Cardiometabolic Disease and Pulmonary Hypertension

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MASSACHUSETTS GENERAL HOSPITAL
DETAILED PROTOCOL

CARDIOMETABOLIC DISEASE AND PULMONARY HYPERTENSION

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1. BACKGROUND

Obesity and cardiovascular disease

Obesity and metabolic disease confer substantial risk of cardiovascular disease. More than one in three adults and nearly one in six youth in the United States are obese.[1] Obesity and metabolic disease such as diabetes mellitus are closely linked,[2] and both confer substantial cardiovascular morbidity and mortality, including increased risk of heart failure.[3-5] While weight loss is central to treating obesity, understanding specific mechanisms driving obesity-related heart failure may help target future prevention strategies.

Obesity, heart failure, and pulmonary hypertension. Cardiometabolic disease has been linked to heart failure with preserved ejection fraction (HFpEF), which frequently coexists with pulmonary hypertension (PH).[2,6,7] Both intrinsic and post-capillary PH strongly predict mortality in HFpEF.[3-5,7-9] Unfortunately, treatment with pulmonary-specific vasodilators has shown mixed results in heart failure,[10-12] highlighting the need for a better understanding of drivers of pulmonary vascular remodeling. Notably, in a recent HFpEF-PH animal model, early but not late metabolic interventions reversed PH.[13] This suggests that prevention strategies targeted at metabolic derangements may be effective in obesity-related PH as an early HFpEF phenotype.

The link between obesity, metabolic disease, and PH

Obesity and metabolic disease are associated with PH in humans. In population-based studies, obesity is associated with higher estimated pulmonary artery pressures (PAP)[14,15] and right ventricular remodeling[16] in the absence of left ventricular dysfunction, and independent of obstructive sleep apnea.[17] Among individuals without known cardiovascular disease, every 10 mmHg increase in PAP is associated with a more than doubling of mortality risk,[18] underscoring the clinical importance of understanding obesity-related PH.

Metabolic disease in pulmonary arterial hypertension. Interestingly, insulin resistance and diabetes mellitus are over-represented in patients with pulmonary arterial hypertension (PAH), where they portend worse outcomes.[19-21] Transcriptomic and metabolomic studies of human PAH lung tissue, cultured pulmonary endothelial cells, and experimental models of PAH demonstrate widespread metabolic dysfunction, including alterations in glucose metabolism, glycolysis, and fatty acid oxidation,[22-24] substantiating the link between metabolic dysregulation and pulmonary vascular remodeling.[25]

Obesity-related PH is multi-factorial. PH associated with obesity can be pre- or post-capillary in origin, with contributions from left ventricular hypertrophy, diastolic dysfunction,[15,26,27] and lung disease including obstructive sleep apnea.[28-30] Our preliminary findings suggest that PH in metabolic disease is in large part due to increases in pulmonary vascular resistance (PVR).[31] This suggests that intrinsic pulmonary vascular dysfunction is an important component of obesity-related PH. No study has examined the association of insulin resistance and PH, with ascertainment of directly measured pre- and post-capillary components leading to PH.

Metabolic dysfunction leads to intrinsic PH in experimental studies. Mouse models of various genetic backgrounds develop adiposity, insulin resistance, and PH when subjected to a high-fat diet.[32-34] This occurs without changes in left ventricular end-diastolic pressures, indicating intrinsic PH. Notably, PH in animal models can be reversed by therapeutically targeting obesity-related pathways, including

inflammation (fatty acid nitroalkenes)[34] peroxisome proliferator-activated receptor-γ (PPARγ; rosiglitazone),[33] and adenosine monophosphate-activated protein kinase (AMPK; metformin).[35] Adipokines may also serve as a potential link between obesity and PH.[36-39] These findings suggest that metabolic disease may lead to intrinsic PH.

Metabolic disease leads to endothelial dysfunction, which in turn may contribute to PH.

Insulin resistance leads to endothelial dysfunction and impaired nitric oxide signaling. In addition to well-recognized effects on glucose homeostasis, insulin has many important vascular actions.[40] Under physiological conditions, insulin activates the phosphoinositide 3-kinase (PI3K)/Akt pathway to mediate endothelial nitric oxide synthase (eNOS) phosphorylation and vasodilation.[41-44] In insulin resistant states, the PI3K pathway is selectively impaired, leading to endothelial dysfunction.[45] Endothelial defects in PI3K/Akt signaling and reduced nitric oxide bioavailability are evident in animal models of insulin resistance[46-48] and human diabetes,[49,50] where endothelial dysfunction contributes to cardiometabolic risk.[46,51-53]

Pulmonary artery endothelial dysfunction is central to pulmonary vascular remodeling. Pulmonary artery endothelial cells (PAECs) play an integral role in the pathobiology of PH.[54,55] PAECs mediate pulmonary vascular remodeling via disordered proliferation and abnormal production of vasoactive peptides, including increases in endothelin-1, and reduced production of vasodilators including nitric oxide and prostacyclin.[56,57]

Metabolic disease leads to PAEC dysfunction in animal models. In rats with streptozotocin-induced diabetes, PH is linked to PAEC dysfunction, characterized by reduced nitric oxide bioavailability, enhanced superoxide production, and recruitment of inflammatory macrophages.[58,59] Whether PAECs are altered in metabolic dysfunction has not been studied in humans. We are poised to study whether insulin resistance leads to pulmonary vascular dysfunction in obesity, using a novel technique to isolate fresh human PAECs at the time of right heart catheterization (RHC). Specifically, we will translate recent work in animal models to human disease, and hypothesize that altered PAEC phenotypes contribute to pulmonary vascular dysfunction.

Dynamic exercise unmasks abnormal pulmonary vascular hemodynamics

Exercise can unmask abnormal pulmonary vascular physiology in cardiopulmonary disease. A major cause of morbidity in heart failure is impaired functional capacity, which can occur in the absence of clinical hypervolemia. Invasive exercise hemodynamic testing can expose abnormal physiology that may not be apparent at rest, including pulmonary vascular dysfunction.[60,61] The ability of the pulmonary vasculature to accommodate increased flow during exercise can be evaluated by plotting the change in mean PAP against cardiac output (ΔmPAP/ΔCO).[62-64] An exaggerated increase in exercise PAP portends worse functional capacity and prognosis in heart failure, valvular disease, chronic obstructive pulmonary disease, and PAH.[65-69]

Pulmonary hemodynamic responses to exercise predict clinical outcomes. Previous cardiopulmonary exercise testing (CPET) studies have established the normal range of ΔmPAP/ΔCO relationships between 0.5-3.0 mmHg/L/min, with a steeper slope indicating abnormal exercise response.[62-64,70] In addition to predicting adverse prognosis in disease states,[65-69] a steep ΔmPAP/ΔCO slope >3.3 mmHg/L/min predicts the future development of PH in patients with connective tissue disease,[71] suggesting that exercise-induced pulmonary vascular dysfunction may indeed represent an early phenotype of pulmonary vascular disease.

Endothelial and pulmonary vascular responses to metformin

Metformin improves endothelial function via effects on AMPK. Metformin is a first-line oral biguanide used in the treatment of diabetes mellitus and insulin resistance. Metformin ameliorates insulin sensitivity,[72] and improves circulating endothelial markers and endothelial dysfunction in metabolic syndrome and diabetes.[73-75] In cultured human endothelial cells subjected to metabolic stressors, metformin increases eNOS expression and phosphorylation at serine[1177] (p-eNOS) via AMPK activation (p-AMPK) and phosphorylation of Akt.[76-79] Metformin also blunts stress-inducible kinases,[77] and modulates endothelial oxidative stress.[76,80]

Metformin improves PH in animal models. In a rat model of obesity-associated PH and HFpEF, metformin reduced PAP and vascular remodeling by activating skeletal muscle sirtuin-3 and AMPK.[13] Similar PAP effects were seen in a monocrotaline PH rat model, where metformin resulted in a more than 6-fold increase in p-eNOS.[81] In PAECs isolated from a sheep model of PH, metformin restored bioavailability of NO via AMPK activation.[35] We hypothesize that insulin resistance leads to PAEC dysfunction and PH, which can be modulated by metformin. We will translate experimental findings to a proof-of-concept patient-oriented intervention trial to investigate the effect of metformin versus placebo on pulmonary vascular dysfunction in obesity. This study may provide important insights into mechanisms driving PH in metabolic disease, and will lay the foundation for future studies focused on disease prevention and optimal therapies in obesity-related PH.

Venous endothelial cells show increased expression of pro-inflammatory proteins in obesity. In addition to PAEC, we will examine venous endothelial cells to ascertain inflammation that may be variably present in different vascular beds. Various investigators have described methods for safe collection of venous endothelial cells (EC) from introducer wires used for insertion of venous catheters, [82,83] and previously endothelial protein expression has been ascertained in order to phenotype venous endothelial cells in various disease states. [83,84]

Rationale for proposed research

In sum, strengths of prior studies include consistency of obesity-related pathways associated with PH across various animal models. Prior human studies support an association of obesity and PH with the following limitations: 1) PAP were estimated non-invasively, limiting assessment of PH subtype (pre- vs post-capillary), 2) studies were observational, precluding causal inferences about underlying mechanisms, 3) potential confounders including existing pulmonary disease were incompletely characterized. We plan to address these knowledge gaps by performing direct hemodynamic evaluations at rest and in response to exercise, by conducting a randomized trial evaluating the effect of metformin on pulmonary vascular function, and by carefully assessing pre-existing pulmonary disease and other potential confounders.

2. STUDY SPECIFIC AIMS

We postulate that obesity-related metabolic disease leads to pulmonary vascular dysfunction. Our laboratory has established specific expertise in measurement of both resting and serial exercise PAP to carefully characterize pulmonary vascular function and early forms of PH. In addition, we have developed a novel protocol to isolate and phenotype fresh human pulmonary artery endothelial cells (PAECs) to examine specific molecular mechanisms underlying PAEC dysfunction and cellular responses to metabolic interventions.

We propose to prospectively study 250 obese non-diabetic individuals with exertional dyspnea in the absence of known cardiovascular disease, in order to test the following primary hypotheses:

1) Systemic metabolic dysfunction and PAEC-specific insulin responses are associated with PH
2) Insulin resistant individuals will have exaggerated increases in PAP in response to dynamic exercise
3) Metformin will improve pulmonary vascular dysfunction and PAEC phenotype in obese individuals

Aim 1. To investigate the association of metabolic disease and PAEC phenotypes with pulmonary hemodynamics in human subjects. We will assess insulin resistance and pulmonary hemodynamics via invasive hemodynamic assessment in those with abnormal noninvasive assessment. Human PAECs will be isolated to examine cellular responses to insulin stimulation including AMPK activation and eNOS phosphorylation. We will relate PAEC and metabolic phenotypes to resting pulmonary hemodynamics.

Aim 2. To study the dynamic pulmonary vascular response to exercise in metabolic disease. Participants will undergo invasive cycle ergometry cardiopulmonary exercise testing with simultaneous hemodynamic monitoring. Multi-point PAP-cardiac output relationships and pre- and post-capillary components of PAP will be defined to precisely characterize pulmonary vascular function. We will relate systemic and PAEC-specific insulin resistance to dynamic PAP responses to exercise.

Aim 3. To examine the effect of metformin on pulmonary vascular function and PAEC phenotype in obese individuals. We will conduct a randomized placebo-controlled double-blinded intervention trial, randomizing 75 individuals exhibiting resting or exercise pulmonary vascular dysfunction in Aims 1 and 2 to metformin versus matching placebo for 3 months. We will compare baseline and post-intervention pulmonary vascular hemodynamics and PAEC phenotypes between metformin and placebo groups.

3. SUBJECT SELECTION AND ENROLLMENT CRITERIA

Subject Selection: The proposed studies will involve prospectively enrolling 250 overweight or obese adults age 30-80 years with dyspnea and without known diabetes mellitus or cardiovascular disease. The study design involves nested samples, whereby participants enrolled in Aim 1 are screened for eligibility for Aim 2, and those enrolled in Aim 2 are screened for eligibility in Aim 3. Thus, one study participant may participate in all three aims, streamlining the recruitment and enrollment process. It will also provide the opportunity to study the same individual both in response to exercise (Aim 2) and then in response to a metabolic intervention (Aim 3). Inclusion/exclusion criteria for each Aim, and corresponding justifications are listed in **Table 1.**

Table 1. Inclusion/exclusion criteria

Criteria	**Justification**
Aim 1:	
• Adult age 30-80 years	• Population of interest
• Obesity or overweight (history of BMI ≥ 30 kg/m^2 and current BMI ≥ 25 kg/m^2 for study volunteers; BMI ≥ 25 kg/m^2 for those with clinically indicated CPET or known HFpEF)	• Focus on obesity-related metabolic disease
• Dyspnea (grade ≥1 by modified Medical Research Council scale)	• Enrich sample for pulmonary vascular dysfunction
• Able to provide informed consent and willing to comply with study	• Assure voluntary and informed participation
• Without known primary pulmonary arterial hypertension or cardiovascular diseases except known HFpEF (previous myocardial infarction within the last year, mod/sev valvular disease)	• Focus on preclinical disease
• Without other comorbidities: moderate to severe COPD, moderate to severe interstitial lung disease, untreated obstructive sleep apnea and planning to start treatment during study, renal (eGFR < 45 ml/min/1.73m^2), liver disease (cirrhosis), anemia (Hemoglobin < 9 g/dL)	• Exclude other causes of dyspnea
• Not pregnant or planning to become pregnant in next 4 months	• Invasive CPET contraindicated
• INR < 1.5, platelets > 75,000	• Safety measures for procedures
• Normal LVEF ≥ 50% on echo	• Exclude LV systolic dysfunction
• No significant valvular disease on echo	• Exclude other causes of dyspnea
• Without diabetes mellitus and not taking metformin (for volunteers only)	• Metformin or other therapies indicated
• Without history of: Acute pulmonary embolism (PE) and V/Q scan moderate or high probability, splenectomy, blood clots in the lung, active cancer (other than skin cancer)	• Conditions predispose to Chronic Thromboembolic pulmonary hypertension (CTEPH)
• Without known HIV infection	• Predisposed to pulmonary arterial hypertension

Aim 2 (all criteria under Aim 1, PLUS below)	
• Abnormal echo (PASP >40mmHg on echo) OR clinically-indicated RHC or CPET for dyspnea, referred by primary clinician	• Condition of interest
• Without contraindications to CPET (acute MI, unstable angina, uncontrolled arrhythmias, active endocarditis, myocarditis, pericarditis, severe aortic stenosis, acute pulmonary embolism or DVT, suspected dissecting aneurysm, uncontrolled asthma or pulmonary edema, room air desaturation < 85%, acute non-cardiopulmonary disorder that may affect exercise performance, mental impairment and inability to cooperate	• Safety measures for CPET procedure
Aim 3 (all criteria under Aim 1 and 2, PLUS below)	
• Abnormal pulmonary vascular function (resting or exercise)	• Condition of interest
• Not taking metformin, and without clinical indications for metformin	• Enable randomization to metformin vs placebo
• Without liver dysfunction (transaminases > 2 x upper limit) or cirrhosis	• Contraindication to metformin
• Without kidney dysfunction (GFR <45 ml/min/1.73m^2)	• Contraindication to metformin
• Not lactating, pregnant, or planning to become pregnant	• Limited information regarding safety of metformin • Contraindication to metformin • Avoid concurrent use of metformin
• No known allergy to metformin	
• Not taking acetazolamide, cimetidine, topiramate, sulfonylurea, insulin	• Other therapies indicated
• No isolated primary pulmonary arterial hypertension (mPAP > 20mmHg, PCWP < 15mmHg, and PVR > 3 wu in the absence of LVH, diastolic dysfunction, or LAE on echocardiogram	

Source of subjects and recruitment methods:

- Potential participants for the proposed study will be identified via two strategies: (1) Participants being referred for clinically indicated RHC or invasive CPET testing with hemodynamic monitoring in the setting of dyspnea by their primary physicians, and (2) Study volunteers recruited specifically to take part in this study
- For study volunteers, potential participants will be self-identified through research volunteer programs in place at MGH (weekly "Research Studies" e-mails sent to all email accounts at MGH, the Research Study Volunteer Program, a registry with >10,000 volunteers, the Partners clinical trials website (rally.partners.org), Researchmatch, a registry with >100,000). Self-identified potential volunteers may also contact study staff directly by email or phone. Study contact information can be found through MGH's research volunteer programs as well as on ClinicalTrials.gov. Other potential participants include past research volunteers who have agreed to be contacted by study staff about studies related to cardiovascular and metabolic disease. Upon contacting the study staff, the potential participant will receive a complete explanation of the protocol procedures by telephone. During that

initial phone conversation, the potential participant will be screened for inclusion and exclusion criteria.

- Potential subjects meeting inclusion and exclusion criteria will be identified by review of electronic medical records for patients scheduled for appointments in the Catheterization or CPET laboratory, General Cardiology, General Medicine, Pulmonary Hypertension, Nutrition, and Weight Center clinics, as well as for patients admitted on in-patient floors at Massachusetts General Hospital. A formal presentation to clinic staff will be given by Dr. Jennifer Ho and the study team once IRB approval is obtained, in order to inform providers about the study. Flyers and study information will be available to participants and providers in the clinic. The study team will also use Epic as a pre-screening tool to identify potential participants.
- To obtain the patient's permission to be contacted by the PI or study staff, one of the two methods will be used: (1) With prior permission of the patient's primary physician who has obtained the patient's permission to be contacted by study staff, the patient and any appropriate family members and/or significant others will be approached in person or by phone, or (2) a Recruitment letter will be sent out containing a letter from the patient's primary physician and a letter from the investigator. The patient will have the option to opt-out. Once interest is expressed, the PI or study staff will identify him/herself. A brief description of the study will be given and the patient asked if they have any interest in participation. For those individuals expressing an interest in participating, formal consent for the study protocol will proceed either at that time or at a mutually agreed upon time. We will also plan to use other methods of recruitment, including posting of approved flyers in MGH outpatient clinics, as well as study recruitment advertisements via the Partners e-mail system.
- We will also use the RPDR or the Biobank Portal to identify eligible patients who are part of the Partners Biobank for this study. We may also use identified information from the RPDR or from the Electronic Medical Record on consented Biobank subjects to review charts to determine eligibility. Participants who are enrolled in the Biobank will have had provided consent per the Partners Biobank IRB approved protocol. Once eligibility is confirmed, our study will collaborate with the Partners Biobank to contact potential study subjects who have consented for re-contact using a re-contact letter to be sent from the Biobank staff. The Partners Biobank will send an invitation letter, co-signed by the Biobank PI and Dr. Ho, and opt-out card to patients. Ten business days after the Biobank sends the re-contact letters to patients, we will call each patient on the list (who did not send us the opt-out card) to ask whether they would like to participate in our study.
- We also plan to use *The Research Opportunities Direct To You (RODY) program* that allows a patient to be contacted directly by researchers without involving their clinician. The patients will be identified through RPDR which shows if the patient response was a *Rody Yes* or *Rody No*. *Rody Yes* patients will be contacted directly with a recruitment letter signed by the researcher. *Rody No* patients will be contacted through the method described above that includes a letter signed by the clinician, a letter signed by the researcher and an opt-out form.
- Study flyers will be used to recruit potential subjects (see attachment).
- We will not target special vulnerable populations (fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others) as part of this proposal

4. SUBJECT ENROLLMENT

Methods of enrollment and obtaining informed consent

- Upon contacting the study staff, the potential participant will receive a complete explanation of the protocol procedures by telephone or in person. During that initial conversation, the potential participant will be screened for inclusion and exclusion criteria. Potential participants who wish to participate in the study and meet no exclusion criteria will be invited to attend a first screening study visit.
- At the time of the first study visit, the participant already will have had the opportunity to read the informed consent and been given the opportunity to ask questions by telephone. At the start of the first visit, the informed consent will be reviewed in person with the potential subject by trained study staff in a private, comfortable area. A board-licensed study physician (who is a co-investigator in this study) will be available if the subjects have any questions regarding the consent. Participants' questions about the protocol will be answered thoroughly, and there will be no time limit to this procedure. The consent form clearly states that subjects may end participation at any time without prejudice, and this will be emphasized to the subject. In particular, subjects who receive their health care at the MGH will be reassured that their decision to decline participation will in no way affect their medical treatment. If the potential participant agrees, a study staff member will obtain written consent and the individual will be enrolled into the study. As part of the informed consent, participants will be asked whether blood, not used in this analysis, may be stored for future analysis. If the participant does not consent to this, samples will be used only for the present study and excess samples discarded.
- At the time of each research visit, participants are debriefed and all questions about the study answered. This will include a review of the study aims, protocol, and any additional issues related to the study. Participants are also provided contact information if they have questions at any time.

Plan for treatment assignment and randomization

Aims 1 and 2 of the study do not involve allocation to treatment groups.

Aim 3 is a randomized placebo-controlled double-blinded intervention study to examine the effect of metformin versus matching placebo on pulmonary vascular function. We anticipate enrolling 75 participants studied in Aims 1 and 2 who display abnormal pulmonary vascular hemodynamics into Aim 3. Participants with contraindications to metformin will be excluded as outlined in Table 1.

In order to allocate evenly, without bias, and in a manner blinded to both participants and investigators, we will randomize participants to treatment group (metformin versus placebo) with the assistance of the investigational drug pharmacy. Randomization will be performed in a 1:1 fashion in groups of 4 to assure balanced study groups, and will be stratified by type of pulmonary vascular dysfunction (resting or exercise-induced).

5. STUDY PROCEDURES

Study visits, procedures, data collection, and testing

Participants will be recruited and enrolled in an ongoing manner until the study goal of 250 participants for Aim 1 is reached. We expect 100 (40%) to have high PAP >40mmHg estimated by echocardiography based on preliminary data. This group (in addition to individuals referred for clinically-indicated RHC or CPET) will undergo invasive CPET testing with hemodynamic monitoring and PAEC phenotyping as part of Aim 2. Of this sample, we expect 75 participants will have abnormal pulmonary hemodynamics as measured by RHC, given significant correlation between invasive and non-invasive measures of PAP (r=0.77).[85] These individuals will part-take in Aim 3 of the study. A flowsheet of the study schedule is provided in **Figure 1**, and data collected is outlined in **Table 2**.

Because fasting blood work will be obtained at the time of Study Visits 1, 3, and 4, the participant will be instructed to fast with no eating or drinking after midnight prior to those visits.

Visit 1 (Screening): At the first study visit, participants will undergo informed consent as outlined above. Information on age, gender, and race/ethnicity will be obtained. A medical history will be obtained by study staff, which includes information on current and past medical issues, medications, and allergies to past medications in order to identify possible study contraindications. Dyspnea will be assessed using the modified Medical Research Council scale (mMRC).[86,87] Seated blood pressure and pulse will be checked. Anthropometric measures will be taken: weight and height will be measured in order to calculate BMI, and waist circumference will be measured. Fasting blood work will be obtained, including glucose, insulin, lipid profile, hemoglobin A1c, and C-reactive protein. We will collect up to 100 ml of blood for these measurements and storage of samples for future use. Participants will also undergo an electrocardiogram (ECG), optional standard 2-hour oral glucose tolerance test (OGTT), optional 6-minute walk test (6MW), transthoracic echocardiography, and collection of venous endothelial cells as detailed below:

ECG: A standard 12-lead electrocardiogram will be performed.

2-hour OGTT (optional): A blood glucose (BG) measurement will be checked in order to assure safety in proceeding with an OGTT, and a pre-OGTT value of > 200mg/dL is listed as a clear stopping rule for the protocol. If there is no contraindication, the participant will receive a 75g oral glucose load and begin an OGTT. An IV will be inserted and levels of insulin and glucose will be measured at 0, 30, and 120 minutes following the OGTT. For the OGTT samples, 40cc of blood is needed.

Venous endothelial cell collection: The venous endothelial cell collection occurs during Study Visit 1, during which participants already undergo IV placement as part of the oral glucose tolerance test, as well as during Study Visit 4. After IV insertion using sterile technique, a standard guide wire (J-wire) is inserted into the vein through the IV and then removed and processed, with collection of up to 4 wires. A vast array of wires of introducer wires are approved by the FDA and are used clinically for the insertion of central and peripheral catheters into veins and are designed to be atraumatic. With respect to safety, insertion of the J wire once the IV has been placed is painless. It is associated with possible bleeding or bruising associated with placement of the IV, and a potential risk of thrombophlebitis. The technique has been applied safely over 2,000 times in Dr. Hamburg's laboratory without reported adverse effects, and MGH co-investigators have undergone formal training in her laboratory.[83,84] Only sterile IV sites will be used for this procedure. The de-identified coded specimen is transferred to the

laboratory of Dr. Hamburg (co-investigator), where the wire is carefully washed and cells are collected for analysis. No immortalized cell lines will be established from the harvested cells.

6MWT (optional): We will perform standardized 6MW testing according to published guidelines.[88] We will record oxygen saturation, blood pressure, and heart rate at the start of the test, and assess dyspnea (as measured with the modified Borg dyspnea scale) at the start and end of the 6MW test. Established reference ranges will be used to evaluate 6MW distance relative to age and sex.[89]

Transthoracic echocardiography: Comprehensive 2D and Doppler echocardiography will be undertaken using the Vivid IQ ultrasound machine (GE Healthcare, Milwaukee, WI). All images will be obtained by a trained research echocardiographer according to a standard protocol. Images will be obtained in digital format and analyzed according to protocol by the research staff. Standard assessment of right and left ventricular dimensions (RV, LV), systolic, and diastolic function, including tissue Doppler will be performed.[90,91] In the absence of pulmonary stenosis, pulmonary artery systolic pressure (PASP) will be estimated using two methods: a) Pulsed wave Doppler interrogation of the pulmonary valve annulus and measurement of pulmonary artery acceleration time (PAAT); PASP will be estimated from PAAT.[92,93] The intraobserver CV for PAAT is 5.9% in our laboratory. b) Doppler interrogation of tricuspid regurgitation jet velocity, with estimation of PASP as $4v^2$ + right atrial pressure.[91] In order to enhance tricuspid Doppler signals, ultrasound contrast may be used.

Participants meeting exclusion criteria based on Visit 1 (screening) will be notified, and study staff will explain why they are excluded from the study. Study staff will offer to speak with the primary care physician, if the potential participant requests, regarding medical reasons for exclusion. If appropriate inclusion/exclusion criteria for Aim 2 are met, including dyspnea ≥ grade 1 on the mMRC scale and abnormal PASP >40mmHg by echo), the subject will be scheduled for a second visit.

Visit 2 (Study procedures): At the second visit, any updates on medical history will be ascertained. Seated blood pressure and heart rate will be checked. Blood work will be obtained, and we will collect up to 150 ml of blood for these measurements and storage of samples for future use. Study volunteers who have not previously undergone clinically-indicated CPET testing will then undergo right heart catheterization (RHC), cardiopulmonary exercise testing (CPET), radionuclide ventriculography, with collection of pulmonary artery endothelial cells (PAEC) for research purposes as detailed below. For interested participants who have previously completed clinical CPET testing, Visit 1 and 2 will be combined, and clinical CPET testing results will be reviewed without the need to repeat the Visit 2 CPET. For interested participants who previously underwent right heart catheterization (RHC), Visit 1 and 2 may be combined without the Visit 2 CPET. The following criteria must be met to justify RHC and CPET for research purposes:

A. Participants must be symptomatic with evidence of ≥ grade 1 dyspnea based on the modified Medical Research Council scale
B. Participants with the most common treatable causes of chronic dyspnea are excluded from our study, as explicitly outlined in our exclusion criteria (existing diagnosis of pulmonary arterial hypertension, severe COPD or asthma, obstructive sleep apnea, chronic kidney disease or liver disease, anemia).
C. Participants with otherwise unexplained dyspnea then undergo comprehensive transthoracic echocardiography in order to assess estimated pulmonary artery systolic pressures. Based on this noninvasive testing, participants who have pulmonary artery systolic pressure ≥ 40mmHg and who otherwise have no contraindications to RHC and CPET then qualify for this testing in our protocol. This approach is in line with the standard of care and is supported by the American College of Cardiology/ American Heart Association 2009 Expert Consensus Document on Pulmonary Hypertension, which states that based on echocardiography, an estimated "pressure of greater than

40mmHg generally warrants further evaluation in the patient with unexplained dyspnea" (McLaughlin VV et al, *Circulation*, 2009).

Invasive CPET with hemodynamic monitoring using right heart catheterization: Participants with dyspnea and (1) clinically-indicated RHC or CPET based on referral by primary physician, or (2) abnormal PASP by screening echo and other criteria outlined above will be taken to the cardiac catheterization laboratory. Under sterile conditions, a pulmonary artery catheter will be placed using standard procedures and fluoroscopic guidance. In brief, topical lidocaine will be used to numb up the site of entry. A high-fidelity 7F balloon-tipped catheter is then inserted in the internal jugular vein under sterile conditions using ultrasound guidance. The catheter is then advanced into the right atrium, right ventricle (through the tricuspid valve), and pulmonary artery (through the pulmonary valve) into wedge position, guided by pressure tracings as well as fluoroscopic guidance. It will be used to measure resting right atrial, right ventricular, pulmonary artery, and pulmonary capillary wedge pressure (RA, RV, PA, PCWP). Fick cardiac output (CO), cardiac index, systemic vascular resistance, and pulmonary vascular resistance will be calculated. Pulmonary hypertension will be defined as resting mean PA pressure >20mmHg.[94,107] Resting hemodynamics will be obtained. The participant will then be transferred to the MGH CPET Laboratory (next door to the cardiac catheterization laboratory) for the exercise portion. Resting spirometry, blood pressure, 12-lead electrocardiogram, gas exchange, and heart rate will be measured. Participants will then undergo maximum incremental upright cycle ergometry at 5 to 15 W/min continuous ramp after an initial 3 minute period of unloaded exercise.[65] Hemodynamic measurements will be made (**Table 2**), and data analyzed in BreezeSuite (MedGraphics, St. Paul, MN). In brief, right atrial, PA, and PCWP will be measured in the upright position at end-expiration while seated at rest on the bicycle, and repeated at 1-minute intervals during exercise. Fick CO will be measured using standard technique, and peak oxygen uptake (VO_2) will be defined as the highest VO_2, averaged over 30s during the last minute of symptom-limited exercise.[95] We have safely performed over 1,000 tests without significant adverse events. Objective established criteria for CPET termination include ischemic electrocardiographic changes, complex arrhythmias, symptomatic fall in systolic blood pressure > 20mmHg, marked hypertension (> 240/120 mmHg), and severe desaturation < 80%.

First-pass radionuclide ventriculography: As part of the invasive CPET, first-pass radionuclide ventriculography will be performed in the CPET laboratory in order to assess biventricular function at rest and during stress. A peripheral IV will be placed, and a radionuclide tracer (sodium pertechnetate Tc-99m and Tc-99m pyrophosphate) will be administered to the participant to label red blood cells. This is a radiopharmaceutical that has been approved for use in our CPET laboratory (permit #15-044). A multicrystal camera will be used to detect technetium-labeled red blood cells in a region of interest placed over either the left or right ventricle to assess resting and exercise ejection fraction.

PAEC collection: We have adapted a novel protocol to isolate fresh human PAECs after routine RHC from the discarded catheter tip. In brief, PAEC collection does not entail modifications to standard clinical RHC procedures. The protocol involves saving the catheter tip after routine removal at the end of the standard RHC/CPET procedure before it is discarded into the biohazard waste. The tip is then processed in media to isolate PAEC. Therefore, there are no added risks beyond the RHC/CPET procedure. The protocol was adapted from protocols used by Dr. Michael Passineau (consultant; Pollet JB et al, *J Heart Lung Transplant*, 2013; Benza RL et al, *Pulm Circ*, 2016; Lenna S et al, *Am J Respir Crit Care Med* (Abstract), 2016). After the catheter is removed from the participant as per usual procedures, the last 2 inches of the Swan-Ganz catheter including the balloon are cut and collected in culture medium. The collected specimen will be labeled using a coded study identification number, and transferred to the Vascular Clinical Research Unit at Boston University, where the specimen will be further processed. Specifically, endothelial cells are recovered by centrifugation in a dissociation buffer

as described previously.[96,97] PAECs plated on microscope slides coated with poly-L-lysine, similar to isolation of peripheral endothelial cells,[50] and either fixed in 4% paraformaldehyde or insulin/metformin stimulation is performed.

Metformin or placebo administration: The participant will then receive, at random, either metformin or placebo in a 1:1 blinded fashion. Randomization will be stratified by type of PH (resting vs exercise-induced) and will be performed in blocks of 4 to assure balanced group sizes. Because we wish to ensure equal gender representation into the treatment and placebo groups, randomization will be done separately for men and women. Participants will be given 500mg capsules of metformin or matching placebo and instructed to take 500mg twice daily for 1 week, followed by 1g twice daily for a total of 3 months. Participants may receive study medication by mail or at study visits. We will exclude individuals with contraindications to metformin use as outlined in the exclusion criteria, and participants will be monitored for clinical symptoms of lactic acidosis and hypoglycemia. Medication compliance will be assessed with pill counts. The proposed use of metformin is IND-exempt.

Visit 3 (Interim): The third study visit will take place at MGH or remotely, approximately 2-4 weeks after initiation of metformin or placebo. An interim medical history will be taken by study staff in person or by telephone to assure that no contraindications to study participation or potential side effects have developed. Seated blood pressure and pulse may be obtained, and weight may be measured. Fasting blood work will be obtained at MGH or a local lab. We may collect up to 100 ml of blood for these measurements and storage of samples for future use.

Visit 4 (Interim): The fourth study visit will take place approximately 7-12 weeks after initiation of metformin or placebo. An interim medical history will be taken to assure that no contraindications to study participation or potential side effects have developed. Seated blood pressure, pulse, and anthropometrics will be obtained. Fasting blood work will be obtained. We will collect up to 100 ml of blood for these measurements and storage of samples for future use. Participants will undergo venous endothelial cell collection as outlined previously, as well as an electrocardiogram (ECG).

Visit 5 (Final measures): At the fifth study visit approximately 3 months (± 2 weeks) after initiation of metformin or placebo, final measures will be obtained. Seated blood pressure and pulse will be obtained. Blood work will be obtained. We will collect up to 150 ml of blood for these measurements and storage of samples for future use. Participants will then undergo invasive CPET with hemodynamic monitoring and PAEC cell collection as outlined previously. In order to minimize participant burden, repeat invasive CPET testing may be conducted without invasive arterial monitoring or first-pass radionuclide ventriculography.

Study staff members are available for questions at any time throughout the study, and contact numbers are provided to the subject. At the end of each study visit, participants will be given the opportunity to ask any questions regarding the study.

Research subjects who complete the study will be compensated for their time and efforts, according to each visit completed as follows: Visit 1 $50, Visit 2 $150, Visit 3 $50, Visit 4 $50, Visit 5 $250. If the subject withdraws from the study, they will receive payment for the visits that were completed. Subjects will be paid upon completion of each visit. We will also provide parking vouchers for study visits.

Additional Visits: If a visit involving invasive CPET (Visit 2 or Visit 5) is scheduled more than 30 days after Visit 1 or Visit 4, respectively, then research subjects may be asked to attend an additional visit

prior to CPET in order to obtain pre-requisite labs and electrocardiogram guided by cath lab safety protocols. Subjects will be compensated $50 and a parking voucher for each such additional visit.

Research subjects may be asked to complete a COVID test (e.g. nasopharyngeal swab) prior to procedures, such as the CPET. This follows institutional guidelines to ensure the safety of hospital staff and patients. Required pre-procedure COVID testing will be paid for by the study fund. Subjects will be compensated $20 per COVID test.

Drugs to be used

A total of 75 subjects will be randomized to 3-months of metformin or matching placebo. Participants will be given 500mg capsules of metformin or matching placebo and instructed to take 500mg twice daily for 1 week, followed by 1g twice daily for a total of 3 months. Metformin is widely used in the treatment of insulin resistance found in diabetes mellitus, and meta-analyses have shown metformin to be safe for use in heart failure,[98] and in the absence of hyperglycemia.[99] We will exclude individuals with contraindications to metformin use (**Table 1**), and participants will be monitored for clinical symptoms of lactic acidosis and hypoglycemia. Medication compliance will be assessed with pill counts. The proposed use of metformin is IND-exempt.

Repository activities

As part of the informed consent, participants will be asked whether blood, not used in this analysis, may be stored for future analysis. If the participant does not consent to this, samples will be used only for the present study and excess samples discarded. All samples will be processed immediately and stored at -80^{o}C for future analysis. Samples will be labeled with study identification numbers only – no other identifiable information will be attached to the samples. Samples will be stored in a locked freezer in a private space, and only co-investigators will have access. Such samples could be used to measure the effects of metformin on circulating markers of endothelial function, or other blood markers related to the causes of cardiovascular disease, depending on the findings of the study. No immortalized cell lines will be created from the harvested cells.

Table 2. Data to be collected (see attached CRFs)

Type	Variable	Description	Study Visit
Demogr aphic	Age		1
	Sex		1
	Race		1
	Ethnicity		1
Exam	Height		1, 4
	Weight		1, 3*, 4
	BP	Blood pressure	1, 2, 3*, 4, 5
	HR	Heart rate	1, 2, 3*, 4, 5
	Waist	Waist circumference	1, 4
History		Medical history as outlined in CRF	1
ECG		12-lead electrocardiogram	1, 4
Lab	CMP	Comprehensive metabolic panel	1, 2, 3, 4, 5
	CBC	Complete blood count without differential	1, 4
	Lipids	Fasting lipid panel	1
	CRP	C-reactive protein	1, 4

	NT-proBNP	N-terminal pro B-type natriuretic peptide	1, 4
	INR	International normalized ratio (blood coagulation)	1, 4
	Adiponectin	Total adiponectin concentrations	1, 4
	Blood HCG	Blood pregnancy test (women only)	1, 2, 3, 4, 5
	Glucose		1, 4
	Insulin		1, 4
	Blood gas	Oximetry during CPET	2, 5
	A1c	Hemoglobin A1c	1, 5
	Lactic acid		3
Echo	LVEF	Simpson's modified biplane LV ejection fraction	1
	LVDD	LV end-diastolic dimension	1
	LVSD	LV end-systolic dimension	1
	LAD	Left atrial end-systolic diameter	1
	LVWT	LV wall thickness = posterior + septal wall thickness	1
	RWT	Relative wall thickness = LVWT/LVDD	1
	FS	Fractional shortening = [(LVDD–LVSD)/LVDD] x	1
	LVM	100	1
	E	LV mass = 0.8 [1.04 ((LVDD+LVWT)^3–	1
	A	(LVDD)^3)]+0.6.(1)	1
	DT	Early mitral inflow velocity on Doppler	1
	E'	Late mitral inflow velocity on Doppler	1
	PAAT	Deceleration time of early mitral inflow on Doppler	1
	TR jet	Early mitral annular velocity on tissue Doppler	1
		Pulmonary artery acceleration time	
		Tricuspid regurgitation jet velocity	
CPET	RA	Right atrial pressure	2, 5
	RV	Right ventricular pressure	2, 5
	PA	Pulmonary arterial pressure	2, 5
	PCWP	Pulmonary capillary wedge pressure	2, 5
	CO_TD	Cardiac output – thermodilution	2, 5
	CO_Fick	Cardiac output – Fick	2, 5
	RER	Respiratory exchange ratio	2, 5
	VO2	Oxygen uptake	2, 5
	VCO2	Carbon dioxide output	2, 5
	VT	Ventilatory threshold	2, 5
	Work	Work load (watts)	2, 5
	VE	Minute ventilation	2, 5
	Vitals	Blood pressure, heart rate, oxygen saturation during	2, 5
	RVEF	exercise	2
	LVEF	RV function rest and exercise	2
		LV function rest and exercise	

* optional

6. BIOSTATISTICAL ANALYSIS

Aim 1: To investigate the association of metabolic disease and PAEC phenotypes with pulmonary hemodynamics in human subjects.

Hypotheses: Peripheral insulin resistance is associated with abnormal resting pulmonary hemodynamics. PAEC phenotype correlates with pulmonary vascular dysfunction in obese individuals.

Analysis plan for Aim 1: We will examine the association of insulin resistance (estimated by HOMA-IR[100]) and pulmonary vascular hemodynamics (mean PAP and PVR by RHC) using the Pearson or Spearman correlation coefficient. Multivariable linear regression models will adjust first for age, sex, body mass index as potential confounders, and then for hypertension and smoking status. If scatter plots suggest a non-linear relationship, we will consider regression models assuming a flexible mean function such as polynomial, exponential or spline functions. We will evaluate the association of PAEC insulin signaling (insulin-stimulated eNOS phosphorylation) and pulmonary hemodynamics using linear regression. Specifically, we will examine the association of % change in the ratio of p-eNOS to total eNOS in response to insulin with mean PAP and PVR. A two-sided P-value <0.05 will be considered statistically significant for primary analyses.

Statistical power for Aim 1: In previous studies, the range of HOMA-IR among non-diabetic obese individuals was broad, with a median and inter-quartile range of 2.7 mg*lU/dL*mL (1.9-4.8), allowing adequate power to study associations with pulmonary vascular hemodynamics. In our preliminary CPET study, we observed a correlation coefficient of $R=0.34$, $P<0.0001$ between PASP and waist circumference (a clinical surrogate of insulin resistance[101]). Assuming a sample size of 100 and two-sided alpha of 0.05, we have at least 80% power to detect a correlation of $R\geq0.28$ between HOMA-IR and mean PAP (and PVR) by RHC. Further, the difference in PASP among obese individuals with and without MetS was 10mmHg in preliminary analyses. We would have 80% power to detect a ≥6mmHg difference in a two-group comparison of participants above and below the median HOMA-IR, assuming a two-sided alpha of 0.05 and a sample size of 100. With the same alpha and sample size, we would have at least 80% power to detect a correlation of $R\geq0.28$ between PAEC insulin response and mean PAP (and PVR) by RHC.

Aim 2: To study the dynamic pulmonary vascular response to exercise in metabolic disease.

Hypotheses: Metabolic dysfunction is associated with abnormal pulmonary vascular hemodynamic response. PAEC phenotype correlates with exercise PAP in obese individuals

Analysis plan for Aim 2: We will relate HOMA-IR to ΔmPAP/ΔCO with exercise. We will test for normality of the distribution of HOMA-IR using QQ plots and the Shapiro-Wilk test. If skewed in distribution, HOMA-IR will be log-transformed. We will use random effects in linear regression models to allow repeated measures and account for multiple time points of mPAP and CO for a given individual during exercise, with HOMA-IR (or PAEC p-eNOS response) as the independent and ΔmPAP/ΔCO slope as the dependent variable. We will relate PAEC insulin signaling to PAP response to exercise. We will use a random effects model with % change in the ratio of p-eNOS to total eNOS in response to insulin as the independent, and ΔmPAP/ΔCO as the dependent variable. All analyses will be adjusted for age, sex, and body-mass index, and additionally adjusted for resting blood pressure and smoking status.

Statistical power for Aim 2: In preliminary analyses, the ΔmPAP/ΔCO slope in diabetics versus non-diabetics was 3.4±1.3 mmHg/L compared with 2.6±1.3 mmHg/L. Assuming a sample size of 100

participants and a two-sided alpha of 0.05, we would have 86% power to detect a similar difference in ΔmPAP/ΔCO slope among individuals above and below the median HOMA-IR. We would have at least 80% power to detect a correlation of R=0.28 or greater between PAEC insulin response (% increase in p-eNOS) and the ΔmPAP/ΔCO slope.

Aim 3: To examine the effect of metformin on pulmonary vascular function and PAEC phenotype in obese individuals.

Hypotheses: Metformin will improve pulmonary vascular hemodynamics compared with placebo. Metformin will improve insulin signaling in human PAECs compared with placebo.

Statistical analyses for Aim 3: We will compare the change in ΔmPAP/ΔCO slope in the metformin vs placebo groups. The "delta" in slope will be defined as the 3-month minus the baseline value. We will apply a two-sample t-test to compare the delta in the two groups in an unadjusted intention-to-treat analysis. An adjusted analysis will be performed using a multivariable random effects linear regression model adjusted for baseline ΔmPAP/ΔCO, such that [delta ΔmPAP/ΔCO] = intercept + β_1*treatment group + β_2*$\Delta mPAP/\Delta CO_{baseline}$, with treatment group and $\Delta mPAP/\Delta CO_{baseline}$ as fixed effects and treatment group modeled as a random effect. Given that the randomization will be stratified by type of pulmonary vascular dysfunction (resting versus exercise-induced), we will use a 'strata' statement to indicate PH type in the model. We anticipate that metformin will improve PAEC insulin resistance (% change in the ratio of p-eNOS to total eNOS) and also pulmonary hemodynamics. In secondary analyses, we will examine the correlation between PAEC and venous endothelial cell insulin resistance among treatment groups.

Statistical power for Aim 3: We will power the study for the between-group comparison (metformin vs placebo) of the delta in ΔmPAP/ΔCO (3 month – baseline). In 15 prior patients with repeat testing within 12 weeks, the reproducibility of ΔmPAP/ΔCO was robust, with an intra-individual CV of 0.92, and a standard deviation (SD) of the delta (12-week minus baseline) of 0.46. We will assume a similar SD in this study. In our experience with intervention studies, attrition from non-compliance is ~15%. With a target enrollment of 75 participants and 15% loss to follow-up, we would have 64 participants completing the study. In preliminary studies, the difference in ΔmPAP/ΔCO slope among diabetics and non-diabetics was 0.7mmHg/L. We estimate >80% power to detect up to 50% of the difference in ΔmPAP/ΔCO between diabetics vs nondiabetics (0.35mmHg/L) among the treatment groups using a two-sided t-test with 5% type I error.

7. RISKS AND DISCOMFORTS

Procedures

Phlebotomy and IV placement: In order to minimize the risks of phlebotomy, participants will be asked about previous difficulty with phlebotomy (particularly pre-syncope or syncope) and appropriate measures will be taken, as needed. During venipuncture, the participant will be in a sitting position. At each study visit, no more than 150 cc of blood is taken, and in total over the course of the study, no more than 450 cc (2 cups) of blood will be obtained. This is within the Red Cross guidelines (less than 500 cc every 2 months). Risks of phlebotomy include anemia, and the amount of blood collected will be reduced if the investigator feels there is a significant risk of anemia. Other risks include discomfort, bleeding or bruising where the needle enters the skin, and rarely, fainting or infection may occur.

Protection against risk: The participants will be asked whether they are feeling well during the blood draw and throughout the visit. If the participant is not feeling well, the specific discomfort will be addressed, and the participant will be referred for evaluation, as needed. If a participant feels light-headed during the venipuncture or blood draw, the procedure is suspended. The participant will be provided with orange juice and observed until the light-headedness resolves. If the participant is willing, s/he may continue the protocol once this symptom has resolved. If anemia is identified at any time during the study (Hemoglobin, Hb < 9 g/dL), no further blood draws will be conducted until Hb is again documented as Hb ≥ 9 g/dL.

6-minute walk test: The 6-minute walk test is a simple and practical non-invasive test to evaluate functional capacity. Rarely there may be an increased risk of arrhythmias or cardiovascular collapse. However, each participant determines the level and intensity of walking during the test, and it has been performed on thousands of older persons and patients with heart failure or cardiomyopathy without serious adverse events.[88] Participants with absolute contraindications are already excluded from the study as outlined in Table 1 (unstable angina, myocardial infarction in previous month). Relative contraindications include a resting heart rate > 120 bpm, or uncontrolled hypertension (systolic blood pressure > 180 mmHg, diastolic blood pressure > 100 mmHg).[88]

Protection against risk: Prior to testing, heart rate and blood pressure will be obtained, and testing will be deferred if criteria are met and participants referred to their treatment team for follow-up as necessary. All study personnel administering the 6-minute walk test will be appropriately trained, and will have completed cardiopulmonary resuscitation training. Testing will be stopped immediately if the participant wishes to do so, or experiences chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, or pale and ashen appearance. Testing will be performed at MGH hospital with medical care immediately available if necessary.

Oral glucose tolerance test: A drawing IV will be placed so that blood draws at three time points can be performed with minimal discomfort. Potential risks include nausea, stomach discomfort, diarrhea, and constipation.

Protection against risk: A blood glucose (BG) measurement will be checked in order to assure safety in proceeding to an oral glucose tolerance test (OGTT), and a pre-OGTT value of > 200mg/dL will preclude OGTT administration.

Venous endothelial cell collection: Insertion of the J wire once the IV has been placed is painless and is associated with possible bleeding or bruising associated with placement of the IV, and a potential risk of thrombophlebitis.

Protection against risk: This technique has been performed safely over 2,000 times in Dr. Hamburg's laboratory without reported adverse effects, and MGH co-investigators have undergone formal training in her laboratory. A vast array of J-tipped wires are approved by the FDA and are used clinically for insertion of central and peripheral catheters into veins and are designed to be atraumatic. The J wire will only be inserted using sterile IV sites.

Transthoracic echocardiography: Transthoracic echocardiography will be performed according to standard medical practice, and is associated with minimal discomfort or risk to study participants. Rarely there is minor transient discomfort during echocardiography due to the pressure of the ultrasound probe against the chest or abdominal wall. In order to better visualize tricuspid Doppler signal, microbubble contrast may be used to permit more accurate determination of right heart hemodynamics (Mulvagh SL et al, American Society of Echocardiography Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography, J Am Soc Echocardiogr, 2008;21:1179).

Protection against risk: If discomfort occurs, the probe will be adjusted, and the study stopped at the participant's request. Microbubble contrast agents are FDA approved for use in echocardiography. These agents are safe without medically significant risks other than rare allergic events at a rate of approximately 1 per 10,000. In order to avoid this potential risk, echo contrast administration will be contraindicated and avoided in patients with known hypersensitivity to perflutren. Echo contrast will be administered by a licensed and trained cardiac sonographer.

Invasive CPET with hemodynamic monitoring and right heart catheterization: The risks of placing a right heart catheter include bleeding and bruising at the site where the catheter is inserted and pneumothorax. Other rare complications may include ventricular arrhythmias, cardiac tamponade, air embolism, infection, and pulmonary artery rupture. Specifically in patients with pulmonary hypertension, right heart catheterization is associated with low morbidity. Of 7,218 right heart catheter procedures performed in patients with pulmonary hypertension as reviewed in one study, 1% had serious adverse events, most frequently related to venous access (hematoma, pneumothorax), and the vast majority of these complications were of mild to moderate intensity with resolution spontaneously or after appropriate intervention.[102] Incremental ramp CPET has been shown to be a very safe procedure. Unlike the Bruce Protocol that contains sharp increments in workload in a stepwise fashion, the CPET starts off with minimal work rate (i.e. unloaded exercise) and very gradually ramps up, providing a warm-up period for individuals performing exercise. This protocol design optimizes subject comfort and safety.[103] CPET testing rarely can precipitate coronary ischemia, arrhythmias, and/or hemodynamic instability. A recently published report on the safety of CPET examined results from over 5000 tests performed on individuals with known coronary artery disease (n=1787, 35%), heart failure (n=1289, 25%), congenital heart disease (n=688, 14%), hypertrophic cardiomyopathy (n=598, 12%), pulmonary hypertension (n=194, 4%), aortic stenosis (n=212), and previous cardiac arrest (n=60, 1%).[104] Despite the high-risk features of this population, there were no mortalities at the time of testing or during a period of 48 hours thereafter. A total of 8 adverse events (0.16% event rate) occurred, most commonly sustained ventricular tachycardia (n=6) which self-terminated without intervention in all 6 cases. There was one myocardial infarction in a post-heart transplant patient with allograft coronary artery disease. A second relevant study evaluated 2037 patients who performed 4401 CPETs in the HF-ACTION Trial (Heart Failure: A Controlled Trial investigating Outcomes of Exercise Training).[105] There were no deaths, and a rate of non-fatal major cardiovascular events of <0.5 per 1000 tests. A third relevant study

to this proposal examined the records of 38,970 patients who underwent standard maximum level exercise testing in a community clinic (mean age 54±12 years, 68% male).[106] The main reason for referral was chest pain evaluation (59%). None of the patients died during testing, and despite 14% of the study population having detectable ischemia (n=5450). Finally, in the personal experience of the co-investigator Dr. Lewis as Director of the MGH CPET Laboratory at MGH there have been no deaths or hospital admissions related to CPET despite performing over 400 studies per year in patients who often have advanced heart and lung diseases.

Protection against risk: We are recruiting participants from two sources: (1) patients who are referred for clinically indicated RHC and CPET by other physicians. In such cases, RHC and CPET are being performed for clinical reasons regardless of our research study; (2) study volunteers that undergo rigorous screening procedures prior to RHC and CPET in order to justify testing for pure research purposes. To assure a reasonable balance in risk versus benefit ratio among the latter group, we will perform studies on individuals who have dyspnea and abnormal estimated PASP (defined as >40mmHg) based on noninvasive imaging, where testing has been deemed reasonable as outlined by expert clinical consensus.[94] Right heart catheterization procedures will be performed at the MGH cardiac catheterization laboratory by licensed and board-certified interventional cardiologists. All safety protocols in place will be followed. Prior to the procedure, we will verify that the participant is at low bleeding risk by checking a complete blood count and coagulation profile. Only individuals with INR <1.5 and platelet counts > 75,000 will be eligible for right heart catheterization (see inclusion/exclusion criteria). In addition, we will perform pregnancy testing in women of child-bearing age and exclude anybody with a positive test. After verifying informed consent, a procedure time-out will be performed. Usual sterile technique will be used, and ultrasound guidance and fluoroscopy will be used to place the pulmonary artery catheter to minimize risks of the procedure. The participant will be monitored continuously with blood pressure, heart rate, and telemetry. In order to minimize the risk to the participant during CPET testing, physician supervision will be mandated for all exercise assessments. Participants with contraindications to exercise testing will be excluded (Table 1). The laboratory will have resuscitation equipment and Advanced Cardiac Life Support-trained physicians and exercise technicians. Ratings of perceived exertion and dyspnea will be monitored during testing, as will heart rate, blood pressure, and continuous electrocardiographic tracings and test will be terminated by the test operator per standard exercise testing guidelines (i.e. a >10mmHg fall in blood pressure, ventricular tachycardia).

First-pass radionuclide ventriculography: This test is performed in the CPET laboratory, and involves intravenous administration of a radionuclide tracer to label red blood cells, risks are summarized under "Radiation" in the section below.

Protection against risk: This is a radiopharmaceutical that has been approved for use in our CPET laboratory (permit #15-044), and staff have been trained in safe handling of the radionuclide tracer. Pregnant or nursing participants are excluded from our protocol. A serum pregnancy test will be checked on Study Visits 1, 2, 3, 4, and 5 in women of child-bearing potential (unless already performed for clinically-indicated purposes, in which case clinical protocols will be followed).

Pulmonary artery endothelial cell collection: The isolation of endothelial cells will be performed on the discarded pulmonary arterial catheter tip after completion of the right heart catheterization, therefore no additional risk beyond that of the routine right heart catheterization procedure is anticipated.

Drug side effects and toxicities

Metformin administration: This drug has been on the market for several decades and is considered first line therapy for diabetes mellitus type 2. Moreover, it has been used extensively in non-hyperglycemic patients with polycystic ovarian disease. Additional studies of the safety of metformin in heart failure have been published. The pertinent risk of metformin is development of lactic acidosis. This risk has been reported primarily in patients with abnormal renal or hepatic function, thus we have chosen to exclude these populations from the study. Additional concerns include hypoglycemia, though this is a rare risk for this drug, particularly in the absence of other hypoglycemic medications (an exclusion criterion for our study), and gastrointestinal distress. Patients will be educated on the signs and symptoms of hypoglycemia and advised to contact study staff immediately if any arise. We will monitor patients by telephone 1 week after metformin initiation, and an interim visit will be conducted 2-4 weeks after metformin initiation, at which point labs will be drawn to evaluate kidney function, glucose, and lactic acid levels. If patients report significant gastrointestinal effects, metformin will not be increased as would otherwise occur in the protocol. If symptoms persist further, the dose will be dropped by 500 mg daily to the highest tolerated dose.

The most common adverse reactions experienced are:

- ≥10% of patients: diarrhea (instant release tablet: 12% to 53%; extended release tablet: 10% to 17%), nausea/vomiting (instant release tablet: 7% to 26%; extended release tablet: 7% to 9%), flatulence (12%), Weakness (9%).
- 1% to 10%: chest discomfort, flushing, palpitation, headache (6%), chills, dizziness, lightheadedness, rash, hypoglycemia, Indigestion (7%), abdominal discomfort (6%), abdominal distention, abnormal stools, constipation, dyspepsia/ heartburn, taste disorder, myalgia, dyspnea, upper respiratory tract infection, decreased vitamin B_{12} levels (7%), increased diaphoresis, flu-like syndrome, nail disorder.
- ≤1% (Limited to important or life-threatening): lactic acidosis, leukocytoclastic vasculitis, megaloblastic anemia, pneumonitis. Lactic acidosis is a rare but serious side effect due to metformin accumulation. When lactic acidosis occurs it is fatal in approximately 50% of cases. Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Contraindications to the use of metformin are: hypersensitivity to metformin or any component of the formulation; renal disease or renal dysfunction (serum creatinine ≥1.5 mg/dL in males or ≥1.4 mg/dL in females) or abnormal creatinine clearance from any cause, including shock, acute myocardial infarction, or septicemia; acute or chronic metabolic acidosis with or without coma (including diabetic ketoacidosis). A boxed warning has been issued for metformin related to the risk of developing lactic acidosis. The risk is increased in patients with acute congestive heart failure, dehydration, excessive alcohol intake, hepatic or renal impairment, or sepsis. All of these conditions are exclusion criteria for our study.

Protection against risk: Conditions that increase the risk of lactic acidosis on metformin treatment are all exclusion criteria for this study. We will monitor patients by telephone 1 week after metformin initiation, and an interim visit will be conducted 2-4 weeks after metformin initiation, at which point labs will be drawn to evaluate kidney function, glucose, and lactic acid levels. In addition, metformin therapy will be discontinued prior to or at the time of intravascular administration of iodinated contrast media (potential for acute alteration in renal function) should a subject require contrast during the course of this study. Metformin will be withheld for 48 hours after the radiologic study and restarted only after renal function has been confirmed as normal. Patients will be encouraged to delay any elective

radiologic studies requiring iodinated contrast until the conclusion of the study. Criteria for patient removal will be: symptomatic hypoglycemia or lactic acidosis. The PI will monitor potential side effects, and the study can be discontinued at any time at the subject's request. If the independent safety officer determines that symptomatic lactic acidosis occurs and is attributable to study drug in one patient the study will be stopped altogether. Patients with symptomatic hypoglycemia unresponsive to dose reduction may withdraw. Inability to tolerate metformin or hypersensitivity to drug will trigger withdrawal. Development of renal dysfunction that would preclude enrollment will require withdrawal. Patients who require additional anti-diabetic drugs prior to study completion will continue to be enrolled. Furthermore, the independent safety officer has the ability to stop the study for safety concerns. Any patient who voluntarily withdraws or withdraws because of an aforementioned adverse event will be requested to allow us to continue to accrue clinical data for analysis, if possible. Participants will be monitored for any of the above side effects as outlined above, and will be encouraged to contact the study staff with any interim symptoms. A board certified medical internist (the PI) is available by pager and telephone at all times, if he/she is not physically present, during the study.

Potential psycho/social risks

Confidentiality: There is a potential risk of breach of confidentiality. All subject records will be handled as confidentially as possible within the law. Records will be coded and kept in a locked office of the research team. Copies of the signed consent form will be kept by the research team and the subjects. Check requests with SS# will be maintained in locked file cabinets in the PI's locked research office. Study data and samples will be labeled with coded number (study number and subject ID number) and kept in a separate location from the source documents and linking code. No individual identities will be used in any reports or publications resulting from this investigation. The Investigators and all key personnel involved in this study will complete a tutorial on the responsible conduct of human subject research such as the Collaborative IRB Training Initiative. This tutorial reviews federal regulations governing human subjects research commonly known as Good Clinical Practices

Radiation risks

Radiation will be used per protocol as is done for clinically-indicated right heart catheterization. Doses reflect approximately 2 millisieverts (mSv) and 8 months from natural background. This will be performed at the MGH cardiac catheterization laboratory by licensed and board-certified interventional cardiologists. All policies and procedures governing the cardiac catheterization laboratory as outlined by the Radiation Safety Committee will be followed.

Radionuclide ventriculography will involve the following doses of sodium pertechnate: 1mCi for patient positioning, 10 mCi for rest image, and 20 mCi for the stress image. The estimated total body adsorbed radiation dose is 3.2 mGy/740 MBq (0.32 rads/20 mCi). This reflects up to 4.7 millisieverts (mSv) and 16 months from natural background. This will be performed at the MGH CPET laboratory, lincensed to perform first pass radionuclide imaging (permit #15-044) with licensed personnel.

Incidental findings

For participants who undergo screening or study visits and are newly discovered to have medically treatable causes of dyspnea, study investigators will report to the participants and/or primary physicians to seek further appropriate medical care. Specific findings that will prompt further action are outlined in the table below:

Cause of dyspnea	Further treatment
Anemia	If severe **anemia** is identified (defined as hemoglobin < 9 g/dL), study blood draws will be deferred until anemia is improved. The participant and primary provider will be notified and follow-up labs/work-up recommended prior to continuation in our study.
LV systolic dysfunction	If **LV systolic dysfunction** (defined as LV ejection fraction < 45%) is identified, the participant will be excluded from our study. Further, the participant and primary provider will be notified and further work-up and potential initiation of therapy for cardiomyopathy recommended.
Valve disease	If significant **valve disease** is identified (defined as moderate or severe MR, MS, AR, AS), the participant will be excluded from our study. Further, the participant and primary provider will be notified and further diagnostic and therapeutic work-up recommended.
Volume overload	If **volume overload** is identified (defined as resting PCWP > 25mmHg), no CPET testing will be performed, and the participant will be referred to primary providers for further care as appropriate, including consideration of diuretics.
PAH	If **PAH** is detected (defined as resting mPAP > 20mmHg, PCWP < 15mmHg, and PVR > 3 wu in the absence of LVH, diastolic dysfunction, or LAE on echocardiogram), the patient will be excluded from the study, and referred to primary providers and/or PH subspecialist for further work-up and care.

8. POTENTIAL BENEFITS

Potential benefits to participating individuals

No direct benefit to the study participant is expected. The participant may benefit by knowing that the results of the study will enhance our understanding of obesity, insulin resistance, and pulmonary hypertension in humans.

Potential benefits to society

Society benefits from research advances in understanding the effect of obesity and insulin resistance on pulmonary hypertension as a precursor to heart failure. Because there are minimal and manageable risks to the participants in this study, the risk versus benefit ratio is low.

9. DATA SAFETY AND MONITORING PLAN

Safety monitoring, evaluating of AEs and SAEs

Monitoring of the study data, including AEs and SAEs will be performed by the investigators of the study. In addition, independent monitoring of study data will be performed by an external Data Safety Monitoring Board (DSMB), with a primary focus on scientific integrity and participant safety. The DSMB will be comprised of 4 experts in the field who are not directly involved with the design and conduct of the study. This includes the following individuals:

- **Jane Leopold, MD** (Chair, Interventional Cardiologist and Pulmonary Hypertension Expert). Leopold is Associate Professor of Medicine at Harvard Medical School and an interventional cardiologist with expertise in WHO group 1-5 pulmonary hypertension at Brigham and Women's Hospital. She also currently serves in a leadership role of NHLBI's PVDOMICS program.
- **James Fang, MD** (Heart Failure, Hemodynamics, and Clinical Trials Expert). Dr. Fang is Professor of Medicine, University of Utah Health Science Center and a practicing cardiologist with expertise in heart failure and pulmonary hypertension. He led an international consensus paper on WHO group 2 pulmonary hypertension (Fang JC et al. WHO pulmonary hypertension group 2: pulmonary hypertension due to left heart disease in the adult. A consensus statement of the PH council of the ISHLT. *J Heart Lung Transplant*, 2012;31:913-33), and currently chairs the DSMB of numerous ongoing heart failure intervention trials.
- **James de Lemos, MD** (Clinical Trials, Heart Failure, DSMB Expert). Dr. de Lemos is Professor of Medicine, University of Utah Health Science Center, and is a cardiologist with longstanding expertise in heart failure, clinical trials, and epidemiology, and currently is Medical Director of the Dallas Heart Study. He also serves as chair of DSMB committees on both heart failure and diabetes trials.
- **Simin Liu, MD, ScD** (Biostatistics and Clinical Trial Expert). Dr. Liu is Professor of Epidemiology, Brown University School of Public Health. He is a recognized national and international expert in biostatistics and epidemiology with a focus on obesity and cardiometabolic disease.

DSMB meetings will occur approximately once every 6 months via conference call and, if needed, more frequently to discuss the study protocol, and a written report provided for each meeting. Responsibilities, organization, and other details are outlined in the DSMB Charter.

Definitions of AEs and SAEs

Adverse events will be defined as "any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research". Specifically for this study, this will include the following:

Procedure	Expected Potential Adverse Event
Phlebotomy	Discomfort, bruising, bleeding, lightheadedness, fainting
6-minute walk test	Dyspnea, chest pain, leg cramps, diaphoresis.
Oral glucose tolerance test	Hyperglycemia, nausea, stomach discomfort, diarrhea, and constipation.
Echocardiography	Discomfort
Invasive cardiopulmonary exercise testing	Uncommon: Allergic reaction to local anesthetic, pain, bleeding, infection, hypo- or hypertension during exercise, fainting during exercise, arrhythmia, chest pain Rare: injury to the nerve around catheter insertion site, pneumothorax, air embolism, blood clot, vascular or myocardial perforation, pericardial effusion, myocardial ischemia/infarction, sustained arrhythmia or hemodynamic instability.
Metformin therapy	Common: Diarrhea, nausea, vomiting, flatulence, weakness Less common: cardiovascular: chest discomfort, flushing, palpitations, headaches, dizziness, lightheadedness; gastrointestional: indigestion, abdominal discomfort or distention, abnormal stools, constipation, dyspepsia/ heartburn, taste disorder; respiratory: dyspnea, upper respiratory tract infection; general: chills, rash, myalgia, hypoglycemia, decreased vitamin B_{12} levels, increased diaphoresis, flu-like syndrome, nail disorder Uncommon: lactic acidosis, leukocytoclastic vasculitis, megaloblastic anemia, pneumonitis, anaphylaxis.

Serious adverse events will be defined as "any adverse event that results in death, is life-threatening, results in hospitalization, persistent disability, congenital anomaly, or based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition". Specifically for this study, this will include the following:

Procedure	Expected Potential Serious Adverse Event
Invasive cardiopulmonary exercise testing	Rare: injury to the nerve around catheter insertion site, pneumothorax, air embolism, blood clot, vascular or myocardial perforation, pericardial effusion, myocardial ischemia/infarction, sustained arrhythmia or hemodynamic instability.
Metformin therapy	Uncommon: lactic acidosis, leukocytoclastic vasculitis, megaloblastic anemia, pneumonitis, anaphylaxis.

Reporting of AEs, SAEs, unanticipated problems

All adverse events will be reported promptly to the investigators and formally entered into an Adverse Event log, which will be submitted to the DSMB for review prior to each scheduled meeting once approximately every 6 months, and to the IRB at the time of the annual Progress Report. All unanticipated problems (unexpected, and related or possibly related to participation in the research, or serious) will be reported to the PHRC and DSMB per “PHRC policy” once the investigator learns of the incident in accordance with PHRC unanticipated problems reporting guidelines.

Triggers for action and stopping rules

The protocol may be terminated early if the extent (incidence and/or severity) of study-associated adverse effects is such that the risk/benefit ratio to participants as a whole is unacceptable. This will be assessed throughout the study by the study investigators. In addition, this will be formally evaluated and determined by the DSMB via review of all AE's and SAE's.

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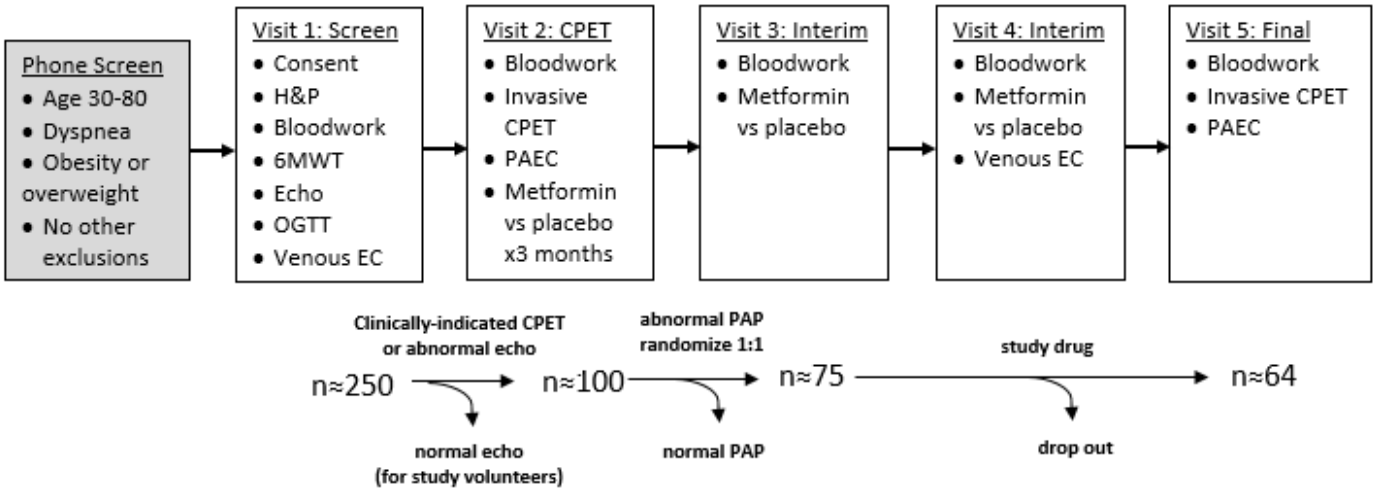
Figure 1


Phone Screen
• Age 30-80
• Dyspnea
• Obesity or overweight
• No other exclusions
Visit 1: Screen
• Consent
• H&P
• Bloodwork
• 6MWT
• Echo
• OGTT
• Venous EC
Visit 2: CPET
• Bloodwork
• Invasive CPET
• PAEC
• Metformin vs placebo x3 months
Visit 3: Interim
• Bloodwork
• Metformin vs placebo
Visit 4: Interim
• Bloodwork
• Metformin vs placebo
• Venous EC
Visit 5: Final
• Bloodwork
• Invasive CPET
• PAEC
Clinically-indicated CPET or abnormal echo
abnormal PAP randomize 1:1
study drug
n≈250
n≈100
n≈75
n≈64
normal echo (for study volunteers)
normal PAP
drop out

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Partners Human Research Committee
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Amendment: Notification of IRB Approval/Activation
Protocol #: 2017P001020/PHS

Date: July 3, 2017

To: Jennifer En-Sian Ho, MD
MGH
Medical Services / Cardiac Unit

From: Partners Human Research Committee
399 Revolution Drive, Suite 710
Somerville, MA 02145

Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension
Version/Number:	170623 JEH Detailed Protocol
Version Date:	6/23/2017
Sponsor/Funding Support:	
	Name: NIH

IRB Amendment #:	1
IRB Review Type:	Expedited
IRB Approval Date:	7/3/2017
Approval Activation Date:	7/3/2017
IRB Expiration Date:	6/13/2018

This project has been reviewed by PHS IRB . During the review of this project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for obtaining and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

Please note that if an IRB member had a conflict of interest with regard to the review of this project, consistent with IRB policies and procedures, the member was required to leave the room during the discussion and vote on this project except to provide information requested by the IRB.

Approves revised Protocol Summary (dated 06/23/2017), Detailed Protocol (dated 06/;23/2017), and CRF Eligibility form adding conditions to the exclusion criteria that predisposes to a rare condition called Chronic Thromboembolic Pulmonary Hypertension (CTEPH).

As Principal Investigator, you are responsible for ensuring that this project is conducted in compliance with all applicable federal, state and local laws and regulations, institutional policies, and requirements of the IRB, which include, but are not limited to, the following:

1. Submission of any and all proposed changes to this project (e.g., protocol, recruitment materials, consent

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Fax: (857) 282-5693

form, status of the study, etc.) to the IRB for review and approval prior to initiation of the change(s), except where necessary to eliminate apparent immediate hazards to the subject(s). Changes made to eliminate apparent immediate hazards to subjects must be reported to the IRB as an unanticipated problem.

2. Submission of continuing review submissions for re-approval of the project prior to expiration of IRB approval and a final continuing review submission when the project has been completed.
3. Submission of any and all unanticipated problems, including adverse event(s) in accordance with the IRB's policy on reporting unanticipated problems including adverse events.
4. Obtaining informed consent from subjects or their legally authorized representative prior to initiation of research procedures when and as required by the IRB and, when applicable, documenting informed consent using the current IRB approved consent form(s)with the IRB-approval stamp in the document footer.
5. Informing all investigators and study staff listed on the project of changes and unanticipated problems, including adverse events, involving risks to subjects or others.
6. When investigator financial disclosure forms are required, updating your financial interests in Insight and for informing all site responsible investigators, co-investigators and any other members of the study staff identified by you as being responsible for the design, conduct, or reporting of this research study of their obligation to update their financial interest disclosures in Insight if (a) they have acquired new financial interests related to the study and/or (b) any of their previously reported financial interests related to the study have changed.

The IRB has the authority to terminate projects that are not in compliance with these requirements.

Questions related to this project may be directed to Anne [redacted]

CC: [redacted]

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Amendment: Notification of IRB Approval/Activation
Protocol #: 2017P001020/PHS

Date: October 18, 2017

To: Jennifer En-Sian Ho, MD
MGH
Medical Services / Cardiac Unit

From: Partners Human Research Committee
399 Revolution Drive, Suite 710
Somerville, MA 02145

Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension
Version/Number:	1701005 Detailed Protocol
Version Date:	10/5/2017
Sponsor/Funding Support:	
	Name: NIH

IRB Amendment #:	2
IRB Review Type:	Full
IRB Approval Date:	10/17/2017
Approval Activation Date:	10/18/2017
IRB Expiration Date:	6/13/2018

This project has been reviewed by PHS IRB . During the review of this project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for obtaining and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

Please note that if an IRB member had a conflict of interest with regard to the review of this project, consistent with IRB policies and procedures, the member was required to leave the room during the discussion and vote on this project except to provide information requested by the IRB.

Approves revised Protocol Summary (dated 10/05/2017), Detailed Protocol (dated 10/05/2017), and Consent Form (dated 10/11/2017), Telephone Script, CRF Eligibility, CRF Intake Form, CRF Visit 1 (Screen), CRF Visit 3 (Interim), CRF Visit 4 (Final Measures), CRF Visit 2 (CPET), and Non-Intervention Pre-Screening Data Collection:

1. Adding venous endothelial cell collection to the procedures at study visit 1 and 4. At these visits, an IV will be placed as part of the approved protocol to perform an oral glucose tolerance test. A soft J-shaped wire will be inserted and removed through the IV, in order to collect venous endothelial cells as part of this protocol;
2. Adding first-pass radionuclide ventriculography to the Protocol. This is

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a test that is routinely performed as part of clinical cardiopulmonary exercise tests (CPET), and is considered standard of care for patients referred for CPET;
3. Clarifying that ECG will be performed at visit 1 of the protocol;
4. Telephone Script, CRF Eligibility, CRF Visit 1 (Screen), CRF Visit 3 (interim), CRF visit 4 (Final Measures), CRF Visit 2 (CPET), and Non-Intervention Pre-Screening Data Collection forms were revised as by Partners Human Research Quality Improvement;
5. Log for Study Drug Phone Calls and Participant Study Medicals Instructions added to the Protocol;
6. Regulatory Binder Consultation Memo (dated 07/24/2017) and Letter from Naomi M. Hamburg, M.D., M.S., (dated September 26, 2017) are noted.

As Principal Investigator, you are responsible for ensuring that this project is conducted in compliance with all applicable federal, state and local laws and regulations, institutional policies, and requirements of the IRB, which include, but are not limited to, the following:

1. Submission of any and all proposed changes to this project (e.g., protocol, recruitment materials, consent form, status of the study, etc.) to the IRB for review and approval prior to initiation of the change(s), except where necessary to eliminate apparent immediate hazards to the subject(s). Changes made to eliminate apparent immediate hazards to subjects must be reported to the IRB as an unanticipated problem.
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5. Informing all investigators and study staff listed on the project of changes and unanticipated problems, including adverse events, involving risks to subjects or others.
6. When investigator financial disclosure forms are required, updating your financial interests in Insight and for informing all site responsible investigators, co-investigators and any other members of the study staff identified by you as being responsible for the design, conduct, or reporting of this research study of their obligation to update their financial interest disclosures in Insight if (a) they have acquired new financial interests related to the study and/or (b) any of their previously reported financial interests related to the study have changed.

The IRB has the authority to terminate projects that are not in compliance with these requirements.
Questions related to this project may be directed to Anne [redacted]

CC: [redacted]

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Amendment: Notification of IRB Approval/Activation
Protocol #: 2017P001020/PHS

Date: November 13, 2017

To: Jennifer En-Sian Ho, MD
MGH
Medical Services / Cardiac Unit

From: Partners Human Research Committee
399 Revolution Drive, Suite 710
Somerville, MA 02145

Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension
Version/Number:	171103 JEH Detailed Protocol
Version Date:	11/3/2017
Sponsor/Funding Support:	
	Name: NIH

IRB Amendment #:	4
IRB Review Type:	Expedited
IRB Approval Date:	11/13/2017
Approval Activation Date:	11/13/2017
IRB Expiration Date:	6/13/2018

This project has been reviewed by PHS IRB . During the review of this project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for obtaining and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

Please note that if an IRB member had a conflict of interest with regard to the review of this project, consistent with IRB policies and procedures, the member was required to leave the room during the discussion and vote on this project except to provide information requested by the IRB.

The following documents have been reviewed and approved, and supporting documents noted:

Protocol Summary (dated 10/18/2017)
Schema
Study Flow
Detailed Protocol (dated 10/17/2017)
MN Consent Form (dated 10/18/2017)
HeH Consent Form (dated 10/18/2017)
Email Blast

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Twitter Posts
Facebook Posts
Study Overview
Demographics
Medical/Psych Hx
MINI International Neuropsychiatric Interview (MINI)
Duke Activity Status Index (DASI)
The Patient Health Questionnaire (PHQ-9)
Altman Self-Rating Mania Scale (ASRM)
Sheehan Disability Scale (SDS)
Well-Being Index (WHO-5)
Perceived Stress Scale (PSS)
Self Efficacy for Exercise (SEE)
International Physical Activity Questionnaire (IPAQ) short form
Cardiac Events
Seattle Angina Questionnaire 7 (SAQ-7)
Adverse Event Questions
World Health Organization Composite International Diagnostic Interview for Bipolar Spectrum Disorder
Fitbit Directions
Patient PI video on study landing page
RISO approval (dated 02/07/2017)
CTO approval (dated 07/13/2017)
Data Linkage Plan
Eureka approval letter
Eureka Security measures
Eureka description
Schedule of assessments
Welcome messages
Fitbit only group messages
MBCT group messages
CBT group messages
Assessment messages
Payment waiver approval (10/02/2017)
DUA with Fitbit
Donation agreement with Fitbit
Fitbit connection directions
Landing page screen shots

As Principal Investigator, you are responsible for ensuring that this project is conducted in compliance with all applicable federal, state and local laws and regulations, institutional policies, and requirements of the IRB, which include, but are not limited to, the following:

1. Submission of any and all proposed changes to this project (e.g., protocol, recruitment materials, consent form, status of the study, etc.) to the IRB for review and approval prior to initiation of the change(s), except where necessary to eliminate apparent immediate hazards to the subject(s). Changes made to eliminate apparent immediate hazards to subjects must be reported to the IRB as an unanticipated problem.

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2. Submission of continuing review submissions for re-approval of the project prior to expiration of IRB approval and a final continuing review submission when the project has been completed.
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The IRB has the authority to terminate projects that are not in compliance with these requirements.

Questions related to this project may be directed to Anne [redacted]

CC: [redacted]

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Partners Human Research Committee
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Continuing Review: Notification of IRB Approval/Activation
Protocol #: 2017P001020/PHS

Date: May 3, 2018

To: Jennifer En-Sian Ho, MD
MGH
Medical Services / Cardiac Unit

From: Partners Human Research Committee
399 Revolution Drive, Suite 710
Somerville, MA 02145

Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension
Version/Number:	171103 JEH Detailed Protocol
Version Date:	11/3/2017
Sponsor/Funding Support:	
	Proposal Title: The Association of Metabolic D
	Name: NIH
	Sponsor Number: [redacted]
IRB Continuing Review #:	1
IRB Review Type:	Full
IRB Approval Date:	4/25/2018
Approval Activation Date:	5/3/2018
IRB Expiration Date:	4/25/2019

This project has been reviewed by PHS IRB . During the review of this project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for obtaining and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

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The following protocol documents have been approved and supporting documents noted by the IRB:
Schema-01
Grant-R01
DSMB/DMC Report-01
Advertisement (2)
Flyer (1)

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Telephone Script
Questionnaire (1)
Package Insert-Metformin
FDA-Exempt-Letter (IND Information)
Log for study drug phone call
Participant Study medications Instructions
Regulatory Binder Consultation Memo
BMC-NHamburg- Letter

As Principal Investigator, you are responsible for ensuring that this project is conducted in compliance with all applicable federal, state and local laws and regulations, institutional policies, and requirements of the IRB, which include, but are not limited to, the following:

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2. Submission of continuing review submissions for re-approval of the project prior to expiration of IRB approval and a final continuing review submission when the project has been completed.
3. Submission of any and all unanticipated problems, including adverse event(s) in accordance with the IRB's policy on reporting unanticipated problems including adverse events.
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The IRB has the authority to terminate projects that are not in compliance with these requirements.

Questions related to this project may be directed to Fausta M [redacted]

CC: [redacted]

PARTNERS HEALTHCARE
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Partners Human Research Committee
399 Revolution Drive, Suite 710
Somerville, MA 02145
Tel: (857) 282-1900
Fax: (857) 282-5693

Amendment: Notification of IRB Approval/Activation
Protocol #: 2017P001020/PHS

Date: May 3, 2018

To: Jennifer En-Sian Ho, MD
MGH
Medical Services / Cardiac Unit

From: Partners Human Research Committee
399 Revolution Drive, Suite 710
Somerville, MA 02145

Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension
Version/Number:	180501 JEH Detailed Protocol_clean
Version Date:	5/1/2018
Sponsor/Funding Support:	
	Proposal Title: The Association of Metabolic D
	Name: NIH
	Sponsor Number: [redacted]
IRB Amendment #:	9
IRB Review Type:	Full
IRB Approval Date:	5/2/2018
Approval Activation Date:	5/3/2018
IRB Expiration Date:	4/25/2019

This project has been reviewed by PHS IRB . During the review of this project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for obtaining and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

Please note that if an IRB member had a conflict of interest with regard to the review of this project, consistent with IRB policies and procedures, the member was required to leave the room during the discussion and vote on this project except to provide information requested by the IRB.

The following has been approved for this amendment:
1) Echo contrast: addition of contrast during the echocardiogram in order to better visualize right heart hemodynamics.
2) Exclusion criteria: We have added known HIV infection to our exclusion criteria.
3) Instruments/ Questionnaires: Changes to eligibility form, visit 1, visit 2, visit 3 and visit 4 in order to reflect more streamlined work-flow during study visits.
4) Recruitment/ Advertisement: Changes have been made to the Direct to patient recruitment letter and to

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the opt-out letter. The opt-out letter has been fixed based on the error.
5) Dyspnea grade score: Addition of a greater or equal sign to indicate a score greater than one would qualify for the study.
Protocol Summary version (dated 05/01/2018)
Detailed Protocol 180501JEH version (dated 05/01/2018)
Consent Form version (5/01/2018)
Advertisement (1)
Recruitment Letter (1)
Questionnaire (5)
Removed the Instruments / Questionaires
Removed - Non_Intervention_Pre_Screening-Information
Removed - 170831
Non_Intervention_Pre_Screening_Information Removed - 171103
Non_Intervention_Pre_Screening_Information

As Principal Investigator, you are responsible for ensuring that this project is conducted in compliance with all applicable federal, state and local laws and regulations, institutional policies, and requirements of the IRB, which include, but are not limited to, the following:

1. Submission of any and all proposed changes to this project (e.g., protocol, recruitment materials, consent form, status of the study, etc.) to the IRB for review and approval prior to initiation of the change(s), except where necessary to eliminate apparent immediate hazards to the subject(s). Changes made to eliminate apparent immediate hazards to subjects must be reported to the IRB as an unanticipated problem.
2. Submission of continuing review submissions for re-approval of the project prior to expiration of IRB approval and a final continuing review submission when the project has been completed.
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The IRB has the authority to terminate projects that are not in compliance with these requirements.

Questions related to this project may be directed to Fausta M Figueroa, FFIGUEROA@PARTNERS.ORG, 857-282-1909.

CC: [redacted]

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Amendment: Notification of IRB Approval/Activation
Protocol #: 2017P001020/PHS

Date: June 1, 2018

To: Jennifer En-Sian Ho, MD
MGH
Medical Services / Cardiac Unit

From: Partners Human Research Committee
399 Revolution Drive, Suite 710
Somerville, MA 02145

Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension
Version/Number:	180501 JEH Detailed Protocol_clean
Version Date:	5/1/2018
Sponsor/Funding Support:	
	Proposal Title: The Association of Metabolic D
	Name: NIH
	Sponsor Number: [redacted]
IRB Amendment #:	10
IRB Review Type:	Expedited
IRB Approval Date:	6/1/2018
Approval Activation Date:	6/1/2018
IRB Expiration Date:	4/25/2019

This project has been reviewed by PHS IRB . During the review of this project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for obtaining and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

Please note that if an IRB member had a conflict of interest with regard to the review of this project, consistent with IRB policies and procedures, the member was required to leave the room during the discussion and vote on this project except to provide information requested by the IRB.

The following has been approved for this amendment:
We are adding approved information from the new Continuing Review to the Partners Clinical Trials website for recruitment of volunteers.

As Principal Investigator, you are responsible for ensuring that this project is conducted in compliance with all applicable federal, state and local laws and regulations, institutional policies, and requirements of the IRB,

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Fax: (857) 282-5693

which include, but are not limited to, the following:

1. Submission of any and all proposed changes to this project (e.g., protocol, recruitment materials, consent form, status of the study, etc.) to the IRB for review and approval prior to initiation of the change(s), except where necessary to eliminate apparent immediate hazards to the subject(s). Changes made to eliminate apparent immediate hazards to subjects must be reported to the IRB as an unanticipated problem.
2. Submission of continuing review submissions for re-approval of the project prior to expiration of IRB approval and a final continuing review submission when the project has been completed.
3. Submission of any and all unanticipated problems, including adverse event(s) in accordance with the IRB's policy on reporting unanticipated problems including adverse events.
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The IRB has the authority to terminate projects that are not in compliance with these requirements.

Questions related to this project may be directed to Fausta M [redacted]

CC: [redacted]

PARTNERS HEALTHCARE
FOUNDED BY BRIGHAM AND WOMEN'S HOSPITAL AND MASSACHUSETTS GENERAL HOSPITAL

Partners Human Research Committee
399 Revolution Drive, Suite 710
Somerville, MA 02145
Tel: (857) 282-1900
Fax: (857) 282-5693

Amendment: Notification of IRB Approval/Activation
Protocol #: 2017P001020/PHS

Date: July 6, 2018

To: Jennifer En-Sian Ho, MD
MGH
Medical Services / Cardiac Unit

From: Partners Human Research Committee
399 Revolution Drive, Suite 710
Somerville, MA 02145

Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension
Version/Number:	180613 JEH Detailed Protocol
Version Date:	7/2/2018
Sponsor/Funding Support:	
	Proposal Title: The Association of Metabolic D
	Name: NIH
	Sponsor Number: [redacted]
IRB Amendment #:	12
IRB Review Type:	Expedited
IRB Approval Date:	7/3/2018
Approval Activation Date:	7/6/2018
IRB Expiration Date:	4/25/2019

This project has been reviewed by PHS IRB . During the review of this project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for obtaining and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

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NOTE TO PI: Please be reminded to re-consent applicable active participants, re: revised study schedule.

The following has been approved for this amendment:

Increased blood draw volumes for visits with Level 3 CPETs.
Updated study contact information to reflect change of staff.
Added an interim visit and updating remuneration.
Removed of OGTT from the final visit.
Revised and updated these documents.

PARTNERS HEALTHCARE
FOUNDED BY BRIGHAM AND WOMEN'S HOSPITAL AND MASSACHUSETTS GENERAL HOSPITAL

Partners Human Research Committee
399 Revolution Drive, Suite 710
Somerville, MA 02145
Tel: (857) 282-1900
Fax: (857) 282-5693

Protocol summary version (dated 07/02/2018)
Detailed Protocol version (dated 07/02/2018)
Consent Form (1)
Advertisement (3)
Flyer (1)
Recruitment Letter (1)
PAEC opt-out Letter (1)
Telephone Script
Questionnaire (3)
Participant Study Medications Instructions

As Principal Investigator, you are responsible for ensuring that this project is conducted in compliance with all applicable federal, state and local laws and regulations, institutional policies, and requirements of the IRB, which include, but are not limited to, the following:

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Questions related to this project may be directed to Fausta M [redacted]

CC: [redacted]

PARTNERS HEALTHCARE
FOUNDED BY BRIGHAM AND WOMEN'S HOSPITAL AND MASSACHUSETTS GENERAL HOSPITAL

Partners Human Research Committee
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Somerville, MA 02145
Tel: (857) 282-1900
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Amendment: Notification of IRB Approval/Activation
Protocol #: 2017P001020/PHS

Date: July 25, 2018

To: Jennifer En-Sian Ho, MD
MGH
Medical Services / Cardiac Unit

From: Partners Human Research Committee
399 Revolution Drive, Suite 710
Somerville, MA 02145

Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension
Version/Number:	180719 JEH Detailed Protocol
Version Date:	7/19/2018
Sponsor/Funding Support:	
	Proposal Title: The Association of Metabolic D
	Name: NIH
	Sponsor Number: [redacted]
IRB Amendment #:	14
IRB Review Type:	Expedited
IRB Approval Date:	7/25/2018
Approval Activation Date:	7/25/2018
IRB Expiration Date:	4/25/2019

This project has been reviewed by PHS IRB . During the review of this project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for obtaining and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

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The following has been approved for this amendment:
-Venous endothelial cell collection will be done during Study Visit 4 instead of Study Visit 5.

-Recruitment will allow for study staff to be contacted directly by self-identified potential volunteers.

-When anthropometric measurements will be obtained was clarified.

PARTNERS HEALTHCARE
FOUNDED BY BRIGHAM AND WOMEN'S HOSPITAL AND MASSACHUSETTS GENERAL HOSPITAL

Partners Human Research Committee
399 Revolution Drive, Suite 710
Somerville, MA 02145
Tel: (857) 282-1900
Fax: (857) 282-5693

Protocol Summary version dated (07/19/2018)
180719 JEH Detailed Protocol version date (07/19/2018)
Consent Form
Questionnaires (3)

As Principal Investigator, you are responsible for ensuring that this project is conducted in compliance with all applicable federal, state and local laws and regulations, institutional policies, and requirements of the IRB, which include, but are not limited to, the following:

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Questions related to this project may be directed to Fausta M [redacted]

CC: [redacted]

Partners Human Research Committee
Partners HealthCare
399 Revolution Drive, Suite 710
Somerville, MA 02145
Tel: 857-282-1900
Fax: 857-282-5693

Notification of IRB Review

Protocol #: 2017P001020

Date:	October 19, 2018	
To:	Ho, Jennifer, MD MGH Partners > MGH > Medical Services > Cardiac Unit	
From:	Partners Human Research Committee 399 Revolution Drive, Suite 710 Somerville, MA 02145	
Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension	
Version/Number:	180927 JEH Detailed Protocol	
Version Date:	09/27/2018	
Sponsor/Funding/Support:	Proposal Title:	The Association of Metabolic Disease and Pulmonary Hypertension
	Principal Investigator:	Ho, Jennifer
	Immediate Sponsor:	NIH
	Award Number:	[redacted]
	Fund #:	

IRB Amendment #:	16
IRB Review Type:	Expedited
IRB Approval Date:	10/19/2018
Approval/Activation Date:	10/19/2018

This project has been reviewed and approved by the **PHS IRB**. During the review of this project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for obtaining and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

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The following documents were reviewed and approved by the IRB:

Detailed Protocol version dated (09/14/20180
Protocol Summary version dated (09/14/2018)

Partners Human Research Committee
Partners HealthCare
399 Revolution Drive, Suite 710
Somerville, MA 02145
Tel: 857-282-1900
Fax: 857-282-5693

Consent Form (2)
Advertisement (10)
Flyer (1)
Recruitment Letter (2)
Telephone Script (1)
Letter

1) The window for Study Visit 4 was broadened to 7-12 weeks from metformin or placebo initiation. 2) The maximum age of participants has been increased from 75 to 80 years. The minimum BMI of participants has been lowered from 30 to 25 to include overweight individuals for those with clinically indicated CPET or known HFpEF. The minimum BMI for other study volunteers will remain 30

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IMPORTANT REMINDER: THE IRB HAS THE AUTHORITY TO TERMINATE PROJECTS THAT ARE NOT IN COMPLIANCE WITH THESE REQUIREMENTS.

Partners Human Research Committee
Partners HealthCare
399 Revolution Drive, Suite 710
Somerville, MA 02145
Tel: 857-282-1900
Fax: 857-282-5693

Questions related to this project may be directed to [redacted]

cc:

[redacted]

Partners Human Research Committee
Partners HealthCare
399 Revolution Drive, Suite 710
Somerville, MA 02145
Tel: 857-282-1900
Fax: 857-282-5693

Notification of IRB Review

Protocol #: 2017P001020

Date:	November 19, 2018	
To:	Ho, Jennifer, MD MGH Partners > MGH > Medical Services > Cardiac Unit	
From:	Partners Human Research Committee 399 Revolution Drive, Suite 710 Somerville, MA 02145	
Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension	
Version/Number:	180927 JEH Detailed Protocol	
Version Date:	09/27/2018	
Sponsor/Funding/Support:	Proposal Title:	The Association of Metabolic Disease and Pulmonary Hypertension
	Principal Investigator:	Ho, Jennifer
	Immediate Sponsor:	NIH
	Award Number:	[redacted]
	Fund #:	

IRB Amendment #:	18
IRB Review Type:	Expedited
IRB Approval Date:	11/19/2018
Approval/Activation Date:	11/19/2018

This project has been reviewed and approved by the **PHS IRB**. During the review of this project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for obtaining and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

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The following documents were reviewed and approved by the IRB:

This amendment is to change the order of "marked" versus "clean" copies of 2 attachments. Clean versions for these attachments were resubmitted to supersede the existing and unchanged marked versions.

Partners Human Research Committee
Partners HealthCare
399 Revolution Drive, Suite 710
Somerville, MA 02145
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Advertisement (1)
Recruitment Letter (1)
Flyer (1)

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Questions related to this project may be directed to [redacted]

cc:

[redacted]

Partners Human Research
Partners HealthCare
399 Revolution Drive, Suite 710
Somerville, MA 02145
Tel: 857-282-1900
Fax: 857-282-5693

Notification of IRB Review

Protocol #: 2017P001020

Date:	January 29, 2019	
To:	Ho, Jennifer, MD MGH Partners > MGH > Medical Services > Cardiac Unit	
From:	Partners Human Research 399 Revolution Drive, Suite 710 Somerville, MA 02145	
Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension	
Version/Number:	180927 JEH Detailed Protocol	
Version Date:	09/27/2018	
Sponsor/Funding/Support:	Proposal Title:	The Association of Metabolic Disease and Pulmonary Hypertension
	Principal Investigator:	Ho, Jennifer
	Immediate Sponsor:	NIH
	Award Number:	[redacted]
	Fund #:	

IRB Amendment #:	21
IRB Review Type:	Expedited
IRB Approval Date:	01/29/2019
Approval/Activation Date:	01/29/2019
IRB Expiration Date:	**04/25/2019**

This project has been reviewed and approved by the **PHS IRB**. During the review of this project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for obtaining and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

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The following documents were reviewed and approved by the IRB:

Partners Human Research
Partners HealthCare
399 Revolution Drive, Suite 710
Somerville, MA 02145
Tel: 857-282-1900
Fax: 857-282-5693

The exclusion criteria of prior myocardial infarction was modified to specify exclusion of participants with acute myocardial infarction within the past year.

Protocol Summary version (dated 01/10/19)
Detailed Protocol
Consent Form
Advertisement (1)
Instrument/Questionnaire (1)

As Principal Investigator, you are responsible for ensuring that this project is conducted in compliance with all applicable federal, state and local laws and regulations, institutional policies, and requirements of the IRB, which include, but are not limited to, the following:

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Questions related to this project may be directed to [redacted]

cc:

Partners Human Research
Partners HealthCare
399 Revolution Drive, Suite 710
Somerville, MA 02145
Tel: 857-282-1900
Fax: 857-282-5693

[redacted]

Partners Human Research
Partners HealthCare
399 Revolution Drive, Suite 710
Somerville, MA 02145
Tel: 857-282-1900
Fax: 857-282-5693

Notification of IRB Review

Protocol #: 2017P001020

Date:	March 01, 2019	
To:	Ho, Jennifer, MD MGH Partners > MGH > Medical Services > Cardiac Unit	
From:	Partners Human Research 399 Revolution Drive, Suite 710 Somerville, MA 02145	
Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension	
Version/Number:	180927 JEH Detailed Protocol	
Version Date:	09/27/2018	
Sponsor/Funding/Support:	Proposal Title:	The Association of Metabolic Disease and Pulmonary Hypertension
	Principal Investigator:	Ho, Jennifer
	Immediate Sponsor:	NIH
	Award Number:	[redacted]
	Fund #:	

IRB Amendment #:	22
IRB Review Type:	Expedited
IRB Approval Date:	03/01/2019
Approval/Activation Date:	03/01/2019
IRB Expiration Date:	**04/25/2019**

This project has been reviewed and approved by the **PHS IRB**. During the review of this project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for obtaining and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

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The following documents were reviewed and approved by the IRB:

Partners Human Research
Partners HealthCare
399 Revolution Drive, Suite 710
Somerville, MA 02145
Tel: 857-282-1900
Fax: 857-282-5693

Revised Detailed Protocol version dated 02/22/19

1) update the Partners clinical trials website to reflect the new name of "Rally" (rally.partners.org)

2) include in-patient populations in medical record review for possible qualifying study volunteers

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Questions related to this project may be directed to [redacted]

cc:

Jennifer, Ho, MD, Cardiac Unit, Medical Services, Principal Investigator

Partners Human Research
Partners HealthCare
399 Revolution Drive, Suite 710
Somerville, MA 02145
Tel: 857-282-1900
Fax: 857-282-5693

[redacted]

Partners Human Research
Partners HealthCare
399 Revolution Drive, Suite 710
Somerville, MA 02145
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Notification of IRB Review

Protocol #: 2017P001020

Date:	April 19, 2019	
To:	Ho, Jennifer, MD MGH Partners > MGH > Medical Services > Cardiac Unit	
From:	Partners Human Research 399 Revolution Drive, Suite 710 Somerville, MA 02145	
Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension	
Version/Number:	180927 JEH Detailed Protocol	
Version Date:	09/27/2018	
Sponsor/Funding/Support:	Proposal Title:	The Association of Metabolic Disease and Pulmonary Hypertension
	Principal Investigator:	Ho, Jennifer
	Immediate Sponsor:	NIH
	Award Number:	[redacted]
	Fund #:	

IRB Continuing Review #:	2
IRB Review Type:	Designated
IRB Approval Date:	03/21/2019
Approval Effective Date:	04/19/2019
Approval/Activation Date:	04/19/2019
IRB Expiration Date:	**03/21/2020**

This project has been reviewed and approved by the **PHS IRB**. During the review of this project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for obtaining and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

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The following documents were reviewed and approved by the IRB:

Partners Human Research
Partners HealthCare
399 Revolution Drive, Suite 710
Somerville, MA 02145
Tel: 857-282-1900
Fax: 857-282-5693

Adverse Event Log
Recruitment Letter
Consent Form
Protocol Summary, 1/10/2019
Detailed Protocol, 4/5/2019
Instrument/Questionnaires
Advertisement
Package Inserts
Telephone Script
Partners Clinical Trial Posting
Letter than Recruitment
DSMB/DMC Report
IND Information
Schema
Flyer
Participant Study Medications Instructions
Log for study drug phone call
Minor Deviation Log

As Principal Investigator, you are responsible for ensuring that this project is conducted in compliance with all applicable federal, state and local laws and regulations, institutional policies, and requirements of the IRB, which include, but are not limited to, the following:

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4. Obtaining informed consent from subjects or their legally authorized representative prior to initiation of research procedures when and as required by the IRB and, when applicable, documenting informed consent current IRB approved consent form(s) with the IRB-approval stamp in the document footer.
5. Informing all investigators and study staff listed on the project of changes and unanticipated problems, including adverse events, involving risks to subjects or others.
6. When investigator financial disclosure forms are required, submitting updated financial disclosure forms for yourself and for informing all site responsible investigators, co-investigators and any other members of the study staff identified by you as being responsible for the design, conduct, or reporting of this research study of their obligation

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to submit updated Investigator Financial Disclosure Forms for this protocol to the IRB if (a) they have acquired new financial interests related to the study and/or (b) any of their previously reported financial interests related to the study have changed.

IMPORTANT REMINDER: THE IRB HAS THE AUTHORITY TO TERMINATE PROJECTS THAT ARE NOT IN COMPLIANCE WITH THESE REQUIREMENTS.

Questions related to this project may be directed to [redacted]

cc:

[redacted]

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Notification of IRB Review

Protocol #: 2017P001020

Date:	May 17, 2019	
To:	Ho, Jennifer, MD MGH Partners > MGH > Medical Services > Cardiac Unit	
From:	Partners Human Research 399 Revolution Drive, Suite 710 Somerville, MA 02145	
Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension	
Version/Number:	180927 JEH Detailed Protocol	
Version Date:	09/27/2018	
Sponsor/Funding/Support:	Proposal Title:	The Association of Metabolic Disease and Pulmonary Hypertension
	Principal Investigator:	Ho, Jennifer
	Immediate Sponsor:	NIH
	Award Number:	[redacted]
	Fund #:	

IRB Amendment #:	23
IRB Review Type:	Expedited
IRB Approval Date:	05/16/2019
Approval/Activation Date:	05/17/2019
IRB Expiration Date:	**03/21/2020**

This project has been reviewed and approved by the **PHS IRB**. During the review of this project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for obtaining and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

Please note that if an IRB member had a conflict of interest with regard to the review of this project, consistent with IRB policies and procedures, the member was required to recuse him/herself and, if applicable, leave the room during the discussion and vote on this project except to provide information requested by the IRB.

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1) Units for a particular lab test (platelets) were corrected on Visit 1 CRF.
2) The opt-out letter addressed to potential volunteers who have completed a clinical CPET was reattached.
3) A general opt-out letter for potential volunteers who have not completed a CPET was included.

Revised Letter Recruitment Letter

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Questions related to this project may be directed to [redacted]

cc:

Jennifer, Ho, MD, Cardiac Unit, Medical Services, Principal Investigator

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[redacted]

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Notification of IRB Review

Protocol #: 2017P001020

Date:	July 23, 2019	
To:	Ho, Jennifer, MD MGH Partners > MGH > Medical Services > Cardiac Unit	
From:	Partners Human Research 399 Revolution Drive, Suite 710 Somerville, MA 02145	
Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension	
Version/Number:	180927 JEH Detailed Protocol	
Version Date:	09/27/2018	
Sponsor/Funding/Support:	Proposal Title:	The Association of Metabolic Disease and Pulmonary Hypertension
	Principal Investigator:	Ho, Jennifer
	Immediate Sponsor:	NIH
	Award Number:	[redacted]
	Fund #:	
IRB Amendment #:	25	
IRB Review Type:	Expedited	
IRB Approval Date:	07/17/2019	
Approval/Activation Date:	07/23/2019	
IRB Expiration Date:	**03/21/2020**	

This project has been reviewed and approved by the **PHS IRB**. During the review of this project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for obtaining and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

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The following documents were reviewed and approved by the IRB:

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Protocol Summary version (dated 06/27/2019)
Detailed Protocol, version 180927 JEH (dated 06/27/2019)

ANCILLARY COMMITTEES

1. **Pharmacy (MGH) : Approved**

As Principal Investigator, you are responsible for ensuring that this project is conducted in compliance with all applicable federal, state and local laws and regulations, institutional policies, and requirements of the IRB, which include, but are not limited to, the following:

1. Submission of any and all proposed changes to this project (e.g., protocol, recruitment materials, consent form, status of the study, etc.) to the IRB for review and approval prior to initiation of the change(s), except where necessary to eliminate apparent immediate hazards to the subject(s). Changes made to eliminate apparent immediate hazards to subjects must be reported to the IRB as an unanticipated problem.
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Questions related to this project may be directed to [redacted]

cc:

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[redacted]

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Notification of IRB Review

Protocol #: 2017P001020

Date:	December 13, 2019	
To:	Ho, Jennifer, MD MGH Partners > MGH > Medical Services > Cardiac Unit	
From:	Partners Human Research 399 Revolution Drive, Suite 710 Somerville, MA 02145	
Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension	
Version/Number:	180927 JEH Detailed Protocol	
Version Date:	09/27/2018	
Sponsor/Funding/Support:	Proposal Title:	The Association of Metabolic Disease and Pulmonary Hypertension
	Principal Investigator:	Ho, Jennifer
	Immediate Sponsor:	NIH
	Award Number:	[redacted]
	Fund #:	
IRB Amendment #:	27	
IRB Review Type:	Expedited	
IRB Approval Date:	12/12/2019	
Approval/Activation Date:	12/13/2019	
IRB Expiration Date:	**03/21/2020**	

This project has been reviewed and approved by the **PHS IRB**. During the review of this project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for obtaining and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

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The following documents were reviewed and approved by the IRB:

Changes to inclusion criteria.

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Protocol Summary version dated (11/27/19)
Detailed Protocol, 180927 JEH Detailed Protocol 11/27/19
Consent Form
Advertisement
Instrument/Questionnaire

As Principal Investigator, you are responsible for ensuring that this project is conducted in compliance with all applicable federal, state and local laws and regulations, institutional policies, and requirements of the IRB, which include, but are not limited to, the following:

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Questions related to this project may be directed to [redacted]

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Fax: 857-282-5693

cc:

[redacted]

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Notification of IRB Review

Protocol #: 2017P001020

Date:	March 17, 2020	
To:	Ho, Jennifer, MD MGH Partners > MGH > Medical Services > Cardiac Unit	
From:	Partners Human Research 399 Revolution Drive, Suite 710 Somerville, MA 02145	
Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension	
Version/Number:	180927 JEH Detailed Protocol	
Version Date:	09/27/2018	
Sponsor/Funding/Support:	Proposal Title:	The Association of Metabolic Disease and Pulmonary Hypertension
	Principal Investigator:	Ho, Jennifer
	Immediate Sponsor:	NIH
	Award Number:	[redacted]
	Fund #:	
IRB Continuing Review #:	3	
IRB Review Type:	Designated	
IRB Approval Date:	02/27/2020	
Approval Effective Date:	03/13/2020	
Approval/Activation Date:	03/17/2020	
IRB Expiration Date:	**03/21/2021**	

This project has been reviewed and approved by the **PHS IRB**. During the review of this project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for obtaining and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

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Partners has implemented the Policy on Conduct of Human Research Activities during COVID-19 Operations. All research must comply with restrictions and requirements outlined in this policy.

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Principal Investigators and research team must review and follow all restrictions related to recruitment and study activities

The following documents were reviewed and approved by the IRB:

Protocol Summary (Version 11/27/19)
Consent Form
Detailed Protocol, 180927 JEH
IND Information (1)
DSMB/DMC Report (2)
Schema (1)
Flyer (1)
Package Insert (2)
Advertisement (3)
Telephone Script (1)
Recruitment Letter (3)
Adverse Event Log (1)
Minor Deviation Log (1)
Instrument/Questionnaire (7)
Letter Other than Recruitment (1)

As Principal Investigator, you are responsible for ensuring that this project is conducted in compliance with all applicable federal, state and local laws and regulations, institutional policies, and requirements of the IRB, which include, but are not limited to, the following:

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Questions related to this project may be directed to [redacted]

cc:

[redacted]

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Notification of IRB Review

Protocol #: 2017P001020

Date:	June 29, 2020	
To:	Ho, Jennifer, MD MGH Partners > MGH > Medical Services > Cardiac Unit	
From:	Partners Human Research 399 Revolution Drive, Suite 710 Somerville, MA 02145	
Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension	
Version/Number:	200609 JEH Detailed Protocol	
Version Date:	06/09/2020	
Sponsor/Funding/Support:	Proposal Title:	Mentoring in Patient-Oriented and Translational HFpEF Research
	Principal Investigator:	Ho, Jennifer
	Immediate Sponsor:	NIH-National Institutes of Health
	Proposal Title:	The Association of Metabolic Disease and Pulmonary Hypertension
	Principal Investigator:	Ho, Jennifer
	Immediate Sponsor:	NIH
	Award Number:	[redacted]
	Fund #:	
IRB Amendment #:	34	
IRB Review Type:	Expedited	
IRB Approval Date:	06/26/2020	
Approval/Activation Date:	06/29/2020	
Next Review:	**Continuing Review**	
IRB Expiration Date:	**03/21/2021**	

This project has been reviewed and approved by the **PHS IRB**. During the review of this project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of

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subjects; (iii) the procedures for obtaining and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

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Note: IRB approval of research does NOT constitute final approval to conduct the research. Human subjects research must be conducted in accordance with MGB's Expansion Plan of Clinical Research.

The following documents were reviewed and approved by the IRB:

Protocol Summary, 06/09/2020
Detailed Protocol, 06/09/2020
Consent Form, (1)
Advertisement, (2)
Flyer, (1)
Instrument/Questionnaire, (2)
Recruitment Letter, (4)
Description of COVID changes
200609 Notification of COVID-19 Protocol Changes Enrolled Pts.

Amended & Approved:

- **Updated to reflect changes.**
- **Updated Study staff contact information**.

As Principal Investigator, you are responsible for ensuring that this project is conducted in compliance with all applicable federal, state and local laws and regulations, institutional policies, and requirements of the IRB, which include, but are not limited to, the following:

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Questions related to this project may be directed to [redacted]

cc:

[redacted]

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Notification of IRB Review

Protocol #: 2017P001020

Date:	July 31, 2020
To:	Ho, Jennifer, MD MGH Partners > MGH > Medical Services > Cardiac Unit
From:	Partners Human Research 399 Revolution Drive, Suite 710 Somerville, MA 02145
Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension
Version/Number:	200729 JEH Detailed Protocol
Version Date:	07/29/2020
Sponsor/Funding/Support:	Proposal Title: The Association of Metabolic Disease and Pulmonary Hypertension Principal Investigator: Ho, Jennifer Immediate Sponsor: NIH Award Number: [redacted] Fund #:
	Proposal Title: Mentoring in Patient-Oriented and Translational HFpEF Research Principal Investigator: Ho, Jennifer Immediate Sponsor: NIH-National Institutes of Health Award Number: [redacted] Fund #:
IRB Amendment #:	36
IRB Review Type:	Expedited
IRB Approval Date:	07/31/2020
Approval/Activation Date:	07/31/2020
Next Review:	**Continuing Review**
IRB Expiration Date:	**03/21/2021**

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This project has been reviewed and approved by the **PHS IRB**. During the review of this project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for obtaining and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

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Note: IRB approval of research does NOT constitute final approval to conduct the research. Human subjects research must be conducted in accordance with MGB's Expansion Plan of Clinical Research.

The following documents were reviewed and approved by the IRB:
Protocol Summary (07/29/20)
Detailed Protocol
Consent Form

To Recruit participants that completed clinically-indicated Right Heart Catheterization.
To Recruit patients from the Pulmonary Hypertension clinic

As Principal Investigator, you are responsible for ensuring that this project is conducted in compliance with all applicable federal, state and local laws and regulations, institutional policies, and requirements of the IRB, which include, but are not limited to, the following:

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responsible for the design, conduct, or reporting of this research study of their obligation to submit updated Investigator Financial Disclosure Forms for this protocol to the IRB if (a) they have acquired new financial interests related to the study and/or (b) any of their previously reported financial interests related to the study have changed.

IMPORTANT REMINDER: THE IRB HAS THE AUTHORITY TO TERMINATE PROJECTS THAT ARE NOT IN COMPLIANCE WITH THESE REQUIREMENTS.

Questions related to this project may be directed to [redacted]

cc:

[redacted]

Mass General Brigham IRB
Mass General Brigham
399 Revolution Drive, Suite 710
Somerville, MA 02145
Tel: 857-282-1900
Fax: 857-282-5693

Notification of IRB Review

Protocol #: 2017P001020

Date:	August 19, 2020
To:	Ho, Jennifer, MD MGH Mass General Brigham > MGH > Medical Services > Cardiac Unit
From:	Mass General Brigham IRB 399 Revolution Drive, Suite 710 Somerville, MA 02145
Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension
Version/Number:	200814 JEH Detailed Protocol
Version Date:	08/14/2020
Sponsor/Funding/Support:	Proposal Title: The Association of Metabolic Disease and Pulmonary Hypertension Principal Investigator: Ho, Jennifer Immediate Sponsor: NIH Award Number: [redacted] Fund #:
	Proposal Title: Mentoring in Patient-Oriented and Translational HFpEF Research Principal Investigator: Ho, Jennifer Immediate Sponsor: NIH-National Institutes of Health Award Number: [redacted] Fund #:
IRB Amendment #:	38
IRB Review Type:	Expedited
IRB Approval Date:	08/19/2020
Approval/Activation Date:	08/19/2020
Next Review:	**Continuing Review**
IRB Expiration Date:	**03/21/2021**

Mass General Brigham IRB
Mass General Brigham
399 Revolution Drive, Suite 710
Somerville, MA 02145
Tel: 857-282-1900
Fax: 857-282-5693

This project has been reviewed and approved by the **MGB IRB**. During the review of this project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for obtaining and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

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The following changes were reviewed and approved by the IRB:

Participants will be asked to complete required COVID testing (e.g. via nasopharyngeal swab) prior to procedures, such as the Cardiopulmonary Exercise Test (CPET). This follows current hospital safety guidelines and protocols as put forth by the CPET laboratory.

A revised Detailed Protocol, Version Date: 08/14/2020; Protocol Summary, Version Date: 08/14/2020; an informed consent, and recruitment materials reflect the changes made.

NOTE TO THE PI: ***Thank you for the updates, which could be communicated to active participants without formal reconsent***.

As Principal Investigator, you are responsible for ensuring that this project is conducted in compliance with all applicable federal, state and local laws and regulations, institutional policies, and requirements of the IRB, which include, but are not limited to, the following:

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3. Submission of any and all unanticipated problems, including adverse event(s) in accordance with the IRB's policy on reporting unanticipated problems including adverse events.
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5. Informing all investigators and study staff listed on the project of changes and unanticipated problems, including adverse events, involving risks to subjects or others.
6. When investigator financial disclosure forms are required, submitting updated financial disclosure forms for yourself and for informing all site responsible investigators, co-investigators and any other members of the study staff identified by you as being responsible for the design, conduct, or reporting of this research study of their obligation to submit updated Investigator Financial Disclosure Forms for this protocol to the IRB if (a) they have acquired new financial interests related to the study and/or (b) any of their previously reported financial interests related to the study have changed.

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Questions related to this project may be directed to [redacted]

cc: [redacted]

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Notification of IRB Review

Protocol #: 2017P001020

Date:	October 09, 2020
To:	Ho, Jennifer, MD MGH Mass General Brigham > MGH > Medical Services > Cardiac Unit
From:	Mass General Brigham IRB 399 Revolution Drive, Suite 710 Somerville, MA 02145
Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension
Version/Number:	200814 JEH Detailed Protocol
Version Date:	08/14/2020
Sponsor/Funding/Support:	Proposal Title: The Association of Metabolic Disease and Pulmonary Hypertension Principal Investigator: Ho, Jennifer Immediate Sponsor: NIH Award Number: Fund #: [redacted] --- Proposal Title: Mentoring in Patient-Oriented and Translational HFpEF Research Principal Investigator: Ho, Jennifer Immediate Sponsor: NIH-National Institutes of Health Award Number: Fund #: [redacted]
IRB Amendment #:	40
IRB Review Type:	Expedited
IRB Approval Date:	10/09/2020
Approval/Activation Date:	10/09/2020
Next Review:	**Continuing Review**
IRB Expiration Date:	**03/21/2021**

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The following changes were reviewed and approved by the IRB:

1) Eligibility CRF was updated to include "lactating/nursing" in exclusion criteria. This reflects the current protocol and informed consent, which excludes enrollment of women who are lactating/nursing, pregnant, or planning to become pregnant while participating in the study.

2) Laboratory units on Visit 3 CRF were updated.

3) Listed side effects on Visit 3, 4, and 5 CRFs were updated for clarity, as "nausea" had appeared twice in the list.

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Notification of IRB Review

Protocol #: 2017P001020

Date:	February 22, 2021
To:	Ho, Jennifer, MD MGH Mass General Brigham > MGH > Medical Services > Cardiac Unit
From:	Mass General Brigham IRB 399 Revolution Drive, Suite 710 Somerville, MA 02145
Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension
Version/Number:	200814 JEH Detailed Protocol
Version Date:	08/14/2020

Sponsor/Funding/Support:		
	Proposal Title:	The Association of Metabolic Disease and Pulmonary Hypertension
	Principal Investigator:	Ho, Jennifer
	Immediate Sponsor:	NIH
	Award Number:	[redacted]
	Fund #:	
	Proposal Title:	Mentoring in Patient-Oriented and Translational HFpEF Research
	Principal Investigator:	Ho, Jennifer
	Immediate Sponsor:	NIH-National Institutes of Health
	Award Number:	[redacted]
	Fund #:	

IRB Continuing Review #:	4
IRB Review Type:	Full
IRB Approval Date:	02/16/2021
Approval/Activation Date:	02/22/2021
Next Review:	**Continuing Review**
IRB Expiration Date:	**02/16/2022**

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The following documents were reviewed and approved by the IRB:

Detailed Protocol
Protocol Summary
Consent From
Schema
Flyer
Advertisement
Minor Deviation Log
Adverse Event Log
Recruitment Letter
Telephone Script
DSMB/DMC Report
Letter Other than Recruitment
Package Insert
Instrument/Questionnaire
IND Information

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Notification of IRB Review

Protocol #: 2017P001020

Date:	February 26, 2021
To:	Ho, Jennifer, MD MGH Mass General Brigham > MGH > Medical Services > Cardiac Unit
From:	Mass General Brigham IRB 399 Revolution Drive, Suite 710 Somerville, MA 02145
Title of Protocol:	Cardiometabolic Disease and Pulmonary Hypertension
Version/Number:	200814 JEH Detailed Protocol
Version Date:	08/14/2020

Sponsor/Funding/Support:		
	Proposal Title:	The Association of Metabolic Disease and Pulmonary Hypertension
	Principal Investigator:	Ho, Jennifer
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	Award Number:	[redacted]
	Fund #:	
	Proposal Title:	Mentoring in Patient-Oriented and Translational HFpEF Research
	Principal Investigator:	Ho, Jennifer
	Immediate Sponsor:	NIH-National Institutes of Health
	Award Number:	[redacted]
	Fund #:	

IRB Amendment #:	44
IRB Review Type:	Expedited
IRB Approval Date:	02/26/2021
Approval/Activation Date:	02/26/2021
Next Review:	**Continuing Review**
IRB Expiration Date:	**02/16/2022**

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The following documents were reviewed and approved by the IRB:

Recruitment Letter

Revised wording of General Opt-Out letter.

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