Study Protocol and Statistical Analysis Plan Cover Page

Official title of study: Reducing Symptom Burden in Patients With Heart Failure With Preserved Ejection Fraction Using Ubiquinol and/or D-ribose

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RESEARCH STRATEGY

A. SIGNIFICANCE

A.1. Lack of Effective Treatment for Heart Failure with Preserved Ejection Fraction (HFpEF) Symptoms. The public burden of heart failure (HF) is manifested by its staggering cost ($39.2 billion in healthcare-related costs/year) in the US,[1] while the personal burden of HF includes debilitating symptoms.[2] It is estimated that there is a 20% lifetime risk of developing HF at age 40 and that 870,000 new cases will be diagnosed yearly in adults who are 55 years of age or older.[3] In 2014, the Food and Drug Administration reported that "the burden of HFpEF was considerable and is projected to worsen" and "there are no approved therapies available for reducing symptoms."[4] Beginning January 2012, the Centers for Medicare and Medicaid Services began reducing payments to hospitals for HF patients readmitted within 30 days of hospital discharge. Of the patients hospitalized with HF, more than 50% have diastolic HF, which is termed heart failure with preserved ejection fraction.[5] These patients have a left ventricular ejection fraction (LVEF) of more than 45 to 50% and symptoms that include lack of energy (fatigue), shortness of breath, peripheral edema, and reduced quality of life.[6, 7] The most recent American College of Cardiology (ACC)/American Heart Association (AHA) HF guidelines for HFpEF acknowledge "huge gaps" in understanding effective treatments for patients with HFpEF.[8] This study will provide an opportunity to evaluate the comparative effectiveness of alternative approaches for reducing symptom burden in patients with HFpEF.

A.2. Improved Scientific Knowledge and Clinical Practice in Measuring HFpEF. This study of ubiquinol (CoQ10, a type of coenzyme Q10) and D-ribose in patients with HFpEF will significantly improve scientific understanding of myocardial bioenergetics. Ubiquinol and D-ribose are naturally produced in the body.[9-11] One of the main functions of these products is to promote cardiac energy metabolism by increasing mitochondrial adenosine triphosphate (ATP) production (Figure 1).[12] Ubiquinol and D-ribose exert this physiological benefit of enhancing cardiac function via two different bioenergetic pathways.[13-15] As an efficient electron carrier, ubiquinol plays an important role in transporting electrons in the electron transport chain (ETC), which produces the proton gradient needed for phosphorylation of ADP and creating ATP. In contrast, D-ribose provides a source for synthesis of adenosine monophosphate (AMP) to ensure there is sufficient ADP to form ATP.[16-18] Therefore, administering these supplements should augment ATP synthesis, increasing both cellular and behavioral energy. The potential benefits of administering ubiquinol and/or D-ribose to patients with HFpEF are increased myocardial energy and diastolic relaxation, which would significantly reduce their cardiac symptoms. We plan to measure HFpEF symptoms using the Kansas City Cardiomyopathy Questionnaire (KCCQ), Vigor scale, and 6-minute walk test (6MWT). Biological measures will include myocardial wall motion, lactate/ATP ratio, and B-type natriuretic peptides (BNP).

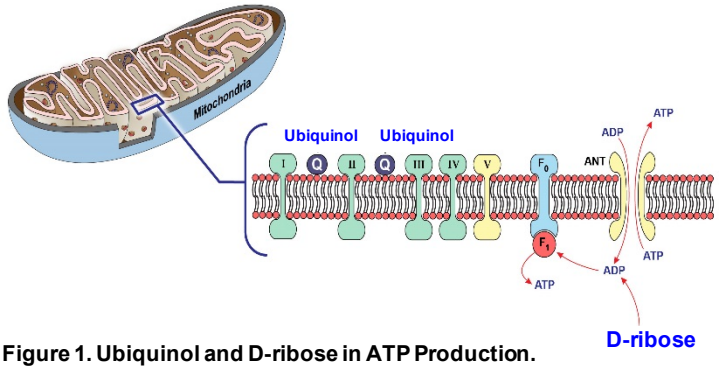


Figure 1. Ubiquinol and D-ribose in ATP Production.

A.3. Using Biobehavioral Symptom Science. Novel discoveries in biobehavioral symptom science require integration of information from the patient's biologic processes, physiologic pathways, and behaviors to treat and manage symptoms of diseases such as HFpEF.[19, 20] We plan to use biobehavioral symptom science to identify complex symptoms that can be characterized with biological and clinical data. In this study, symptoms of HFpEF patients that result in a person's feeling a lack of energy will be measured using a questionnaire to evaluate the patient's level of vigor and overall health status. We will also measure their lactate/ATP ratio, cardiac performance, B-type natrieutric peptides, and conduct a 6MWT. This study could assist in illuminating a therapeutic clinical intervention (ubiquinol and/or D-ribose) for patients with HFpEF by quantifying subjective symptom experiences and measuring biologic and physiologic underpinnings of the symptoms.

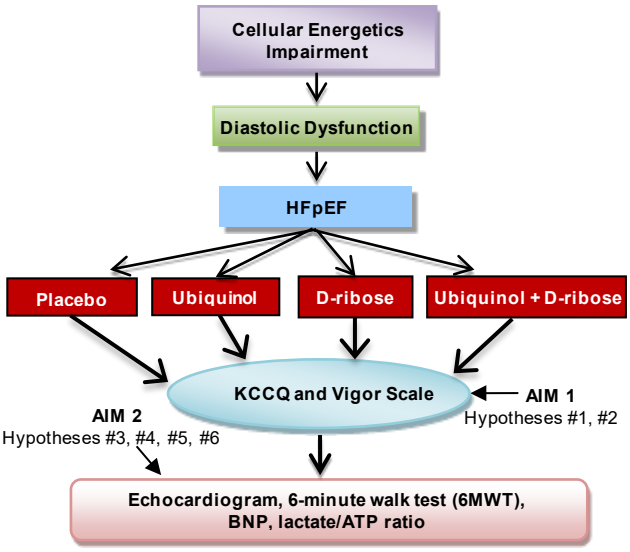
A.4. Technologies and Treatments That Could Reduce the Symptoms of HFpEF. We plan to use a sophisticated echocardiographic software program called speckle tracking to measure myocardial wall tension and motion to evaluate diastolic function. In addition, we will quantify our term "energy" using point-of-contact instrumentation to measure lactate/ATP ratio and BNP concentration. The two important outcomes for patients with HFpEF are improved heart function and patient energy. If a patient with HFpEF takes ubiquinol and/or D-

ribose, we hypothesize that the increased cellular bioenergetics would decrease myocardial stiffness, resulting in improved cardiac output and level of vigor. With more energy, the patient should have improved health status in the five KCCQ domains (i.e., clinical summary, functional status, self-efficacy, social interactions, quality of life). Thus, if the aims are achieved, patients with HFpEF will have successful symptom management and improved assessment of diastolic function. In addition, we will determine whether the comparative effectiveness of the treatments will maintain or increase ATP levels, prevent additional stiffness of the heart, and thus improve cardiac function, thereby reducing symptoms. A reduced myocardial tissue content of CoQ10 has been demonstrated in patients with HF, correlating with the severity of symptoms and the degree of left ventricular dysfunction.[21] According to Sharma (2016), the pathophysiological rationale for the use of CoQ10 in HFpEF exists, and well-conducted clinical trials will be required to demonstrate how CoQ10 decreases the signs and symptoms in this population.[22] This study will produce new knowledge that will provide information about comparative benefits and outcomes that is significant to patients with HFpEF and that will help these patients make informed critical decisions about using ubiquinol and/or D-ribose.

B. INNOVATION

B.1. New Applications of Theoretical Concepts to Address HFpEF Symptoms. This study is a novel design to compare ubiquinol and/or D-ribose as supplemental treatments for HFpEF using a biobehavioral model (Figure 2). A deficiency in ubiquinol and/or D-ribose is an underlying pathophysiologic mechanism that results in cellular energetic impairment that diminishes ATP production and decreases sarcoplasmic reticulum Ca^{2+}-ATPase.[23] This results in decreased actin-myosin cross-bridge detachment, which is reflected in increased diastolic stiffness and decreased ventricular compliance. In addition, increased free radical production in HFpEF can result in damage to mitochondria and nuclei.[24] We will examine the bioenergetics of ubiquinol and/or D-ribose in patients with HFpEF both behaviorally (health status per KCCQ and Vigor scale) and biologically (6-minute walk test, echocardiographic imaging, lactate/ATP ratio, and BNP measurements). With emphasis on patient-centered care, it is important to assess patient perception of changes in health status and level of vigor as ubiquinol and/or D-ribose is administered. To our knowledge, the effects of combining ubiquinol and D-ribose in HFpEF patients have not been published and thus are innovative because of their synergistic potential.

Figure 2. Biobehavioral Model.



B.2. Patient-centered Perspective. Since HFpEF is related to changes in cellular bioenergetics, it is important to evaluate behavioral measures of energy such as the Vigor scale as well as biological clinical outcomes. After meeting with 30 HFpEF patients and 10 caregivers, we found they were extremely interested in the question of whether ubiquinol, D-ribose, or both could improve their health status (i.e., reduce their shortness of breath, increase their ability to perform daily activities, etc.) and their energy levels. With the advanced speckle tracking echocardiogram images, lactate/ATP ratio, and BNP measurements, we can answer that question. Our data will help us compare the effectiveness of ubiquinol and D-ribose with usual treatment in this patient population.

B.3. Potential Impact of Racial/Ethnic and Cultural Differences. Studies raised concerns that the incidence of HF might vary among different racial/ethnic groups.[25, 26] Thus, in this study we will oversample minorities as reviewers suggested, which will enable us to examine the relationship between HFpEF and racial/ethnic differences. Most of the data regarding treatments for HFpEF are derived from White populations,[27] and therefore it is important to include other racial/ethnic groups and examine whether the effects of ubiquinol and/or D-ribose follow similar patterns to those among whites.

B.4. Translational Research. This is our opportunity to translate what we have observed in the laboratory and in the cardiovascular clinic to decrease patients' debilitating symptoms of HFpEF. In a rat model, we have observed a significant decrease in myocardial nuclear damage (apoptosis) and mitochondrial superoxide

production associated with ubiquinol administration during an acute oxidative stress condition. Mitochondrial damage as assessed by electron microscopy was greatly reduced with the administration of ubiquinol. In the clinic setting, we have observed significant improvements in cardiac function leading to improved symptoms in patients with HFpEF who received ubiquinol and/or D-ribose. Translating these significant findings via a human study will provide essential data to support the use of these supplements in clinical practice.

B.5. Advanced Echocardiographic Imaging. In this study we will use a novel software program termed speckle tracking with an echocardiographic instrument to assess cardiac function in HFpEF patients with and without administered ubiquinol and/or D-ribose. Speckle tracking echocardiography is an innovative technique that measures myocardial velocities and deformation parameters such as strain, strain rate, and torsion. These parameters provide superior assessment of diastolic function relative to conventional echocardiography. Using this advanced echocardiographic imaging method to objectively measure the effectiveness of ubiquinol and/or D-ribose in HFpEF patients is innovative and provides highly specific data for clinicians and researchers.

B.6. Use of Biomarkers with Imaging. Our study is innovative because of its unique strategy of evaluating biomarkers (BNP, lactate/ATP ratio) with advanced cardiovascular imaging (speckle tracking echocardiogram) to assess a treatment (usual care, ubiquinol, and/or D-ribose) for a major healthcare problem (HFpEF). We will use biomarkers to evaluate the comparative effects of usual care, ubiquinol, and/or D-ribose. Our use of handheld on-site measurement of lactate/ATP ratio in patients with HFpEF is pioneering because it provides an assessment of cellular energy, the major mechanism for HFpEF, available in 5 minutes. The rapid ATP method is an innovative approach that is not a conventional technique and has not been used in assessing bioenergetics in patients with HF.

C. APPROACH

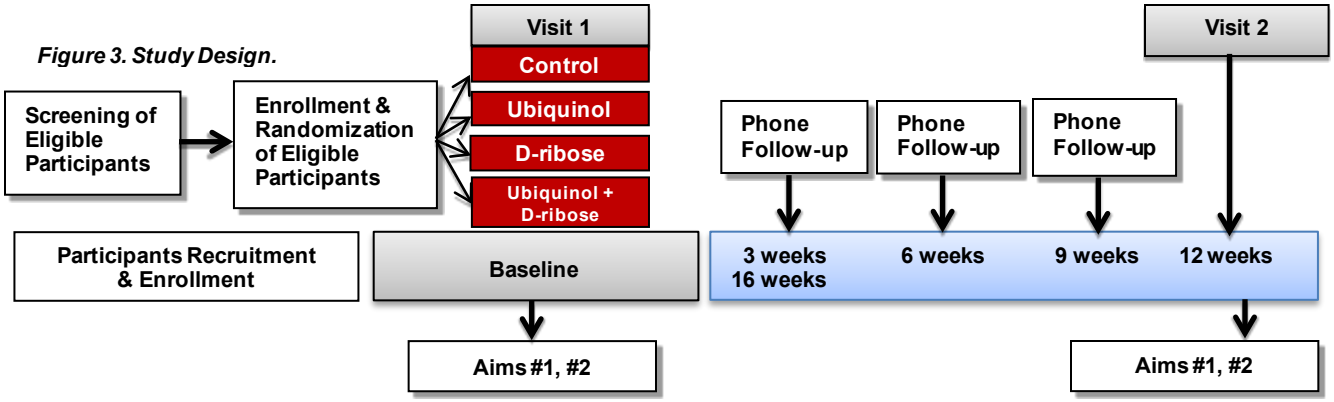
C.1. Study Population and Environment. The research protocol will first be approved by the Institutional Review Board, and all subjects will be provided with a written informed consent. The subject population, > 50 years of age, male and female with HFpEF, will be enrolled from the University of Kansas Medical Center (KUMC) Healthcare Enterprise Repository for Ontological Narration (HERON) database, Pioneers Recruitment Registry (Pioneers), and chronic HF clinic at the University of Kansas Hospital (KUH): 69 in the control (placebo) group; 69 in the ubiquinol group; 69 in the D-ribose group; and 69 in the ubiquinol plus D-ribose group, (total = 276). HERON provides clinical/translational investigators with the numbers of patients at KUH who meet the inclusion criteria for clinical trials and contact information for patients who sign up with KUMC's Frontiers participant registry. Based on the HERON, there will be approximately 7,100 subjects with HFpEF available to be screened for enrollment in this study. As suggested by the reviewers, we will oversample minority populations to increase the generalizability of data for minority groups (30% Black/African Americans (AA), 30% Hispanic/Latino, 30% White, and 10% American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander). In addition, two nurse practitioners and a cardiologist on this application who work in the outpatient HF clinics will refer patients to the research team. All patients **included** in this study will: be 50 years old or older; have left ventricular ejection fraction (EF) ≥ 50% documented by an echocardiogram within 12 months of enrollment; be diagnosed with HFpEF within a 12-month period;, have symptoms of dyspnea and New York Heart Association (NYHA) Classification II or greater symptoms, have a diagnosis of HFpEF defined by one of the following: (1) previous hospitalization for HF with radiographic evidence (pulmonary venous hypertension, vascular congestion, interstitial edema, or pleural effusion) of pulmonary congestion, (2) invasive hemodynamics, (3) echocardiographic evidence of diastolic dysfunction, (4) elevated NT-pro (>400 pg/ml) or BNP (>200 pg/ml), or (5) no use of intermittent sublingual nitroglycerin within 12 months; have willingness to provide informed consent; have a telephone or reliable phone contact; and have their own means of transportation to the study site. Patients will be **excluded** based on any of the following criteria: (1) acute coronary syndrome in the past 12 weeks; (2) significant valvular heart disease;(3) severe cardiac fibrosis (galectin-3 level > 26 ng/ml); (4) constrictive pericardium; (5) pulmonary fibrosis; (6) congenital heart disease; (7) hypertrophic or infiltrative cardiomyopathy; (8) heart transplant; (9) left ventricular assist device; (10) HF associated hospital admission or emergency room visit within past 30 days; (11) recent percutaneous coronary intervention; (12) significant renal and/or hepatic dysfunction; (13) severe cognitive impairment; or (14) consumption of any CoQ10 (ubiquinol) or D-ribose supplements. Hepatic and renal dysfunction will be defined as an ICD-10 code with diagnosis of renal and/or hepatic failure in the patient's healthcare record. For retention we will schedule the sessions at a convenient time for each participant. Part of the recruitment plan includes subjects' preferences for conducting telephone calls and collecting data. All subjects will be asked to

come to the Clinical and Translational Science Unit (CTSU), a newly renovated facility with private examination rooms, pharmaceutical rooms, and storage area (for echocardiogram, i-stat instrument, etc.), and computer access to the Velos eResearch for patient data. The facility has plentiful free/close parking.

C.2. Study Design and Materials. Both HFpEF patients and stakeholders had a meaningful influence on the study design. We held focus groups, made individual phone calls, and had in-person meetings with patients with HFpEF. Our Stakeholder Advisory Panel (SAP) consists of diverse individuals including patients, caregivers, clinicians, and hospital administrators (Appendix 1) who have met three times. The patients and caregivers were particularly interested in whether ubiquinol, D-ribose, or both could enhance health status, decrease symptoms, and improve energy levels. We invited 30 HFpEF patients and their caregivers to provide input and feedback regarding the development of our research hypotheses and methods. We found their opinions extremely valuable in designing this patient-centered study.

Study Design, Including Screening, Enrollment, Visits, and Phone Follow-up (Figure 3).

Figure 3. Study Design.



Based on the power analyses (see C.5.), this randomized, double-blind, controlled trial will have a total sample size of (N) = 276. All participants will receive usual care for HFpEF. Efforts will be made to recruit 50% females, which is the actual proportion of HFpEF patients in Kansas City.

N1 = 69 subjects: Control, receive no ubiquinol and no D-ribose; placebo capsules & powder per day.
N2 = 69 subjects: Ubiquinol group, receive 600 mg of ubiquinol/day, D-ribose placebo powder per day.
N3 = 69 subjects: D-ribose group, receive 15 g of D-ribose/day, placebo capsules for ubiquinol per day.
N4 = 69 subjects: Ubiquinol + D-ribose group, receive 600 mg ubiquinol and 15 g D-ribose per day.

Initially, potential subjects from HERON, Pioneers, and KUH outpatient HF clinics will be interviewed by phone for potential recruitment in the study. Two nurse practitioners and a cardiologist on our research team work in the outpatient HF clinics and will refer patients to us. Patients will be required to speak English, and the informed consent and patient information will be written at the 8th grade level. We will collaborate with our Human Subject Protection Program to ensure our consent form complies with the US Department of Health and Human Services (HHS) federal guidelines and obtain informed consent from eligible patients (Appendix 10). Patients that have consented will be provided a 1-week supply of placebo ubiquinol pills (instructed to take 2 pills/day) and placebo D-ribose powder (instructed to take 3 scoops/day) as a pre-randomization run-in period to evaluate compliance to the supplements. Patients will be scheduled for an appointment at the CTSU in 1 week following the run-in period. Patients that demonstrate an 80% compliance rate of ubiquinol intake (as evidenced by pill count) and an 80% compliance rate of D-ribose powder intake (as evidenced by weight of the containers) will be eligible to be randomized into a group assignment. The enrolled patients with 80% compliance will then be randomized into four groups (69 subjects in each group) to receive ubiquinol (600 mg daily), D-ribose (15 g daily), ubiquinol plus D-ribose, or placebo for a period lasting 12 weeks. Both the ubiquinol and the D-ribose supplements used in the study will have a certificate of analysis from the manufacturer (Appendix 9). The Project Director will receive the identified list of recruited subjects from the Principal Investigator (PI) and will randomly assign subjects to one of the groups using a list created by a computer-based random number generator. All supplements and the placebo will be indistinguishable in packaging and will be distributed by the Project Director independent of the PI so that the allocation of subjects to a treatment or placebo group will be concealed from both subjects and research personnel.

All subjects will complete the demographic form at baseline. The KCCQ (Appendix 2) and Vigor scale from the Profile of Mood States (POMS) will be completed in CTSU visits at baseline and 12 weeks (Appendix 3) along with the subject's height and weight. The patient will be escorted to a private room and asked to remove clothing above the waist. A disposable gown will be provided and the patient will lay supine on the bed while an echocardiogram is completed. Approximately 0.5 ml of blood will be collected via finger stick to measure lactate, ATP, and BNP. Next, the subject will complete a 6MWT (Appendix 4, Borg scale). Approximately 2 hours will be required for each subject's visit to the CTSU. Follow-up calls will occur at 3, 6, and 9 weeks during the trial.

Potential Problem and Alternative Solutions. Serum CoQ10 and D-ribose values in some of the treatment patients might be below threshold levels at 6 weeks, possibly due to subject non-adherence. If this occurs, the Project Director, who is not blinded to the list of placebo and treatment subjects, will call and ask if there are any problems with consuming the ubiquinol and/or D-ribose. The Project Director and Research Associate will conduct a phone follow-up interview at 3, 6, and 9 weeks during the trial using a structured interview. Questions asked will relate to any side effects and compliance history in taking their capsules or powder.

Various cardiovascular risk factors will be recorded such as tobacco usage, diabetes mellitus, hypercholesterolemia, hypertension, and family history of cardiovascular disease. Smoking status will be recorded as either smoker or non-smoker. Patients who use tobacco will be given contact information for a tobacco/smoking cessation program. Diabetes mellitus will be determined by a history of the disease or use of medication for diabetes. Hypercholesterolemia will be defined as a fasting total serum cholesterol level ≥ 4.9 mmol/l or use of medication. Hypertension will be defined as either systolic or diastolic blood pressure ≥ 140/90 mmHg or use of hypertensive medications.

C.3. Aims and Hypotheses.

AIM #1: *To determine the effects of oral ubiquinol, D-ribose, or a combination of the two administered during 12 weeks on symptoms accompanying low bioenergetics in patients with HFpEF.*

Hypothesis #1. Ubiquinol (600 mg daily), D-ribose (15 g daily), or a combination of the two will enhance the health status of patients with HFpEF as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ).

Primary outcomes of the study are patient-centered, thus the measurement of health status will be a priority. Bioenergetics has both biological and behavioral components. The biological component (i.e., improved heart function) and its measurement will be discussed below (Aim #2). In this section we will discuss the behavioral component that relates to patients' perceptions of their health status (i.e., symptoms) and the impact of their health status on daily functioning (e.g., hobbies, work, and energy).

We will assess patients' perceptions of their symptoms using the KCCQ, a self-administered questionnaire that measures patients' perceptions of five domains of their health status relevant to HFpEF.[28] These domains are: (1) physical limitations, (2) symptoms, (3) self-efficacy, (4) quality of life, and (5) social interference. The KCCQ consists of 24 items to which patients respond on a scale indicating limitations due to HF. For example, for activities such as dressing, doing yard work, or climbing a flight of stairs, patients are asked to check a response that indicates the degree to which HF has limited their ability: "Extremely Limited," "Quite a bit Limited," "Moderately Limited," "Slightly Limited," "Not at all Limited," or "Limited for other reasons or did not do the activity." Another item is: "Over the past 2 weeks, how many times has shortness of breath limited your ability to do what you wanted?" Response alternatives are: "All of the time," "Several times," "At least once a day," "3 or more times per week but not every day," "1-2 times per week," "Less than once a week," and "Never over the past 2 weeks." The KCCQ takes only 4 to 6 minutes to complete and has been used in more than a hundred studies. It has excellent psychometric properties and clinical usefulness including: (1) high test-retest reliability; (2) high internal consistency within each area (e.g., Cronbach's alpha ranged from 0.78 to 0.90); (3) patients' scores concerning their health status correlate well with objective measurements of their functional capacities; and (4) the scale's sensitivity for detecting clinical changes in HF patients is significantly greater than that of the *Minnesota Living with Heart Failure Scale*. We will use the KCCQ to compare the changes in health status of patients with HFpEF taking ubiquinol, D-ribose, ubiquinol + D-ribose, or placebo.

Hypothesis #2. Ubiquinol (600 mg daily), D-ribose (15 g daily), or a combination of the two will increase the level of vigor in patients with HFpEF as measured by the Vigor subscale of the Profile of Mood States (POMS).

Using the Vigor subscale from the POMS questionnaire,[29-31] patients will rate themselves on eight adjectives (lively, active, energetic, cheerful, alert, full of pep, carefree, and vigorous) on a five-point scale (0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, and 4 = extremely). The Vigor scale has very high internal consistency (Cronbach's alpha = 0.90), and it takes only 1 minute to complete. In many studies it has been found to be effective for assessing vigor changes associated with exercise.[32-34] The KCCQ and POMS Vigor scale will be administered to patients after they have been sitting quietly for 10 minutes at the beginning of each visit (baseline and 12 weeks). The total time for patients to complete both questionnaires will be 5 to10 minutes. We anticipate that during the course of treatment the patients taking these supplements will report increasingly greater improvements in health status, daily functioning, and levels of energy.

Potential Problem and Alternative Solutions. Some older subjects may have difficulty reading the KCCQ or the POMS Vigor scale due to visual problems. We will have copies of both items in LARGE font available for those subjects. If that is not sufficient to solve the problem, we will read each item to the subject and complete the KCCQ and POMS Vigor scale for them if given verbal consent.

AIM #2: *To determine the effects of oral ubiquinol, D-ribose, or a combination of the two over 12 weeks on biological measures in patients with HFpEF.*

Hypothesis #3. Ubiquinol (600 mg daily), D-ribose (15 g daily), or a combination of the two will improve left ventricular diastolic function measured by advanced echocardiographic imaging in patients with HFpEF.

HFpEF is characterized by a stiff left ventricle (decreased compliance) that results from impaired relaxation. This decreased compliance leads to increased end-diastolic pressures. Signs and symptoms of diastolic HF are similar to those of patients with systolic dysfunction.[35] One difference is that the pathophysiologic underpinning of HFpEF is decreased myocardial ATP.[36] The 2013 ACC/AHA Guidelines for treatment of patients with chronic HFpEF include beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin II receptor blockers.[8] These agents have been shown to be effective in systolic HF; however, clinical trials have failed to demonstrate decreased morbidity and mortality in HFpEF.[37] These data support the need for studies that target different and novel mechanisms in HFpEF.[38, 39] Thus, we believe our proposal will address the pathophysiology underlying HFpEF with a treatment that would reduce its signs and symptoms.

Diastole is the phase in the cardiac cycle when the left ventricle fills and prepares for systole. At normal heart rates, diastole comprises two-thirds of the cardiac cycle.[40] Diastolic filling is influenced by passive elastic properties of the left ventricle, by the highly energy-dependent process of active relaxation, and atrial systole.[36] Relaxation of cardiac muscle requires higher amounts of ATP than systole.[41, 42] Diastolic dysfunction is the major pathological mechanism of HFpEF, in which there is impairment in left ventricular relaxation because of increased stiffness and decreased compliance. Higher left ventricular end-diastolic pressure results in increased pulmonary pressures, pulmonary congestion (dyspnea), elevated plasma BNP, and subsequent heart failure.[43] The increased ventricular stiffness is attributable to the increase in cytoplasmic calcium resulting from decreased sarcoplasmic reticulum calcium ATPase. The elevated cytoplasmic calcium results in impairment of detachment of the actin/myosin cross bridges.[44, 45] The decreased end-diastolic volume (EDV) reduces stroke volume (SV) resulting in a compensatory increase in heart rate to maintain an adequate cardiac output (CO). Thus, the degree to which CO can be increased with activity (e.g., exercise) is limited.

Two-dimensional Doppler echocardiography is a safe imaging technique frequently used to assess HFpEF. However, LV diastolic dysfunction is difficult to assess using standard echocardiography.[46] **Speckle tracking echocardiography** is a novel, objective, and non-invasive advanced imaging technology that provides an accurate and precise way to assess diastolic ventricular function.[47, 48] This technology has been systematically validated by sonomicrometry, tagged cMR, and color-coded tissue Doppler echocardiography. Speckle tracking echocardiography is superior to Doppler imaging in measuring left ventricular deformation as it overcomes limitations such as angle-dependent high frame rates and tethering effects. It allows investigators to easily calculate and assess myocardial deformation (rotation, torsion, and strain) and tissue velocity, which are important parameters for left ventricular diastolic function.[49] Studies using speckle tracking

echocardiography on patients with HFpEF have demonstrated more sensitive measurements of changes of LV structure than regular echocardiography. Speckle tracking consistently showed early diastolic strain rate, reduced peak strain, and fibrosis as evidenced by increased myocardial reflectivity, which parallels the degree of diastolic dysfunction.[50-52] In this study, a speckle tracking echocardiography technician will perform the echocardiograms during each visit (baseline and 12 weeks). Drs. Shah (an expert in speckle tracking research), Vacek, and Hiebert (cardiologists) will determine EF and the ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e') (E/e' ratio) (SV, EDV, EF) from the echocardiogram. Using speckle tracking software, we will measure myocardial deformation, rotation, torsion, strain, strain rate, and tissue velocity. Changes in the early apical diastolic untwisting rate (rotR) and negativity of time from apical peak diastolic untwist (trotR) to mitral valve opening (MVO) are two major variables that reflect diastolic function. Decreases in rotR and trotR are indications of diastolic dysfunction.[53] Speckle tracking analysis with two-dimensional imaging will be performed as previously described by Leitman et al. at high frame rate parasternal short-axis images at the level of the mitral valve to generate rotation and rotation rate data.[47] Frame-by-frame rotation and rotation rate will be exported in Excel, and the temporal data will be normalized to the percentage duration of systole and diastole separately as previously described by Nakai et al.[54] We anticipate that ubiquinol and/or D-ribose will change rotR, trotR, strain, strain rate, and tissue velocity.

Potential Problem and Alternative Solutions. One issue that might arise relates to scheduling the echocardiographic technician when the subject is available to come to the CTSU. A solution is to utilize an additional on-call echocardiographic technician should scheduling issues occur.

Hypothesis #4. Ubiquinol (600 mg daily), D-ribose (15 g daily), or a combination of the two will increase the distance that patients with HFpEF can walk in 6 minutes.

Exercise-based testing is essential in evaluating the functional capacity and response to therapy and prognosis of patients with HF.[55] The 6-minute walking test (6MWT) is a simple clinical tool which has been shown to be linearly related to oxygen uptake.[56] The ease and cost of the 6MWT gives it advantages compared to other tests.[57] Mortality and morbidity in chronic HF have been predicted with the 6MWT. It was found that patients with a walking distance of less than 300 meters (325 yards) had 50% mortality at 1 year; the mortality of those walking more than 450 meters was less at 1 year. In addition, there was an inverse relationship between distance walked and hospitalization rates.[58]

We will examine the effects of ubiquinol and/or D-ribose on the 6MWT at baseline and 12 weeks. Participants will be asked to wear appropriate clothes and shoes and walk the longest distance possible in 6 minutes. Prior to exercising, there will be a 10-minute rest period during which heart rate and blood pressure will be recorded. Subjects will walk indoors on a flat, straight 30-meter path marked every 3 meters, and they will be informed that they can slow down or stop at any time. A one-lap demonstration will be completed before the test begins. The distance walked will be recorded. Following the 6MWT, a 0.02 ml blood sample will be obtained for lactate measurement. Lactate provides a measure of the oxygen debt occurring during exercise and correlates directly with reported dyspnea and fatigue. The patient will also record perceived dyspnea and fatigue at baseline and at the end of each walk by using the Borg scale, where 0 = nothing at all, 5 = severe, and 10 = very severe. Words of encouragement will be offered during the walk and water provided afterward.

Hypothesis #5. Ubiquinol (600 mg daily), D-ribose (15 g daily), or a combination of the two will decrease venous blood B-type natriuretic peptide (BNP) levels in patients with HFpEF.

B-type natriuretic peptides are a cardiac neurohormone secreted from the atria and ventricles in response to volume expansion. This natriuretic peptide system assists in regulating extracellular volume by inducing renal diuresis.[59] Serum levels of BNP increase in cardiac disease conditions associated with increased atrial and ventricular stretch and left ventricular diastolic filling pressures. Miller et al. found that BNP concentrations were increased in outpatients with HF and were directly correlated with the magnitude of HF.[60] In one study of 1,653 subjects, the BNP levels increased as left ventricular dysfunction increased.[61] Ruskoaho found that in the outpatient setting serum BNP values had a sensitivity of 97% and a negative predictive value of 98%.[62] Increased BNP concentrations with diastolic dysfunction have been strongly related to left ventricular hypertrophy.[63] HF recommendations were updated in 2010 to include natriuretic peptides (i.e., BNP) in the urgent-care setting when the clinical diagnosis of HF is uncertain.[64] In HF patients with EF > 40%, natriuretic

peptides were the strongest independent predictor of diastolic dysfunction.[65] At time of discharge, a BNP level of 400 pg/ml was 89% sensitive for events, and the negative predictive value was 96%.[66] Independent of other prognostic variables, BNP levels have been shown to predict mortality in patients with HF.[67]

BNP concentration will be measured using a portable i-STAT handheld analyzer. A blood sample (20 µl) will be obtained from a finger stick after the subjects have completed the questionnaires at baseline and 12 weeks. We will measure BNP concentration at each visit. Prior to running the BNP test, the cartridge initiates a series of preset quality control diagnostics, from monitoring the quality of the sample to validating the reagent. The i-STAT can detect BNP levels ranging between 5 and 5000 pg/ml, with results available in 10 minutes.

Hypothesis #6. Ubiquinol (600 mg daily), D-ribose (15 g daily), or a combination of the two will decrease the lactate/ATP ratio in patients with HFpEF.

CoQ10 is a key component in mitochondrial bioenergy transfer.[14, 68] Its enzymatic processes facilitate electron transfer in the generation of ATP. CoQ10 functions in electron transfer chain (ETC) from enzyme complex I and enzyme complex II to complex III.[69] Thus, CoQ10 is critical in ATP generation because 95% of ATP generation is via ETC.[70] D-ribose is a naturally occurring compound and a simple sugar molecule that has been shown to increase cellular energy synthesis in the heart. The myocardium's ability to resynthesize ATP is then limited by the supply of D-ribose,[71, 72] and supplementing D-ribose would increase ATP production. We plan to measure the effects of ubiquinol and/or D-ribose on mitochondrial ATP production by using an indirect measure (serum lactate/ATP ratio). Several studies have measured the effects of CoQ10 on mitochondrial function.[68, 73-75] In HFpEF, ATP production is limited due to myocardial mitochondrial dysfunction, which results in anaerobic metabolism and increased lactate production. When exercise intolerance occurs, fatigue and lack of energy ensue.[76, 77] Pyruvate is the principal substance used in the production of energy. In a series of reactions, glucose is converted to pyruvate, which in the presence of adequate oxygen leads to mitochondrial ATP production. Insufficient oxygen supply results in pyruvate being converted to lactate. When mitochondrial function is impaired (e.g., CoQ10 deficiency) the pyruvate to ATP pathway is compromised resulting in pyruvate being converted to lactate.[78-81] There have been studies measuring the lactate/pyruvate ratio in HF patients receiving ubiquinone.[75, 82] In most studies, ubiquinone decreased this ratio. Dai et al. found that ubiquinone supplementation in patients with HF significantly lowered plasma lactate/pyruvate ratio.[75] However, our review found only one case history that examined lactate/pyruvate ratios and ubiquinol deficiency.[83] A direct measure of lactate and pyruvate levels from cardiac myocytes would be optimal; however, it is not feasible in an outpatient clinic setting. The pyruvate measurement takes approximately 3 hours to complete and requires reservation of instrumentation at a location other than the CTSU. We found a new reliable ATP test system called the EnSURE™, which is a handheld instrument that is sensitive to detect down to 0.1 fmol of ATP in 15 seconds. Chida et al. used serum lactate/ATP ratio as a new real-time biomarker in patients to assess changes in energy with impaired mitochondria, the lactate/ATP ratio is elevated.[84]

A capillary finger stick blood sample (1.0 ml) will be obtained after subjects have completed the questionnaires and echocardiograms. Lactate concentration will be measured with a portable i-STAT handheld instrument using a CG4+ cartridge that requires 0.5 ml blood and takes 2 minutes to complete. Quality control tests will be performed on the i-STAT instrument each time prior to sampling. The lactate cartridge initiates a series of preset quality control diagnostics, from monitoring the quality of the sample to validating the reagent. The lactate cartridge contains sensitive biosensors on a silicon chip that is configured to perform that specific test. We will use 0.5 ml of venous blood for the ATP measurements and place it in 10 ml of distilled water. Using a probe called the AquaSnap Total system, ATP in solution will be measured. The specifically designed tip will collect 100 µl of solution, and then we will place the probe into the EnSURE™ instrument (ATP Test System). The EnSURE™ quality monitoring system detects real-time ATP down to 0.1 fmol within 15 seconds.

C.4. Preliminary Data. Dr. Hiebert, our senior cardiologist, has more than 10 years of clinical experience in prescribing CoQ10, and for the past 4 years has prescribed the combination of ubiquinol (600 mg/day) and D-ribose (15 g/day) for patients with HFpEF. He has observed significant improvement in the health status of these patients using this combination of supplements. All subjects in our preliminary study reported that they complied with these doses by taking all daily required supplements in the morning with breakfast (compliance). Each subject tolerated these doses without any reported side effects (tolerance).

Table 1 summarizes the results of this preliminary study. Patients with HFpEF were given the KCCQ and the POMS Vigor subscale before and after 12 weeks of taking ubiquinol or ubiquinol plus D-ribose. We observed significant improvements (paired samples t-tests, $p < 0.05$) in the KCCQ clinical summary, functional status, self-efficacy, social interactions, quality of life, symptoms, and physical limitation scores as well as significant improvements in POMS Vigor scores. The increase in self-efficacy and social interactions was not a direct change but may have resulted from the improved level of vigor and reduced signs and symptoms of HF.

Table 1	Ubiquinol Only (N = 5)		Ubiquinol + D-ribose (N = 5)	
Variables	**Baseline**	**Change after 12 weeks[a]**	**Baseline**	**Change after 12 weeks[a]**
KCCQ Clinical Summary Score	48.0 ± 21.9	+16.3 ± 7.0	42.2 ± 28.3	+30.0 ± 13.2
Functional Status	46.6 ± 22.6	+16.3 ± 8.5	39.4 ± 29.3	+31.7 ± 12.3
Self-efficacy	57.5 ± 16.8	+15.0 ± 10.5	62.5 ±16.3	+12.5 ± 8.8
Social Interactions	56.0 ± 20.1	+12.0 ± 7.6	53.0 ± 22.0	+22.0 ± 17.5
Quality of Life	43.3 ± 29.7	+23.3 ± 12.4	40.0 ± 34.1	+33.3 ± 13.2
Symptoms	46.0 ± 25.1	+16.0 ± 10.7	39.0 ± 29.3	+38.5 ± 12.9
Physical Limitation	47.3 ±19.6	+16.7 ± 6.2	40.0 ± 29.7	+22.7 ± 13.6
Vigor Score (POMS)	15.2 ± 10.7	+7.6 ± 4.2	8.8 ± 9.3	+9.6 ± 3.0
Values are mean ± standard deviation. ***a:*** *For each patient, a change in a variable was computed by subtracting the baseline variable measure from a measure taken at the end of 12 weeks.*				

Table 2 presents a summary of echocardiographic data from a retrospective chart review of patients with HFpEF: E/e'; pulmonary artery pressure; and B-type natriuretic peptide (BNP) levels. Variables were retrieved from charts before and 12 weeks after taking the supplements (ubiquinol 600 mg/day, D-ribose 15 grams/day).

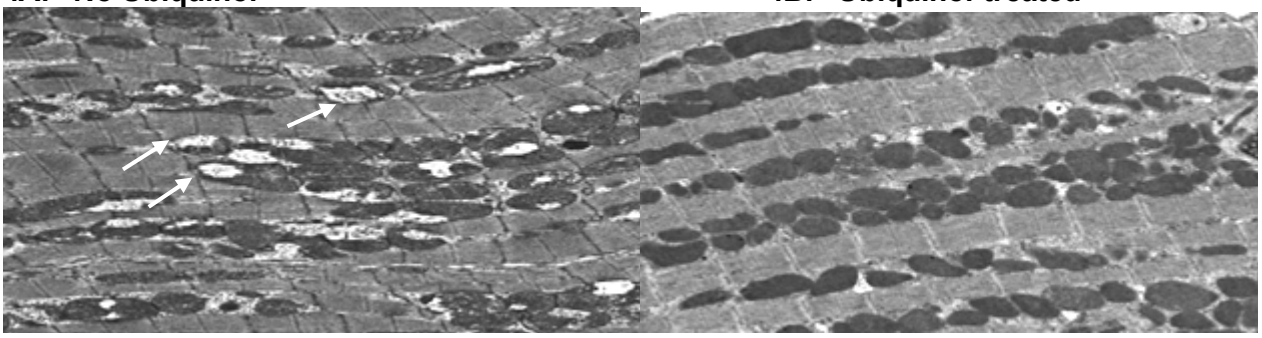
Table 2	No Ubiquinol		With Ubiquinol		With Ubiquinol + D-ribose			
Variable	**Baseline**	**Change after 12 weeks[a]**	**Baseline**	**Change after 12 weeks[b]**	**Baseline**	**Change after 12 weeks[c]**	**Observed Effect Size Ubiquinol**	**Observed Effect Size Ubiquinol+ D-ribose[e]**
E/e' ratio	9.3 ± 2.4 (N=6)	+5.5 ± 2.4	17.9 ± 6.1 (N=8)	−7.7 ± 4.6	18.2 ± 4.2 (N=8)	−6.5 ± 2.9	−3.5	−4.4
Pulmonary Artery Pressure	32.1 ± 5.4 (N=12)	+13.2 ± 8.6	37.8 ± 5.8 (N=10)	−13.6 ± 10.3	41.1 ± 5.9 (N=8)	−10.4 ± 6.0	−2.8	−3.3
BNP (pg/ml)	1892 ± 2381 (N=13)	+4598 ± 4986	2194 ± 1806 (N=8)	−1494 ± 1641	2122±116. 5 (N=4)	−1262.8±92.7	−1.5	−1.3

Values are mean ± standard deviation. **a:** For each patient, a change in a variable was computed by subtracting the baseline variable measure from a measure taken at the end of 12 weeks. **b:** In this nonrandomized pilot study, all changes after 12 weeks on ubiquinol were significantly different from their corresponding changes without ubiquinol, according to independent-samples t-tests ($p<0.05$). **c:** In this nonrandomized pilot study, changes after 12 weeks on ubiquinol + D-ribose were significantly different from their corresponding changes without ubiquinol, according to independent-samples t-tests ($p<0.05$). **d:** Cohen effect size comparing mean change on ubiquinol vs without ubiquinol was computed. **e:** Cohen effect size comparing mean change on ubiquinol + D-ribose versus without ubiquinol was computed.

Comparative data were also reviewed from a group of patients who were not taking ubiquinol. These data indicate that E/e' ratio, PAP, and BNP levels significantly deteriorated among patients who did not take ubiquinol. In contrast, 12 weeks of ubiquinol (or ubiquinol + D-ribose) supplementation resulted in a marked improvement of left ventricular function, as reflected by significant decreases in E/e' ratio, PAP, and BNP.

In another study we investigated the effects of ubiquinol on heart nuclear membrane damage (apoptosis) and mitochondrial structure injury during severe oxidative stress in anesthetized rats (Figure 4).

4A. No Ubiquinol **4B. Ubiquinol-treated**



Oxidative stress was produced by removing 40% of the rat's total blood volume and sustaining shock for 1 hour, after which the blood and lactated Ringers were re-infused. One group received ubiquinol and monitored for 2 hours, after which the animals were euthanized and the heart excised for analysis. The findings indicate that ubiquinol significantly attenuated myocardial oxidative stress damage, which is implicated in the pathophysiology of HFpEF. In summary, a commonality between our preliminary data in rats and HFpEF patients is impaired mitochondrial energetics and oxidative stress. The proposed measurements in HFpEF patients will enhance our understanding of how ubiquinol and D-ribose is beneficial at the cellular level to improve cardiac performance and reduce HF symptoms.

C.5. Statistical Analyses.

Groups and Number of Subjects (69 per group/Total = 276 subjects). The power analyses require 62 subjects/group, but there will be 69 subjects/group based on the expected 10% attrition.	
1. Control Group (Usual Care) N_1 = 69 subjects: Receive no ubiquinol and no D-ribose; placebo capsules and powder per day.	**2. Ubiquinol Group** N_2 = 69 subjects: Receive 600 mg of ubiquinol per day; D-ribose placebo powder per day.
3. D-ribose Group N_3 = 69 subjects: Receive 15 g of D-ribose per day; placebo capsules for ubiquinol per day.	**4. Ubiquinol + D-ribose Group** N_4 = 69 subjects: Receive 600 mg ubiquinol and 15 g of D-ribose per day.

Power and Statistical Analyses. Our power computations described below suggest including 62 subjects in each of the four study groups (ubiquinol, D-ribose, ubiquinol + D-ribose, and placebo). Since we expect about a 10% attrition rate, we will include 69 subjects in each group for a total of 276 subjects who will be randomized to one of the four groups. Efforts will be made to recruit 50% females. As suggested by the reviewers, we will oversample minority populations to increase the generalizability of data for minority groups (30% Black/AA, 30% Hispanic/Latino, 30% White, and 10% Other). In each group there will be Black/AA = 21, Hispanic/Latino = 21, White = 21, American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander = 6 (Total = 69). A 10% attrition rate is anticipated since this is the approximate rate Dr. Carol Smith (Co-PI) has experienced with her heart failure clinical trials at the same locations. Reasons for the subject's attrition were that they did not want to continue in the study, change in geographic location, or illnesses.

Hypotheses #1 and #2. The change in the KCCQ Clinical Summary score from baseline to the end of the 12 weeks of treatment will be computed for each patient as KCCQ score at 12 weeks minus KCCQ score at baseline. A two-tailed independent samples t-test will test the null hypothesis of no difference in mean change between patients on ubiquinol and patients on placebo. Similar tests will be used to compare D-ribose with placebo, ubiquinol + D-ribose with placebo, and ubiquinol versus ubiquinol + D-ribose. Next, we state and justify the assumptions underlying our proposed sample size. Soto et al. (2004) conducted a study of 1516 patients and found that a 10-point decline in KCCQ scores had an important prognostic significance, in that patients whose KCCQ Clinical Summary scores declined by ≥ 10 points had a 107% increased risk of dying or being hospitalized during the next 12 weeks (event rate = 11.4% vs. 5.5%, $p<0.001$).[85] Thus, we believe that an increase of at least 10 points with use of ubiquinol will be clinically important. In addition, our pilot study with ten subjects also found that, after 12 weeks of treatment, all subjects with ubiquinol or ubiquinol + D-ribose had an increase in the KCCQ Clinical Summary score of at least 10 points, which is consistent with the study findings of Soto et al. (2004). The combined estimated standard deviation for the increase was 12.3 points.

This implies that Cohen effect sizes of at least 0.81 (= 10/12.3) are clinically important. Therefore, a sample size of 62 subjects per group will provide at least 98% power to detect this or larger effect sizes at a nominal significance level of 0.05 (with Bonferroni correction for four comparisons).

Analogous two-tailed independent samples t-tests will be used to compare changes in POMS scores. According to a linear regression of changes in POMS Vigor scores versus changes in the KCCQ Clinical Summary scores using our pilot data, a 10-point increase in KCCQ Clinical Summary scores predicted about a 6.5 point increase in Vigor scores. Thus, we believe that a 6.5-point increase in vigor in our subjects will be of clinical importance. Our pilot study also yielded an estimated standard deviation of 3.6 for 12 week changes in Vigor score, which implies that Cohen effect sizes of at least 1.8 are clinically important. Our sample sizes will provide 99% power to detect this or larger effect sizes at a nominal 0.05 significance level with Bonferroni correction for four comparisons. If assumptions of the t-test are not satisfied, transformations or the Mann-Whitney test will be applied. The five subjects of our pilot study who received ubiquinol showed a significant increase of 16.3 points in KCCQ Clinical Summary scores with respect to baseline (t=5.23, df=4, two-tailed paired samples p=0.0064). Similarly, the other five subjects of our pilot study who received ubiquinol + D-ribose showed a significant increase of 30 points with respect to baseline (t=5.10, df=4, two-tailed paired samples p=0.007). The 13.7-point increase produced by the independent effect of D-ribose was borderline significant (t=2.06, df=9, two-tailed independent samples p=0.08). These results from our small pilot study suggest a high likelihood that ubiquinol, and probably D-ribose, will produce clinically important increases of 10 points in KCCQ scores, which gives additional confidence in the success of our proposed study and in the potential clinical applications of ubiquinol.

Hypothesis #3. The change in the E/e' ratio from baseline to the end of 12 weeks of treatment will be computed for each patient as E/e' ratio at 12 weeks minus E/e' ratio at baseline. A two-tailed independent samples t-test will be used to test the null hypothesis of no difference in mean E/e' ratio change between patients on ubiquinol and patients on placebo. Our pilot data (Table 2) showed a substantially strong and clinically important Cohen effect size of ubiquinol on E/e' ratio (−3.5). With 62 subjects per group, our t-test will have a very large power of 99% to detect this or larger effect sizes with a 0.05 level of significance (with Bonferroni correction for 4 comparisons, since both D-ribose alone and combined with ubiquinol will additionally be compared with placebo, and ubiquinol will be compared with ubiquinol + D-ribose). There are no studies comparing E/e' ratio on D-ribose versus placebo or on the combination of ubiquinol and D-ribose versus placebo. However, our sample sizes will be able to detect effect sizes of at least 0.7 in absolute value with at least 90% power. A study comparing D-ribose with dextrose found a significant improvement in atrial velocity with D-ribose, reporting means and SDs that suggest an effect size of about 0.85.[9] Thus we are confident that our study will have sufficient power to investigate this other proxy of left ventricular diastolic function. Analogous computations and tests will be made to examine the effects of ubiquinol, D-ribose, and the combination of ubiquinol with D-ribose on PAP changes. The large and clearly clinically important effect size of ubiquinol on PAP observed in our pilot study (−2.8; Table 2) suggests that our sample sizes will provide 99% power for at least the ubiquinol-placebo comparison.

Hypothesis #4. A two-tailed independent samples t-test will be used to test the null hypothesis that the mean change in the 6MWT from baseline to the end of 12 weeks in patients taking ubiquinol is different from the mean change for placebo. Comparisons of D-ribose versus placebo, of ubiquinol + D-ribose versus placebo, and of ubiquinol versus ubiquinol + D-ribose will likewise be made. Our proposed sample sizes (62 per group) will allow detecting Cohen effect sizes on the 6MWT of at least 0.7 with at least 90% power at a nominal 0.05 level of significance with Bonferroni correction for four comparisons. Published data[86] suggest the possibility of a much larger effect size of ubiquinol on a 6-minute walk (3.9), giving us confidence in our design for at least the ubiquinol vs. placebo comparison.

Hypothesis #5. Our pilot data suggested that ubiquinol has a large effect size on BNP (−1.5; Table 2). Thus, two-tailed independent samples t-tests comparing changes in BNP from baseline to the end of 12 weeks will have a large power (99%) for investigating Hypothesis #5 using Bonferroni corrections. In general, our sample sizes will be able to detect effect sizes of at least 0.7 in absolute value with at least 90% power.

Hypothesis #6. The change in lactate/ATP ratio from baseline to 12 weeks will be computed for each patient. A one-tailed independent samples t-test will examine the null hypothesis of no differences in mean changes

between ubiquinol and placebo groups against the alternative that the mean change in patients on ubiquinol will be numerically smaller, which includes the possibility of a negative change. Similar tests will compare D-ribose versus placebo, the combination of ubiquinol + D-ribose versus placebo, and ubiquinol versus ubiquinol + D-ribose. Our sample sizes will give us a power of at least 90% to detect effect sizes of at least 0.7 in absolute value by using a 0.05 significance level and Bonferroni correction for the four comparisons.

Statistical Analyses of Interaction. The study will give us an opportunity to examine whether there is an interactive effect with synergism on KCCQ scores when simultaneously administering ubiquinol and D-ribose. To investigate whether ubiquinol and D-ribose interact synergistically, a linear regression model of KCCQ score change from baseline to week 12 will be built. The model will include indicators for ubiquinol and D-ribose treatment as independent variables, as well as the product of these two indicators (the interaction term), gender, and race/ethnicity demographics. Analogous regressions will be conducted with KCCQ subscales, with the POMS Vigor score, as well as with indicators of left ventricular diastolic function. In addition, this study will give us an unparalleled opportunity to: (1) examine the mediating role of the lactate/ATP ratio in the effect of ubiquinol on left ventricular diastolic function in patients; and (2) examine whether there is an interactive effect with synergism on this function when simultaneously administering ubiquinol and D-ribose. A structural equation model will be built to explore our mechanistic[87] hypothesis that a reduction in lactate/ATP ratio mediates the association between ubiquinol treatment and reduction in E/e' ratio. We will control for potential confounders such as demographics, baseline lactate/ATP ratio, and baseline E/e' ratio. This modeling approach will take full advantage of the fact that subjects will provide measures of lactate/ATP and E/e' ratios at two time points (baseline and 12 weeks), which will allow disentangling the dynamic effects of time, a crucial variable in causality analyses. In a published article, Dr. Diaz has described the use of structural equations in examining mechanistic pharmacological hypotheses of mediation.[88] Similar models will be built by using the other indicators of left ventricular diastolic function in place of E/e'. To investigate whether ubiquinol and D-ribose interact synergistically, a linear regression model of E/e' change from baseline to week 12 will be built that will also include as independent variables indicators for ubiquinol and D-ribose treatment, as well as the product of these two indicators (the interaction term), gender, and race/ethnicity. Analogous regressions will be conducted with other indicators of left ventricular diastolic function. If necessary, transformations will be performed to achieve the assumptions of regression models.

Statistical Analysis of Effect of Treatment Duration. The effect of ubiquinol treatment duration on KCCQ Clinical Summary changes will be further investigated by fitting a random intercept linear model that will use the repeated measures provided by the subjects. Each subject will contribute to the model if any of the following two measures of the dependent variable are available: (1) a change in KCCQ score from baseline to the end of the 6th week, and (2) a change from baseline to the end of the 12th week. One dummy variable indicating whether the change corresponds to a treatment duration of 6 weeks (dummy=0) or 12 weeks (dummy=1) will be included as an independent variable as well as an indicator of ubiquinol treatment, gender, and race/ethnicity. This analysis will include subjects with complete or incomplete data. A positive and significant regression coefficient for the treatment duration dummy will signal that 6 weeks are not sufficient to obtain a change in KCCQ score equivalent to the change obtained after 12 weeks of treatment. Further, a significant regression coefficient for the ubiquinol treatment indicator will provide additional evidence of differences in KCCQ score changes between ubiquinol and placebo groups. To explore whether there is heterogeneity of ubiquinol effects across subjects, an additional random effects linear model will treat the regression coefficient of the ubiquinol indicator as a random coefficient. Analogous analyses will be made with the other continuous variables: POMS Vigor scale, E/e' ratio, PAP, and BNP and with D-ribose in place of ubiquinol. Random effects linear models use the information provided by participants with incomplete data such as participants discontinuing treatment. These models are robust to the presence of missing values under a missing-at-random assumption. To explore the sensitivity of the models to the presence of possible non-ignorable missing data, such as missing data caused by informative drop-out, a joint random intercept linear model will be fitted that will simultaneously model the KCCQ score and the missingness process.[89]

C.6. Project Milestones and Timeline. This research proposal is designed to be completed within a 3-year time period (Figure 5). After the arrival of equipment and supplies and hiring of personnel, we will start screening, recruitment, and enrollment of subjects. We will simultaneously collect data on Aims 1 and 2 until we reach the sample size. Data analyses and publication of the findings will then follow.

<table>
<tr><th>Year 1</th><th>Year 2</th><th>Year 3</th></tr>
<tr>
<td rowspan="2">• Personnel recruitment, purchase equipment & supplies.
• Screening, recruitment & enrollment of subjects.</td>
<td>AIM #1: To determine the effects of oral ubiquinol, D-ribose, or a combination of the two administered during 12 weeks on symptoms accompanying low bioenergetics in patients with HFpEF.</td>
<td rowspan="2">• Clean data, data analyses.
• Prepare manuscripts for publication.
• Presentations at national and regional conferences.</td>
</tr>
<tr>
<td>AIM #2: To determine the effects of oral ubiquinol, D-ribose, or a combination of the two over 12 weeks on biological measures in patients with HFpEF.</td>
</tr>
</table>

Figure 5: General timeline for the proposed study.

Our research team is a diverse group of clinicians, scientists, and HFpEF patients who have the ability and experience to gain new knowledge by addressing each of the study aims. We have added a cardiovascular researcher (Dr. Shah, Director of HF at Northwestern University) who is world renowned for HF and speckle tracking analysis. We also have a large Stakeholder Advisory Panel (SAP) that will meet every 6 months (Appendix 1) to provide guidance related to our research. The SAP consists of 13 stakeholders including patients, caregivers, clinicians, and hospital administrators. Our novel approach addresses the use of ubiquinol and/or D-ribose to manage adverse symptoms (lack of energy, shortness breath, fatigue, leg edema) in patients with HFpEF, thus reducing their symptoms and improving quality of life.

PARTICIPATION OF HUMAN SUBJECTS

The University's Institutional Review Board (IRB) will review and approve this study prior to implementation. Recruitment of subjects (patients with diastolic heart failure, or HFpEF) will be conducted by the Principal Investigator (PI) and research staff including Project Director and Research Associate in Kansas City, Kansas, and through the University of Kansas Hospital. Patients with HFpEF will be asked for permission to be contacted, have the study explained, be invited to participate, and will be provided written informed consent. The potential subjects will be informed that the purpose of the study is to examine the effects of oral ubiquinol, D-ribose, or a combination of the two in treating patients with HFpEF. Consent forms and Health Insurance Portability and Accountability Act (HIPAA) disclosure information per IRB will be given to all subjects and their signatures will be obtained and witnessed, if they agree to participate. The consent forms will include a description of the study, nature of the data collection, the potential benefits and adverse reactions anticipated, and the methods used to ensure confidentiality. The standard care of subjects will not be changed, withdrawn, or reduced for any subject in this study. The research team personnel will abide by all tenets of the University confidentiality policies as well as the Privacy Protection for Research Subjects. All research staff will keep their required Human Subjects Protection and HIPAA certification current.

The University of Kansas Medical Center (KUMC) *Tutorial for Human Subjects' Protection* program examines the historical context for human subjects' protection; the foundational principles that govern the ethical conduct of research; policies and practices that promote the welfare of research volunteers; and the collective responsibilities shared by the institution, faculty, and staff. The KUMC *Tutorial for HIPAA* provides legal and ethical information about protected healthcare information. Research regulations are reviewed by the KUMC HIPAA Compliance Program Office. Training on HIPAA regulations will be conducted for project staff by R. Spaniol, PhD, who directs HIPAA Compliance at the University.

1. Risks to Human Subjects.

1.1. Human Subjects Involvement, Characteristics, and Design. The involvement of human subjects in the work outlined in the Research Strategy includes two visits to the Clinical and Translational Scientific Unit (CTSU), obtaining echocardiograms and digital punctures (finger sticks), completing questionnaires, and receiving three follow-up phone calls by research staff. As suggested by the reviewers, we will oversample minority populations to increase the generalizability of data for minority groups (30% African American (AA), 30% Hispanic/Latino, 30% White, and 10% American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander. All patients **included** in this study will: be 50 years old or older; have left ventricular ejection fraction (EF) ≥ 50% documented by an echocardiogram within 12 months of enrollment; be diagnosed with HFpEF within a 12-month period; HFpEF, have symptoms of dyspnea and New York Heart Association (NYHA) Classification II or greater symptoms, have a diagnosis of HFpEF defined by one of the following: (1) previous hospitalization for HF with radiographic evidence (pulmonary venous hypertension, vascular congestion, interstitial edema, or pleural effusion) of pulmonary congestion, (2) invasive hemodynamics, (3) echocardiographic evidence of diastolic dysfunction, (4) elevated NT-pro (>400 pg/ml) or BNP (>200 pg/ml), or (5) no use of intermittent sublingual nitroglycerin within 12 months; be 50 years old or older; have left ventricular ejection fraction (EF) ≥ 50% documented by an echocardiogram; are diagnosed with HFpEF within a 6-month period; have willingness to provide informed consent; have a telephone or reliable phone contact; and have their own means of transportation to the study site. Patients will be **excluded** based on any of the following criteria: (1) acute coronary syndrome in the past 12 weeks; (2) significant valvular heart disease; (3) severe cardiac fibrosis (galectin-3 level > 26 ng/ml); (4) constrictive pericardium; (5) pulmonary fibrosis; (6) congenital heart disease; (7) hypertrophic or infiltrative cardiomyopathy; (8) heart transplant; (9) left ventricular assist device; (10) HF associated hospital admission or emergency room visit within past 30 days; (11) recent percutaneous coronary intervention; (12) significant renal and/or hepatic dysfunction; (13) severe cognitive impairment; or (14) consumption of any CoQ10 (ubiquinol) or D-ribose supplements. Hepatic and renal dysfunction will be defined as an ICD-10 code with diagnosis of renal and/or hepatic failure in the patient's healthcare record. For retention we will schedule the sessions at a convenient time for each participant. Two nurse practitioners and a cardiologist on this application who work in the outpatient HF clinics will refer patients to the research team. Also, potential patients with HFpEF who are in the Frontiers participant registry will be contacted, screened, and enrolled in the study. In this randomized, double-blind, placebo-controlled trial, eligible subjects will be randomized to receive either ubiquinol (600 mg daily po), D-ribose (15 g daily po), a

combination of the two, or matched placebo for a period of 12 weeks, using a randomly generated number from a statistical software package.

1.2. Sources of Materials. Research material or data collected will be from clinical measurements (echocardiograph with speckle tracking software, 6-minute walk test), laboratory testing (lactate, ATP, and b-natriuretic peptides (BNP)), and questionnaires (Kansas City Cardiomyopathy Questionnaire, Profile of Mood States, and Demographic Questionnaire). Existing patient medical records of current diagnosis, drug list, and hospitalization history will be obtained with the patient's permission. All data will be gathered for the explicit purposes of this study using procedures to ensure confidentiality. All personal data will be identified by code number only. A list that links the assigned code number to the subject's name will be kept separately in a locked file. Only the Project Director and Research Associate will have the access to individually identifiable private information about study subjects. All subjects will be encouraged to contact the Human Subjects Committee with any concerns in the informed consent document.

1.3. Potential Risks. No appreciable risk of physical, psychological, financial, legal, or other harm to the study subjects is expected. Ubiquinol is naturally produced in the human body, and the safety of high doses of orally-ingested CoQ10 for long periods is well established.[90-92] Specifically with ubiquinol, Hosoe et al. found that it was safe, tolerable, and bioavailable at various oral dosages. They also found effectiveness of oral ubiquinol in just 4 weeks.[91] No serious adverse events were observed and no significant safety concern was raised. Thus, ubiquinol was found to have an acceptable safety profile as a dietary supplement with multiple daily doses. Only mild gastrointestinal symptoms have been reported in a small number of subjects; these were not dose-related and occurred in both ubiquinol and placebo groups.[91] D-ribose is a simple sugar that is also naturally produced in the human body and used for energy production. Extended toxicity studies have shown that oral administration of D-ribose up to 15 g/kg/d is safe. Only minor side effects were reported, including diarrhea, gastrointestinal discomfort, and nausea.[93-95] The time and efforts required for two visits to the CTSU may be an inconvenience to patients with HFpEF, especially when they are experiencing symptoms. Subjects may experience minimal pain/discomfort from digital puncture, or possible bruising and swelling around the puncture site, especially for subjects who are taking anticoagulant therapy; uncommonly, faintness is associated with the procedure. Although the potential risks for subjects participating in the 6-minute walk test (6MWT) may be changes in blood pressure, heart rate, and lightheadedness, it is often well tolerated and without reported complications.[96]

2. Adequacy of Risk Protection.

The CTSU visits will be scheduled at a convenient time when patients with HFpEF feel comfortable to travel. The follow-up telephone calls made by the Project Director or Research Associate will include structured questions that are brief (less than 5 minutes), between the hours of 9 a.m. and 6 p.m. (or other times if specified by the subject), and are neutral in voice and tone.

2.1. Recruitment and Informed Consent. All recruitment, consent, and data forms for the study proposal will be submitted to the University's IRB prior to subject enrollment. Informed consent will be obtained by a trained research team member (either the Project Director or Research Associate) who has completed an approved Human Subjects' protection certification program. Consent includes the standard elements: Study description, potential risks, benefits, and options for non-participation. Prior to proceeding with enrollment, personnel will ask the subjects to confirm that they know what components of the study involve. Consent will be documented as a signed form and will be kept in a locked file cabinet in a locked study office at the CTSU. In this study, recruitment materials will target subjects with HFpEF. Invitation letters and advertisement flyers about the study will be sent by the research team at the University of Kansas Medical Center (KUMC). Using this process, the PI will not have any knowledge or contact with a potential study participant without permission. A list of potential subjects who enrolled in the Frontier Participant Registry will also be obtained upon approval by HERON. In addition, the Pioneers Recruitment Registry (Pioneers) will be used to assist with recruiting Black/AA, Hispanic/Latino, American Indian/Alaska Native, Asian, and Native Hawaiian/Pacific Islander subjects. The Pioneers Registry has an agreement with Swope Health Services to recruit minorities for studies. The two nurse practitioners and Dr. Vacek at MidAmerica Cardiology will also provide potential HFpEF patients for the research team to approach for participation in the study. Following permission, the Project Director or Research Associate will contact the potential participant and use a scripted approach to discuss the consent for the study and to answer all the participant's questions. If individuals agree to participate in the study, they

must verbally indicate that they understand the purpose of the study and their rights as participants. The returned, signed consent forms will be considered indicative of informed consent for this study. Due to time commitment to the study, subjects will be compensated for their time at each visit to the CTSU. A bonus incentive will be paid to subjects that complete two CTSU visits.

2.2. Risk Protection. Although no appreciable risk of physical or mental harm is expected to result from the proposed protocol, procedures for dealing with adverse effects are established. Participants will be instructed to take the supplements (ubiquinol, D-ribose, a combination, or placebo) with a meal to prevent or minimize gastrointestinal symptoms. The procedures listed below will be followed to avert negative reactions to procedures or questions posed during the CTSU visits or the follow-up telephone calls: (1) all subjects will be informed that they are free to skip questions, (2) end data collection, (3) not participate in any component of clinical evaluation and laboratory testing, or (4) withdraw from the study without changes in their standard or usual medical or nursing care. Subjects will be instructed to report immediately to the PI, Project Director, Research Associate, or the cardiologists (consultants) any negative side effects when consuming the supplements. Appointments will be cancelled and rescheduled if subjects express an inability to travel for scheduled CTSU visits. Furthermore, personnel are trained to discontinue any data collection in which the participant becomes emotionally upset or notes discomfort. The Research Associate or the PI will refer that person to our cardiologists or call 911 if immediate medical assistance is required. Subjects who express worry or distress from perceived loss of privacy or have concerns about inconvenience or rights as a research subject (explained in the consent form) will be assured that they do not have to participate, that their medical care will not be affected, or, if already enrolled in the study, that they may withdraw at any time without prejudice. In addition, any such concerns will be documented and reported to IRB.

We will use several procedures to protect subjects against the risk of compromising their confidentiality. First is the decoupling of all subjects' names from all study materials. All forms will make use of a subject code number only, and informed consent forms that include the subject's signature will be stored separately in locked file cabinets. Methods chosen will ensure that patient identifiers and study data are uncoupled. Only selected research staff (the Project Director and Research Associate) will have access to the subjects' data. Information protection procedures are in place specific to the data/communications, Internet computer environment. All subjects and staff are informed that subjects' names and patient medical treatment are not to be discussed or placed on the Internet so that incidental disclosure does not occur.

Privacy and security under the HIPAA standards requires six basic concepts; (i) notice, (ii) permission, (iii) access, (iv) security, (v) responsibility, and (vi) oversight.[97] Subjects' informed consent includes the HIPAA compliance documentation approved by IRB. These documents and privacy concepts were used to develop and deliver interventions in other studies without untoward events.[98] The research team personnel will abide by all tenets of the University confidentiality policies as well as the Privacy Protection for Research Subjects.

3. Potential Benefits of the Proposed Research to Human Subjects and Others.

The administration of oral ubiquinol, D-ribose, or a combination of both to patients with HFpEF will potentially reduce the signs and symptoms of heart failure. This would occur by ubiquinol and/or D-ribose enhancing cellular energetics in cardiac muscle, thus improving diastolic function and enhancing the health status and vigor of patients with HFpEF. The study will generate scientific data that will provide evidence to support expanded use of ubiquinol, D-ribose, or a combination in the clinical management of patients with HFpEF. This study addresses major problems related to lack of effective treatments for HFpEF in order to reduce morbidity and mortality and strives to improve HFpEF clinical outcomes. With the suggestions of the reviewers, we will have more generalizability of data for minorities since there will be oversampling of minority populations.

4. Importance of the Knowledge To Be Gained.

One benefit of gaining knowledge from this proposed study is to present valid and reliable data from these subjects with HFpEF in abstracts and full-length publications so that healthcare practitioners will have a better understanding of the effectiveness of oral ubiquinol, D-ribose, or both in treating patients with HFpEF. This would potentially change the clinical practice of cardiologists and healthcare practitioners in managing HFpEF and have a significant impact on implementing new changes in clinical guidelines for HFpEF.

5. Racial/Ethnic Data for Kansans.
Wyandotte County, Kansas - where the University of Kansas Medical Center is located - is profiled as multi-cultural, urban-centered, and medically underserved. The 163,369 residents make it one of the most densely populated counties in Kansas (1,039 persons per square mile). Females comprise 50.4% of the population in the county. Culturally, over 24.3% of the population is Black/AA; 27.8% Hispanic/Latino; 40.8% White; 1.3% Native American; 4.1% Asian; and 1.7% Alaskan Native, Native Hawaiian/Pacific Islander.[99] Kansas City, Kansas, is the largest city in the county; comprising 92.6% of the county population; 18.9% of residents (all ages) are Medicaid enrolled. The state of Kansas has 105 counties with a population of 2,911,641 with a racial/ethnic designation of 6.3% Black/AA, 11.6% Hispanic/Latino, 77.1% White, 1.2% American Indian, 2.9% Asian, and 0.9% Alaskan Native, Native Hawaiian/Pacific Islander. Out of 25,731 annual deaths (both sexes) in Kansas, 21.2% were due to heart disease. KU Hospital/KUMC is only 30 feet from the Kansas City, Missouri state line. The ethnicity of Kansas City, Missouri, includes: Black/AA 29.7%, Hispanic/Latino 10.1%, White 57.1%, American Indian 0.5%, Asian 2.4%, and 0.2% Alaskan Native, Native Hawaiian/Pacific Islander. KUMC receives referrals related to heart failure from both Kansas and Missouri. Data sources that document these data are: Kansas: Burden of Chronic Disease; CDC, 2012; Kansas Cancer Registry of The Kansas Department of Health and Environment (2000-2014); Kansas Department of Health & Environment, 2014; US Census Bureau (2015).

6. Recruitment Is from Sites Related to the PI's Community Involvement.
This includes the University of Kansas Hospital, Institute for Community Engagement and Frontiers: Heartland Institute of Clinical and Translational Research (HERON), Pioneers Community Registry, all of which have HF patients signed up to volunteer to participate in HF research. In addition, the Pioneers group has an agreement with Swope Health Services which is an inner city clinic that is over 60% Black/AA, 30% Hispanic/Latino, and 10% other races/ethnicity. Thus, we will screen at least 900 patients with HF across the 3-year study timeline. Of these 900 from various sources, we expect 600 patients will be eligible to enroll. Based on Dr. Smith's recent HF trial, enrolling patients (N=276) from various registries and lists should be feasible.

7. We Proposed Several Research Plans to Overcome Any Problems.
Potential participants will be identified prospectively by the Mid-America Cardiology nurse study coordinator who reviews electronic medical records for 40 cardiologists. During recruitment, we will explain the various required time periods for testing and the different potential groups to which patients might be assigned. Our Project Director will assist us in recruiting subjects. Further, several previous study participants from Dr. Smith's grant have volunteered to become involved in this study.

8. Investigators Involvement in Human Subjects Training.
The PI will assure that all members of the investigative team have completed and adhere to all requirements for the protection of human subjects. The PI will be involved in providing discussion and on-going education on the ethical conduct of research for the research team. The five NIH required instructional components (format, subject matter, faculty participation, duration, and frequency) are discussed herein. At each team quarterly meeting (duration and frequency) a standing agenda item will be core conduct of research topics. NIH recommends including conflict of interest, policies regarding human and animal subjects, research team members' responsibilities in collaborative research, peer review processes, quality data acquisition, and coding (subject matter). Samples of research misconduct and policies on responsible authorship and publication (subject matter) are reviewed. In the past meetings, formats of instruction have included report readings of NIH human subjects concerns, case study reviews, discussions regarding any current study issues arising from consultant input or collaborative work (format). We will invite our KUMC faculty leading the KUMC monthly ethics seminar/discussions to lead (faculty participation) some of these discussions on human and data safety and monitoring of scientific rigor and human safety. All staff members undertake the required human subjects research training, pledge to maintain the highest levels of scientific quality, and strive for meaningful translational influence of findings.

Data and Safety Monitoring Plan (DSMP).
The DSMP for this study follows the NIH policies and also policies of the University of Kansas Medical Center (KUMC) Office of Sponsored Projects, written by our Director of Research Compliance and Director of Research Administration. This plan will be approved and annually recertified by the Institutional Review Board (IRB) at the KUMC and carried out by an advisory group of reviewers that will be called the Data Safety

Monitoring Board (DSMB). This plan will be completed by the DSMB members, following review of the National Institute of Aging (NIA) Policy (if funded by this agency). The DSMB chairperson will send all reports to NIH and to our KUMC IRB.

1.0 Participants Safety

1.1. Potential Risks and Benefits for Participants

Ubiquinol has been found to have an acceptable safety profile as a dietary supplement with multiple daily doses. The potential risk to study participants for ubiquinol includes mild gastrointestinal symptoms at high doses around 1000 mg/day. For D-ribose oral administration of D-ribose up to 15 g/kg/d is safe. Minor side effects include diarrhea, gastrointestinal discomfort, and slight nausea. Subjects may experience minimal pain/discomfort from digital puncture, possible bruising and swelling around the puncture site, especially for subjects who are taking anticoagulant therapy; uncommonly faintness is associated with the procedure. Although the potential risks for subjects participating in the 6-minute walk test (6MWT) may be changes in blood pressure, heart rate, and lightheadedness, it is often well tolerated and without reported complications.

The potential benefits to study participants include improved energy level, increased overall health status (reduced physical limitations, less symptoms of heart failure with preserved ejection fraction (HFpEF), increased self-efficacy, expanded social interactions, and improved quality of life), and enhanced cardiac performance.

1.2. Adverse Event and Serious Adverse Event Collection and Reporting

Adverse occurrences or unanticipated problems reported by a subject during the course of their participation in the study will be immediately documented according to study protocol. A report will be sent to IRB if the adverse events is serious, unexpected, and related to the study. We will report to the DSMB and the National Institute on Aging (NIA) administrator all serious adverse events. For each occurrence, the PI or the designated Co-I will evaluate independently to determine severity, expectedness, and attribution of the occurrence to the study protocol or not and report to NIA, IRB, and DSMB if required per policy. Determinations regarding adverse and serious adverse events will be made by James Vacek, MD who is the designated cardiologist on the study who is unblinded. After Dr. Vacek makes this final determination, the adverse event will be reported by Dr. Janet Pierce (PI) or Dr. Qiuhua Shen (Co-PI) to the NIA and Chair of the DSMB (Dr. Pete Miller). All DSMB members are available in real time to review and recommend appropriate actions regarding any adverse or unanticipated events or other safety issues. Any action taken to suspend or terminate the project will be reported immediately to KUMC IRB, NIH Office of Sponsored Projects, and the study Program Officer at NIA.

1.3. Protection Against Study Risks

Informed Consent Process: The consent process will inform a volunteer about the study, indicating the participation is voluntary and he/she has the right to stop at any time. Risks will be enumerated in the informed consent form and described orally during the consent process.

Protection Against Risks: Although no appreciable risk of physical or mental harm is expected to result from the proposed protocol, procedures for dealing with adverse effects are established. Participants will be instructed to take the supplements (ubiquinol, D-ribose, a combination, or placebo) with a meal to prevent or minimize gastrointestinal symptoms. The procedures listed below will be followed to avert negative reactions to procedures or questions posed during the CTSU visits or the follow-up telephone calls: 1) all subjects will be informed that they are free to skip questions, 2) end data collection, 3) not participate in any component of clinical evaluation and laboratory testing, or 4) withdraw from the study without changes in their standard or usual medical or nursing care. Subjects will be instructed to report immediately to the PI, Project Director, Research Associate or the cardiologists (consultants) any negative side effects when consuming the supplements. Appointments will be cancelled and rescheduled if subjects express an inability to travel for scheduled CTSU visits. Furthermore, personnel are trained to discontinue any data collection in which the participant becomes emotionally upset or notes discomfort. The Research Associate or the PI will refer that person to our cardiologists or call 911, if immediate medical assistance is required. Subjects who express worry or distress from perceived loss of privacy, have concerns about inconvenience or rights as a research subject (explained in the consent form), will be assured that they do not have to participate, that their medical

care will not be affected, or if already enrolled in the study that they may withdraw at any time without prejudice. In addition, any such concerns will be documented and reported to IRB.

2.0 Interim Analysis

There are no advance plans for interim and/or futility analysis at this time.

3.0 Data and Safety Monitoring

The Principal Investigator (PI) will be responsible for ensuring participants' safety on a daily basis. The DSMB will act in an advisory capacity to the NIA Director to monitor participant safety, evaluate the progress of the study, to review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses.

3.1. Frequency of Data and Safety Monitoring

The DSMB will meet annually to evaluate the study progress, either in-person or by teleconference call to review study progress, data quality, and participants safety. The PI (Dr. Pierce) will be informed of serious adverse events as soon as they occur and will notify the NIA and the DSMB within 2 business days of notification.

3.2. Content of Data and Safety Monitoring Report

The content of the data and safety monitoring report will include: study status, participant descriptive information, safety information, and study quality. Prior to subject recruitment, the members of the DSMB will read the written study protocols, informed consent procedures, Data Safety Monitoring (DSM) policies, and plan.[100] Members of the DSMB will initially discuss the plan for clarification of their responsibilities, the board structure, and organization and rules of operation, as noted in the policies. All trial progress and DSMB advice on continuation, modification, or termination are reported to the Principal Investigator (Dr. Janet Pierce), IRB, and the NIA Program Officer.

3.3. DSMB Membership and Affiliation

Each of the individuals will formally accept the position as part of the DSMB and the DSMB membership will be reviewed and approved by the NIA. Should there be any questions regarding the independence of the DSMB, it will be addressed and corrected if necessary at that time. This DSMB will include external scientists (cardiologist, supplemental specialist, and a biostatistician) selected and chosen by NIA.

3.4. Conflict of Interest for DSMB's

DSMB members will have no direct involvement with the study investigators or intervention. Each DSMB member will sign a Conflict of Interest Statement which includes current affiliations, if any, with pharmaceutical and biotechnology companies (e.g., stockholder, consultant), and any other relationship that could be perceived as a conflict of interest related to the study and/or associated with commercial interests pertinent to study objectives.

3.5. Protection of Confidentiality

Data will be presented in a blinded manner during the open sessions of the DSMB. At DSMB meetings, data and discussion are confidential. Participant identities will not be known to the DSMB members.

3.6. DSMB Responsibilities

If approved by NIA, the DSMB Charter responsibilities will include:

- Review the research protocol, informed consent documents and plans for data safety and monitoring;
- Recommend subject recruitment be initiated after receipt of a satisfactory protocol;
- Evaluate the progress of the trial, including periodic assessments of data quality and timeliness, recruitment, accrual and retention, participant risk versus benefit, performance of the trial sites, and other factors that can affect study outcome;
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;

- Review study performance, make recommendations and assist in the resolution of problems reported by the Principal Investigator (Dr. Janet Pierce);
- Protect the safety of the study participants;
- Report to NIA on the safety and progress of the trial;
- Make recommendations to the NIA and the Principal Investigator concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- If appropriate, review interim analyses in accordance with stopping rules, which are clearly defined in advance of data analysis and have the approval of the DSMB;
- Ensure the confidentiality of the study data and the results of monitoring; and,
- Assist the NIA by commenting on any problems with study conduct, enrollment, sample size, and/or data collection.
- The DSMB will evaluate the final study manuscripts and final reports to assure results are fairly presented and conclusions are appropriate.[101]

Inclusion of Women and Minorities.

Subjects may participate regardless of gender, socioeconomic level, or ethnic background. All subjects will be 50 years or over, as HFpEF is more prevalent in older adults. National statistics show the prevalence of heart failure to be divided roughly equally between males and females.[102] Efforts will be made to recruit 50% females, which is the actual proportion of HFpEF patients in Kansas City.

The regional HF statistics indicate are: 10% Black/African Americans (AA), 13% Hispanic/Latino, 76% White, and 1% Asian, Native American/Alaskan Native, Native Hawaiian/Pacific Islander. The racial and ethnic population distribution planned coincides with these national and regional figures. The Kansas City Metropolitan Statistical Area confirms these percentages in the general population.[99] In this study, we will oversample minorities (reviewer's suggestion), which will enable us to examine the relationship between HFpEF and racial/ethnic differences. Most of the data regarding treatments for HFpEF are derived from white populations,[27] and therefore it is important to include other racial/ethnic groups and examine whether the effects of ubiquinol and/or D-ribose follow similar patterns to those among whites. For this study, a total of 276 subjects will be randomized to one of the four groups. As suggested by the reviewers, we will oversample minority populations to increase the generalizability of data for minority groups (30% Black/AA, 30% Hispanic/Latino, 30% White, and 10% Other). Each group will be Black/AA = 21, Hispanic/Latino = 21, White = 21, American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander = 6 (Total = 69). The University of Kansas Medical Center (KUMC) Healthcare Enterprise Repository for Ontological Narration (HERON) database, Pioneers Recruitment Registry (Pioneers), and chronic HF clinic at the University of Kansas Hospital (KUH) will be used to recruit subjects. These registries provide clinical/translational investigators with the numbers of patients at KUH who meet the inclusion criteria for clinical trials and contact information for patients who sign up with KUMC's Frontiers participant registry. Based on the HERON, there will be approximately 7,100 subjects with HFpEF available to be screened for enrollment in this study. The Swope Health Services in Kansas City, Missouri has a large Black/AA and Hispanic/Latino population. The Pioneers Registry has a relationship with Swope Health Services and can assist us with electronic informed consent forms, email verification, and subject recruitment at this site.

Inclusion of Children.

All subjects will be 50 years or over, as HFpEF is more prevalent in older adults. Children (the age to 18 years and younger) will not be included in this study because diastolic heart failure is very rare in the pediatric population.

Appendix 9: Safety and Efficacy of Ubiquinol (CoQ10) and D-ribose

Ubiquinol

Safety

- CoQ10 is generally well tolerated at doses not exceeding 1000 mg/day.[11, 103, 104]
- Occasionally, a side effect is gastrointestinal upset, which is significantly reduced if CoQ10 is taken with food. Several studies have reported that patients tolerated ubiquinol well and that they had no adverse side effects.[105-107]
- For this study, we will use Kaneka ubiquinol which is the only ubiquinol ingredient made in the USA. The Kaneka ubiquinol will have pure ubiquinol and be free of the following (does **NOT** contain): sugar, starch, salt, preservatives, corn, soy, wheat, dairy, gluten, mold, or metals. The ubiquinol will be Kosher and Vegan/Vegetarian.
- Kaneka ubiquinol has a Current Good Manufacturing Practice (CGMP) certification by US Food and Drug administration (FDA). This assures proper design, monitoring, and control of manufacturing processes, and facilities at Kaneka. They also have a certificate of analysis for the ubiquinol product.
- Kaneka QH has the National Safety Foundation (NSF) certification to be 100% pure without fillers or additives. The NSF is a Public Health and Safety Organization that certifies dietary supplements to ensure through testing and evaluations that a product is safe.
- There are no established toxic effects of CoQ10 supplementation in humans, and CoQ10 has an excellent safety profile.[11]
- Administration of 300 mg of ubiquinol (Kaneka QH) has significant absorption of ubiquinol from the gastrointestinal tract, and no safety concerns on standard laboratory tests for safety or on assessment of adverse events.[91]
- In our study, we shall advise subjects to take ubiquinol with food to reduce the potential for gastrointestinal upset.[108]
- Ubiquinol needs to be protected from extreme heat and light. It should be stored in a cool and dry place.
- The ubiquinol dosage of 600 mg/day is well within the clinically recommended range. Several studies have indicated that CoQ10 produced no adverse effects or drug interactions.[109-112]

Efficacy

- Low serum CoQ10 levels may result from excessive use, impairment of biosynthesis, insufficient dietary intake, or any combination of the three.[113, 114]
- In heart failure patients, it is necessary to increase serum CoQ10 levels to a minimum of 3.5 mcg/mL to achieve clinical benefits.[115]
- Administering ubiquinone in some studies resulted in poor gastrointestinal absorption. In addition, the ability to convert ubiquinone to ubiquinol (active form) was decreased.[116-119] This conversion is not an issue for individuals in the 20-40 year age range[120, 121] but it becomes increasing difficult for individuals older than the age of 40.[122, 123]
- With the use of ubiquinol, there is no impairment of absorption in patients of any age. With the introduction of ubiquinol the efficacy has greatly increased in many diseases[105, 124, 125] including congestive heart failure.[126, 127]

D-ribose

Safety

- D-ribose is safe and well tolerated in the daily doses smaller than 20 grams.[128-130] In this study, subjects will be consuming 15 grams/day. Subjects may experience loose stools. This effect can be

circumvented by avoiding D-ribose ingestion on an empty stomach or by taking three 5 gram doses at various times of the day.

- For the study, we will use Dual Health 100% Pure D-Ribose Powder. It is a pharmaceutical USP Grade D-Ribose that is a white to slightly yellow crystalline powder, characterized by a fruity sweet odor and slightly sweet taste.
- The Dual Health D-ribose is produced in the USA and from a CGMP manufacturer and has a certificate of analysis for the product.
- The D-ribose from Dual Health is United States Pharmacopeia (USP) and Food Chemical Codex (FCC) graded and is 100% pure without fillers or additives. Thus, it is a certified dietary supplement that through testing and evaluations is a safe product for human consumption.
- D-ribose readily dissolves in water, juice, milk, and other cold liquids and has been determined to be safe with few adverse side effects.[131]
- D-ribose may lower blood pressures [132]

Efficacy

- Impairment of adenosine triphosphate (ATP) synthesis results in energy demand exceeding energy supply, which results in depletion of ATP accompanied by diastolic dysfunction. Research has shown that supplementing exogenous D-ribose accelerated synthesis of ATP by six-fold.[133]
- Increased ATP levels by D-ribose improved cardiac energy metabolism and contributed to significant recovery of myocardial contractility.[134,135]
- D-ribose significantly improved diastolic function and patients' exercise tolerance, which enhanced patients' quality of life.[71]

Combined Regimen of Ubiquinol and D-ribose

- Reports have shown no evidence for adverse interactions between CoQ10 and D-ribose.[136] They reported these supplements enhanced low and high-intensity exercise. There were no side effects in animal studies using these supplements thus investigators stated that they were safe for human consumption.[137]
- Several studies have used the combination of antioxidants together for the treatment of patients with mitochondrial dysfunction. They found that D-ribose or ubiquinol with other antioxidants such as vitamin C, methylcobalamin, and N-acetyl-L-cysteine resulted in significant improvement with no accompanying side effects.[138-140]
- The combination of these supplements has contributed to the cardiac function by maintaining cardiac energy by preserving ATP substrates.

Placebo Products – Capsules and Powder

Safety

- To reduce the risk of allergic reaction, all the placebo products (capsules and/or powder) will be free-from the eight most common food allergens in the United States, as declared by the US Food and Drug Administration (FDA).[141]
- Both the placebo capsules and powder will contain no wheat, no gluten, no soybeans, no dairy, no egg, no fish/shellfish, and no peanuts/tree nuts.
- All placebo products will be manufactured at a pharmaceutical packaging facility that is certified by the Good Manufacturing Practice (CGMP) facilities and also FDA registered and inspected. This company will produce placebos to match our comparators (both the ubiquinol and D-ribose). Stark pharmacy in Overland Park, KS will prepare, package, and label the placebo capsules and powder.

Efficacy

- The inactive ingredients within the placebo capsule will have microcrystalline cellulose in each capsule. The capsules will be the same color and size and in the same type of plastic container.
- The ubiquinol and placebo capsules will both be non-marked light brown color, oval shape capsules. The study product and placebo capsules will be similar in capsule odor, texture, hardness, and packaging.
- The D-ribose powder will be a pure product that has no inactive ingredients. Thus, the placebo powder will also not have inactive ingredients and consist of only microcrystalline cellulose. Both powders will be white in color, similar consistency, and in the same type of plastic container.

Placebo Products – Capsules and Powder Label Information from Stark Pharmacy

Below are examples of the bottle labels that will be provided by Stark Pharmacy. The first label (#1) will be used for the ubiquinol or placebo capsules. The second label (#2) will be used for either the D-ribose or placebo powder.

Ubiquinol, D-ribose, or Placebo Sample Labels

#1
University of Kansas Medical Center
3901 Rainbow Blvd., KCKS 66160
913-588-5000
Participant Number: _____
Date: _____
Medication: Ubiquinol 300 mg capsule or Placebo
Directions: Take 2 capsules daily for 12 weeks.
Lot Number: _____

#2
University of Kansas Medical Center
3901 Rainbow Blvd., KCKS 66160
913-588-5000
Participant Number: _____
Date: _____
Medication: D-Ribose powder or Placebo
Directions: Take 3 scoops daily mixed in water for 12 weeks.
Lot Number: _____

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