or storage devices and non-compliance with security controls occur, study staff have been instructed to follow Boston VA's standard operating procedure on incidence reporting. Electronic access to research study data and protected electronic folder will be revoked by informing the O&IT personnel for the study personnel who are no longer part of the research team. Access to paper data will be revoked by the PI by not providing access to the storage cabinets and room.

Data analysis using deidentified data will be performed using SAS statistical program.

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3. Nagaya N, Nishikimi T, Uematsu M, et al.: Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. Circulation. 2000:102:865-870.
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