JHM IRB - eForm A – Study Protocol & Analysis Plan

- **Use the section headings to write the JHM IRB eForm A, inserting the appropriate material in each. If a section is not applicable, leave heading in and insert N/A.**
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Title: Sleep Disordered Breathing in Marfan Syndrome- Susceptibility and Hemodynamics

NCT No: NCT03985657

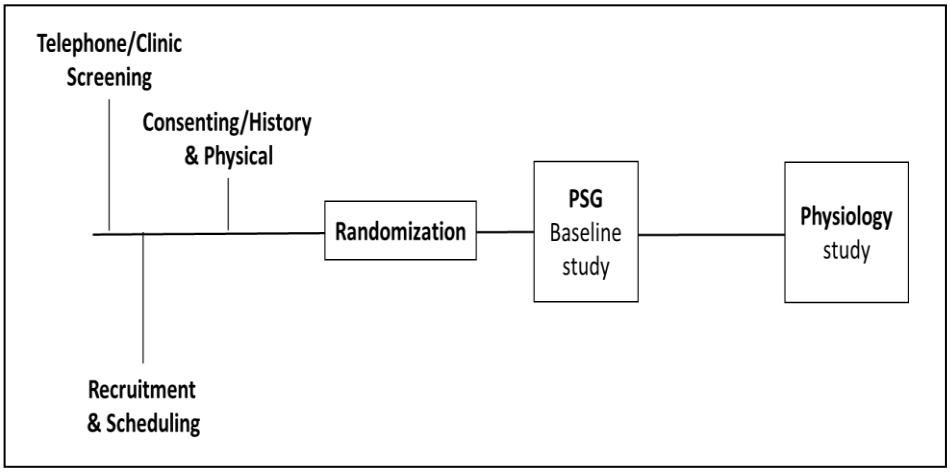
Date: December 16th, 2019

1. Study Procedures

a. Study design, including the sequence and timing of study procedures (Distinguish research procedures from those that are part of routine care).

Study Design/Protocol:
Individuals interested in our study will complete a basic telephone or in-person health screen to verify inclusion/exclusion criteria followed by consenting, history and physical and then sleep studies as outlined in the Figure. Qualifying individuals will come into the lab for the purpose of obtaining informed consent and completing a history and physical. Participants will then be admitted to the sleep laboratory at the Johns Hopkins Bayview Clinical Research Unit for a contiguous or separated two night stay. The first two hours will be required initially for set-up and anthropometric measurements, and the remainder of the night will be spent monitoring and recording sleep and breathing patterns as described below and in the Study Procedures section.

Figure: *Study Desi*gn



Baseline Night: Participants will undergo an overnight polysomnography (PSG). The parameter to monitored include electroencephalogram (EEG), electrocardiogram (ECG), electro-oculogram (EOG), thoraco-abdominal movements, submental electromyogram (EMG), pulse oximetry, continuous blood pressure monitoring (portable probe worn on the finger), chest movement activity (measured by bio-impedance electrodes placed on the chest) and airflow using a pnuemotachograph.

Physiology Night: During this night, continuous positive airway pressure (CPAP) will be administered via a nasal mask. In the first 90-120', nasal pressure will be titrated until non-flow limited breathing is achieved and UAO eliminated. The pressure at non-flow limited breathing is considered the ideal treatment pressure and participant will remain at this pressure for the rest of the night. Pressure and airflow data from the titration portion will be used to calculate the Pcrit [10,11,12]. The standard PSG parameters listed above will also be assessed on this night.

In either night, you may receive a sleep aid (Benadryl) if needed to aid sleep initiation.

Additional measurements: Participants will undergo arterial pulse wave analysis (using the EndoPAT; described at end of section) the morning after the baseline and physiology study. On one of the nights, pleural pressure changes will measured continuously using an esophageal catheter (see description of procedure below).

Pressure Catheter: A thin tube (about the thickness of a strand of spaghetti) will be placed through the participant's nose into the food tube (esophagus) after numbing the inside of the nose with some numbing medicine (such as lidocaine). This tube allows us to measure pressure changes in the lungs. This procedure will be carried out on both the baseline and physiology nights.

Bio-impedance measurement: Three EKG patches will be placed horizontally on the chest at the level of the armpit. The EKG patches will be connected to an external bio-impedance monitoring device which allows us to quantify respiratory effort similar to the esophageal pressure swings. This procedure will be carried out on both the baseline and physiology nights.

Objective snoring assessment: A mobile device with a microphone will be placed approximately 60cm from the participant to record snoring sounds.

Blood Test: Following, the sleep studies, a venous blood sample will be collected for serum biomarkers of aortic wall stress.

Peripheral arterial tonometry (EndoPAT): A blood pressure cuff is placed on the non-dominant arm while the participant is in the supine position; the contralateral arm is used for control comparisons. Measurements will be taken for 5 minutes before, 5-min during occlusion of the brachial artery and for 5 minutes upon release of the cuff. The occlusion will be achieved by

inflation of the automated cuff 50 mmHg above systolic blood pressure. Endothelium-mediated vasodilation is assessed using a finger pulse wave amplifier (a probe worn on one finger).

Randomization: It is documented that in the research setting sleep structure is altered specifically in the first sleep session due to exposure to a new sleep environment. Studies with

multiple sleep study nights are often confounded by this first night effect phenomenon [16]. To prevent this potential confounding effect, we will ensure that the order in which participants are assigned to a baseline and physiology night study is randomized. So that the findings in either night will not be attributed in part to the sequence in which the visits occurred.

2. Study Statistics

a. Analyses and Sample Size:

Specific Aim 1:

a. The sample size for this aim is designed to detect differences in Pcrit between matched groups. Our published data indicate a ΔPcrit of 1±0.9 cmH_2O as significant clinically. Therefore sample size calculations estimate 15 subjects each in MFS and control groups necessary to detect a baseline difference in Pcrit of 1.0±0.9 cmH_2O with a power of 85% (two-sided test, with α type 1 error = 0.05). These considerations lead us to propose a final sample size of 15 MFS patients and 15 non MFS controls (n=30 participants). We will recruit 30 MFS and 30 non MFS controls in total to allow for attrition, sub group analyses and missing data.

b. Overnight UAO exposure will be determined by 1) apnea-hypopnea-index (AHI) and b) a composite measure of pleural pressure swings during UAO. Wilcoxon non- parametric t-test comparisons will be used to determine differences in these parameters between MFS and matched controls.

Specific Aim 2:

a. We have estimated the required sample size of 15 in each group to see a difference of 10 units in hemodynamic parameters between groups at 90% power and a significance alpha level of 0.05 [15]. We will compare hemodynamics (heart rate and pulse pressure) at baseline vs CPAP in pair wise t-test comparisons after accounting for sleep stage, body position and respiratory phase.

Stratified regression analyses will be used to determine whether the magnitude of hemodynamic parameters are predicted by genotype (MFS vs non MFS) at baseline and CPAP after accounting for sleep stage, body position and respiratory phase.

b. We will utilize descriptive techniques such as scatter plots, correlation analyses to explore the relationship between hemodynamic response to UAO and measures of aortic disease progression (aortic diameter, rate of aortic diameter increase in the past five years and augmentation index) in MFS. This relationship will also be examined using a multivariate

c. regression model adjusting for age, sex and body surface area. Augmentation index will be obtained from the morning EndoPAT measurements (see section 2) and aortic parameters will be obtained from the protocol; **IRB00157483**.