Massachusetts General Hospital
Cardiopulmonary Exercise Laboratory

Cardiopulmonary Exercise Testing Manual of Operating Procedures for the SEQUOIA-HCM Protocol CY 6031 PA3

Version 1.3 March 8, 2023

Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM

Full Title:

A Phase 3, Multi-Center, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of CK-3773274 in Adults with Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction

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1.0 INTRODUCTION

1.1 ABBREVIATIONS AND GLOSSARY OF TERMS

BP	Blood pressure
CPET	Cardiopulmonary exercise test
CCS	Cardiovascular Clinical Studies, Inc
CV	Coefficient of variation
ECG	Electrocardiogram
f	Breathing frequency
FVC	Forced vital capacity
HCM	Hypertrophic Cardiomyopathy
HR	Heart rate
IC	Inspiratory capacity
MOP	Manual of operating procedures
oHCM	Obstructive hypertrophic cardiomyopathy
O_2 Pulse	Oxygen uptake divided by HR
OUES	Oxygen uptake efficiency slope
$PaCO_2$	Partial pressure of carbon dioxide
$P_{ET}CO_2$	Partial pressure of end tidal carbon dioxide
$P_{ET}O_2$	Partial pressure of end tidal oxygen
Peak VO_2	Peak oxygen uptake during exercise
RER	Respiratory exchange ratio
SaO_2	Arterial oxygen saturation
SV	Stroke volume
VCO_2	Carbon dioxide output
VC	Vital capacity
V_D	Dead space volume
V_E	Minute ventilation
$VO2_{VT}$	Oxygen uptake at the ventilatory anaerobic threshold
W	Workload in Watts

1.2 SEQUOIA-HCM PROTOCOL OVERVIEW

This study will utilize cardiopulmonary exercise testing (CPET) to evaluate patient eligibility and evaluate the effect of CK-3773274 on exercise capacity between Baseline and Week 24 in patients with symptomatic oHCM. The primary endpoint is the change in peak oxygen uptake (Peak VO_2) from Baseline to Week 24.

The following efficacy endpoints will be evaluated from the CPET

Peak VO_2 (ml/kg/min) (primary endpoint)
Peak workload achieved (Watts)
VE/VCO2 slope
Ventilatory anaerobic threshold (by the V-slope method)
Circulatory power (Peak VO_2 × Peak systolic BP)

Only subjects who meet CPET criteria as well as all other eligibility criteria specified in the CY-6031 protocol will be enrolled in the study. Subjects should undergo the CPET after all other inclusion and exclusion criteria are met. The inclusion criteria specific to CPET are as follows:

- **Subjects must have a Peak VO_2 ≤90% predicted (see Table 1) (primary endpoint)**
- **Subjects must have a peak respiratory exchange ratio (RER) of ≥ 1.05**

CPET should be performed at approximately the same time of day where possible (±2 h).
CPET **MUST** be performed at least 4 hours after the last meal.

Table 1. Peak VO_2 Inclusion Criteria

	Normal Values for Peak VO_2*	Criteria (ml/kg/min) for subjects <90% Normal Value
18-29 M	**43±7.2**	**< 38.7**
20-29 F	**36±6.9**	**< 32.4**
30-39 M	**42±7.0**	**< 37.8**
30-39 F	**34±6.2**	**< 30.6**
40-49 M	**40±7.2**	**< 36.0**
40-49 F	**32±6.2**	**< 28.8**
50-59 M	**36±7.1**	**< 32.4**
50-59 F	**29±5.4**	**< 26.1**
60-69 M	**33±7.3**	**< 29.7**
60-69 F	**27±4.7**	**< 24.3**
> 70 M	**29±7.3**	**< 26.1**
> 70 F	**27±5.8**	**< 24.3**

***Fletcher GF et al. *Circulation*. 1995; 91:580-615.**

2.0 SITE ASSESSMENT AND CERTIFICATION

Previous multicenter trials evaluating exercise gas exchange have been confounded by methodological differences in exercise protocols and lack of uniformity in interpretation of gas exchange data[1-3]. The CPET Core Laboratory at Massachusetts General Hospital will work with individual centers to promote uniformity in CPET administration, reporting, and quality control measures. The CPET Committee recognizes that most sites participating in this study have laboratories with significant experience and expertise in administering CPETs. However, site assessment, certification, and strict adherence to this detailed protocol will be essential to ensure the consistency and validity of derived results. This manual has been divided into 8 sections, which includes printable forms to guide sites through qualification procedures, patient education, and CPET administration.

2.1 CPET EQUIPMENT REQUIREMENTS

Treadmill/Cycle: Treadmill will be the preferred exercise modality for the SEQUOIA-HCM Trial. For CPET laboratories that do not perform treadmill ergometry an alternative cycle ergometry exercise protocol has been devised (**Section 3**). Regardless of the exercise modality, the metabolic cart computer should be able to control the work rate of the treadmill or cycle. Electrically-braked cycles are preferred, as opposed to friction-braked cycles, based on their higher precision of work rate relative to friction-braked cycles and the ability to implement a continuous ramp protocol.[4] It will be essential to conduct the qualifying CPETs on the same equipment that will be used for the CPETs conducted for this trial.

Airflow or volume transducers: The accurate measurement of ventilation parameters during exercise is critically dependent on the accuracy of the flow-sensing device. Transducers used in exercise testing should meet established standards by the American Thoracic Society for flow and volume measurement during spirometry.[5]

Gas analyzers: Breath-by-breath analysis requires precise knowledge of gas analyzer delays and response kinetics.[6] Participating laboratories will need to follow standards for gas analyzer performance in breath-by-breath mode; these will include a transfer delay time of <1 second, a rise time <0.1 seconds, calibration stability of ± 3% over 20 minutes and calibration linearity ± 3% over the entire range.[7] Each site will be required to maintain a calibration logbook so that long-term trends can be monitored.

Electrocardiographic monitoring: Participating laboratories will be required to use electrodes and detection electronics designed for movement artifact rejection. Silver or silver chloride electrocardiogram (ECG) electrodes with circumferential adhesive provide good electrical contact and minimize movement artifact. Continuous display of ECG tracings with 12-lead ECG placement will be performed as described by Mason and Likar.[8] The timing of ECG monitoring must be synchronized with the timing used by the gas exchange system, preferably through an integrated ECG-metabolic cart system. ECGs will be performed for precise heart rate monitoring and for safety purposes, but tracings will **not** be transmitted to the **MGH** core lab for interpretation. **ECG tracings will be sent to ECG core lab for interpretation. Please refer to instructions from ERT Core Lab for specifics.**

Metabolic measurement systems: The core laboratory encourages sites to utilize standard metabolic cart processing software. This will promote uniform generation, formatting, and acquisition of breath-by-breath data. Medgraphics Inc (St. Paul, MN) metabolic carts interfaced with BREEZESUITE software represent the most commonly used metabolic measurement systems in the United States. Therefore, CPET data acquired and configured with BREEZESUITE software is preferred. The second most common type of metabolic cart used in CPET is Viasys (previously Sensormedics), which the core lab is equipped to interpret. For Viasys/Sensormedics equipment, sites will be strongly encouraged to use ENCORE/Vmax software formatted data to facilitate data manipulation and simple transfer of data to the core laboratory. Carefusion and COSMED metabolic carts are frequently in use in Europe. Data from these carts should be transmitted as tabular data exported to an excel sheet. Additional systems are commonly used in Europe and will be permissible but must allow real-time tabular and graphical display of exercise variables, 5-of-7 breath moving average integration of gas exchange variables, and data conversion to unencrypted format such as Excel that will lend itself to interpretation by the core laboratory.

2.2 CPET EQUIPMENT CALIBRATION

CPET equipment should be calibrated by following instructions given by the manufacturer of the equipment. Equipment calibration is not mandated prior to participation in the trial, though may become necessary if qualification studies demonstrate abnormal values for gas exchange-work rate relationships. Should calibration be deemed necessary at your site, instructions are included below.

Prior to initiation of cardiopulmonary exercise testing for the SEQUOIA-HCM Trial, the following calibration procedures are recommended.

- Treadmills should have belt speed verified by timing revolutions using a mark made on the treadmill belt with a subject on the treadmill. Grade may be determined by using a plumb line and tape measure.
- It is recommended that electrically braked cycle ergometers that have not been previously calibrated or are newly purchased should be dynamically calibrated with the use of a dynamometer (torque meter). Because many labs do not have dynamometers, cycle ergometer manufacturers may be required to provide this service. This calibration should be repeated if the cycle is moved or jarred or if certification testing results in abnormal values for gas exchange-work rate relationships.

Prior to each test

- Record barometric pressure, temperature, relative humidity
- Perform flow calibration with a 3L syringe (<1-15sec duration) to achieve ± 3% agreement with calculated volumes.
- Perform gas analyzer calibration with two precision-analyzed gas mixtures. This is commonly done with one 6% CO_2 and 15% O_2 tank and one 0% CO_2 and 21% O_2 tank. The air baseline setting for O_2 and CO_2 should be checked before each test to correct for baseline drift since calibration.
- Determine transport delays between the gas sampling point and each gas analyzer. This should be an automated process.

2.3 SITE QUALIFICATION PROCEDURES

Before baseline studies may be performed in subjects, **each site will be required to submit two incremental symptom-limited CPETs on the same "standard normal subject".** The standard subject should be a healthy, young to middle-aged adult. These tests must be performed on separate days, preferably no more than 5 days apart. Prospective CPET laboratories will be evaluated based on their ability to: (1) follow a site qualification protocol (see Section 7.), (2) generate reproducible CPET data, and (3) transmit data to the core laboratory. Test results will be compared to data available on normal individuals from the core laboratory and the published literature.[7, 9] Sites should await feedback from the core laboratory confirming that their site has qualified prior to scheduling study subjects for testing (See Appendix I).

Sites may subsequently use repeated studies of the "standard normal subject" to verify accuracy of their systems. The Core Laboratory will require sites to maintain a detailed log of physiologic calibration testing as described above, but this information will not need to be transmitted to the core laboratory as part of the initial qualifying procedures.

After confirmation is received that your site has been selected by Cytokinetics, for the SEQUOIA-HCM Trial, an email invitation will be extended to join the Mass General Brigham MGB Secure File Transfer Service through which qualification studies and subsequent study files can be transferred via a secure email system (see Section 4.2 for detailed instructions). After registering for the MGH Secure File Transfer Service, transmit two qualification studies formatted as described below and summarized in Section 7.

3.0 CPET PROCEDURES

3.1 CPET PREPARATION

Treadmill will be the preferred exercise modality for the SEQUOIA-HCM trial. A specific protocol of gradual increment in both speed and grade (Section 7.3) that is appropriately suited to the study of oHCM patients[10] is required. In order to achieve within subject consistency, it is important that a laboratory commits to performing all study tests on the same treadmill or cycle ergometer. In addition, if a participating laboratory has more than one treadmill/cycle ergometer or metabolic cart, the same equipment should be used for each test in a given subject.

The Week 24 CPET should be performed at approximately the same time of day (e.g., within 2 hours) as the baseline CPET, and by the same CPET Lab Staff when possible. The CPET **MUST** be performed at least 4 hours after the last meal. Investigational Product (IP) is to be administered on site prior to CPET.

Each subject should use the same protocol for all their CPET tests.

1. **Provide patients with pre-test instructions.** The Patient Education Form, Section 6.0 is to be used by participating sites to provide uniform instructions to SEQUOIA-HCM subjects. Subjects should be given instructions to fast for 4 hours prior to the CPET and take all their medications as normal, particularly medications that influence heart rate (such as beta blockers).

2. **Review of contraindications to exercise testing.** Table 2 below lists contraindications to exercise testing. Questions regarding exercise eligibility should be brought to the attention

of the site principal investigator. Principal investigators may email the MGH CPET Core Lab at cpetcore@partners.org and CC Dr. Gregory Lewis at glewis@partners.org.

Table 2: Contraindications to Exercise Testing (most of which are also exclusion criteria for trial entry).

Absolute Contraindications
• Acute myocardial infarction (3-5 days) or unstable angina • Uncontrolled symptomatic arrhythmias • Active endocarditis • Acute myocarditis or pericarditis • Symptomatic severe aortic stenosis • Acute pulmonary embolism or DVT • Suspected dissecting aneurysm • Uncontrolled asthma • Uncontrolled pulmonary edema • Room air desaturation to <85% • Acute illness (i.e. infection) or orthopedic injury that is anticipated to affect exercise performance • Mental impairment leading to inability to cooperate • History of exercise-induced ventricular arrhythmia

3. **Initial patient data entry.** Upon initiating a study using BREEZESUITE or analogous software, click on the "Patient" or equivalent demographic information tab. The following information should be entered into the designated text boxes.

Patient

Site Certification:
For site certification studies, identify the tests by entering study protocol name (6031), followed by the site number (six digits), then the test description (CERTIFICATION), and designate the study either A or B. If further studies are required, they should be designated C and D.
- Site certification identifiers may look like this: 6031-000001-Certification-C).

Subject Identification:
For the Screening test, enter study protocol number (6031), followed by the site number (six digits), the subject screening number (three digits), and followed by test description (SCR). For subjects that are re-screened, indicate test description RESCR.

- Screening subject's identifier may look like this: 6031-000001-001-SCR

For subjects that are rescreened, please use the protocol number (6031) site number (six digits), subject number (three digits), and test description (RESCR),
- Rescreening subject's identifier may look like this: 6031-000001-001-RESCR

For the Week 24 test, please use the study protocol number (6031), site number (six digits), subject number (three digits), and test description (W24).

- Week 24 subject identifier may look like this: 6031-000001-001-W24

Input of accurate year of birth, gender, height and weight is important to determine eligibility and to provide accurate VO_2 endpoint data. Subjects should be weighed at the time of each CPET to provide accurate data for weight-based peak VO_2 assessment. *It is not permissible to rely on subject's stated weight or height.*

Visit Demographics

Enter the following:

Year of Birth
Age
Gender
Height (cm) – (only required for SCR CPET)
Weight (kg)
Reason for cessation of exercise
Referring physician (CPET lab physician)
Technician (CPET lab technician conducting the study)
Site: Indicate which metabolic cart is being used, if your laboratory has more than one cart please designate the cart being used (i.e., cart1 and cart2)

Patient History

Pre-test comments: Free text the name and contact information for the responsible CPET lab personnel who conducted the CPET
Name: _____Email: _____Phone #: _____

3.2 CPET PROCEDURES

Blood pressure measurement procedures: Pre-exercise blood pressure should be obtained with the subject in a relaxed, comfortable, seated position without clothing in between the cuff and the arm. Choose the correct cuff size, the bladder width should encircle 40% of the circumference of the arm and there should be at least 2 cm between the bottom of the cuff and the brachial artery. Record the blood pressure at which you hear the first Korotkoff sounds for two consecutive beats as systolic blood pressure and the pressure at which time the sounds disappear (K5) as diastolic blood pressure. CPET laboratory staff should adhere to this protocol in measuring exercise blood pressure as well.

12-lead electrocardiogram recording: Skin preparation is important to ensure a high-fidelity signal, free from motion artifact and electrical interference that is sent to the electrocardiograph and the metabolic cart system where heart rate will be recorded. Proper skin preparation involves

removing the hair with a disposable safety razor, cleansing the skin with alcohol or acetone to remove skin oils, followed by light abrasion to remove stratum corneum.
Standard limb lead placement on the wrists and ankles must be modified for exercise by moving them to the anterior trunk in a Mason-Likar configuration (Figure 1). A 12-lead electrocardiogram should be recorded during this rest period. Heart rate at rest and during exercise will be transmitted to the core laboratory. However, interpretation of cardiac rhythms and pattern interpretation on electrocardiograms will need to be performed contemporaneously by site cardiologist with exercise testing (and not by the MGH core laboratory) to ensure patient safety.

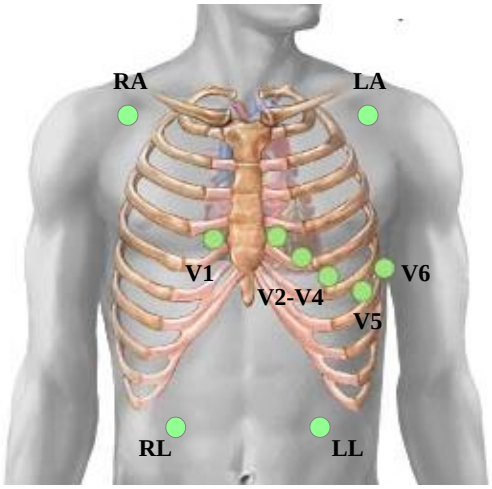


Figure 1. Electrode placement for electrocardiogram recording during exercise. RA indicates right arm, LA indicates left arm, RL indicates right leg, LL indicates left leg.
Model adapted from ADAM at www.nlm.nih.gov/.../ency/imagepages/19865.htm

Gas exchange measurements: With subjects standing on the treadmill a nose clip is placed and the mouthpiece is inserted. At this time the importance of maintaining a tight seal around the mouthpiece should be emphasized to the patient. Use of a mask is permitted but it is critically important to ensure a tight seal of the mask.

Metabolic cart, software interface preset data displays: Metabolic measurement systems should allow real-time graphical and tabular display according to the recommended format in Table 4. Because significant differences can arise as a result of time interval selection for averaging breaths in patients with HF,[11] participating laboratories will be required to provide the core laboratory with data on all breaths. However, to standardize data output across metabolic carts we will request that tabular data be displayed using **5-out-of-7 breath retrograde time averaging** which is a standard option for BREEZESUITE. An alternative is 10-second averages or mid 7-of-9 breaths in Viasys or COSMED, metabolic cart software. The following screening procedures for outlier values in Table 3 below should be programmed into BREEZESUITE or analogous software systems.

Table 3. Parameters to eliminate outlier values for breath-by-breath gas exchange variables

Measurement Variable	Minimum Value
RER	0.5
VCO_2	50 ml/min
VO_2	50 ml/min
Tidal vol	180 ml

RER indicates respiratory exchange ratio, VCO_2 indicates carbon dioxide output, VO_2 indicates oxygen uptake, and tidal vol indicates tidal volume.

Resting phase of CPET

A 5-minute rest period will be implemented. During this period CPET lab personnel should observe key variables in comparison to reference values to ensure proper calibration and performance of the metabolic measuring system. Table 4 below provides an example of key resting variables and their expected values.[12]

Table 4. Reference values appropriate for resting conditions.

Heart Rate (min^{-1})	VO_2 (ml/kg/min)	VO_2 (ml/min)	VCO_2 (ml/min)	RER	RR (min^{-1})	V_E (L/min)	$P_{ET}O_2$ (mmHg)	$P_{ET}CO_2$ (mmHg)
60-100	3.5	200-300	140-300	0.7-1.0	12-20	6-10	100-105	38-42

VO_2 indicates oxygen uptake, VCO_2 indicates carbon dioxide output, RER respiratory exchange ratio, RR respiratory rate, V_E minute ventilation, $P_{ET}O_2$ end tidal oxygen, $P_{ET}CO_2$ end tidal carbon dioxide. Values for VO_2, VCO_2, and VE apply to normal adults, and will tend to be lower for younger subjects.

Some clinical conditions can account for departures from expected values. However, departures can usually be explained by pre-test anxiety, leaks in the patient interface such as a poor fitting mask or failure to apply the nose clip or improper calibration of the metabolic cart. Anxiety is typified by a heart rate > 85 min^{-1}, V_E > 10 L/min, $P_{ET}CO_2$ < 35, RER > 1.0 whereas a system leak results in proportionately low V_E, VO_2, VCO_2.

Warm up phase, unloaded cycling or walking on the treadmill: Following the rest period, at a verbal signal the patient should start pedaling with the cycle unloaded (i.e. free-wheeling) or walking slowly on the treadmill for 3 minutes according to the appropriate protocol outlined in Section 7.3. If available, an accessory motor should be utilized to rotate the flywheel at a rate of 60 rpm in order to eliminate the inertial force needed to start the flywheel rotating and reach the desired speed. The patient should be coached to pedal at 60 rpm on the unloaded cycle to become accommodated to this pace*. The pedal rate meter should be displayed in clear view of the patient to facilitate compliance with this goal pedaling frequency.

> *If a true unloaded (0 Watt) phase is not available on a site's cycle ergometer, then the site must reach out to the Core Lab cpetcore@partners.org and program the lowest possible resistance level on their cycle ergometer during the 3-min period of low-level exercise. The Core lab will assess this exception and make a determination as to whether it is permissible.

Incremental exercise: The pace and grade will increase every minute. Subjects will be encouraged to reach a maximal effort by monitoring the respiratory exchange ratio [goal respiratory exchange ratio (RER, VCO_2/VO_2) ≥ 1.1]. The technician and physician should work

cooperatively to observe the subject's facial expression while encouraging the subject to keep their eyes open during exercise. Blood pressure and oxygen saturation will be monitored and recorded every two minutes. ECG monitoring will be used to monitor patients during exercise testing. Heart rate, as measured by ECG, will be recorded every minute. The recognition and treatment of conditions that manifest with ECG abnormalities during exercise will be the responsibility of the on-site supervising physician due to the time-sensitive nature of such findings. If ECG abnormalities arise during testing, these should be indicated in the comments section on Section 7 worksheets. Standardized guidelines for operators to stop an exercise test are listed in Table 5 below.

Criteria for CPET Termination: The standard accepted criteria for terminating an exercise test are listed in Table 5. These are only guidelines and should be used in conjunction with clinical judgment of trained CPET lab personnel and study investigators.

Table 5. Objective criteria for termination of CPET:

Criteria for CPET Termination
Definitive ischemic ECG changes with associated chest pain
Complex ectopy (i.e. ventricular tachycardia)
Mobitz 2 second degree or third degree heart block
Marked hypertension (systolic BP > 240 mmHg, diastolic BP >120 mmHg
Severe oxygen desaturation, SpO2<80% when accompanied by signs of severe hypoxia
Neurologic compromise such as mental confusion or loss of coordination

Recovery period: To avoid orthostatic hypotension when stopping exercise, the subject should be encouraged to walk slowly on the treadmill. Record blood pressure during the second and fourth minute of recovery. **Gas exchange and heart rate should continue to be measured for five minutes into recovery.**

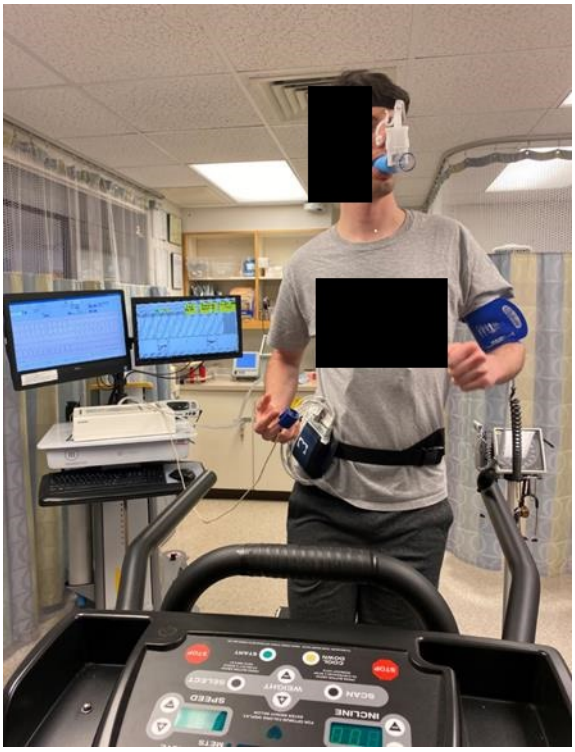
End of test: CPET laboratory personnel should elicit the reason for cessation of exercise. Viasys Vmax/Encore software prompts users with a "Metabolic End of Test Comments" menu. A primary reason for test cessation should be selected. Secondary reasons for cessation of exercise may also be recorded as added text. It is particularly pertinent to indicate if the test was stopped by the operator prior to the patient reaching a point of maximum exertion.

3.3 CPET PROTOCOL SCHEMATIC SYNOPSIS

Initial measurements of heart rate and blood pressure will be conducted in subjects prior to mouthpiece insertion. The 5-minute rest period will start upon mouthpiece insertion and initiation of gas exchange collection with the metabolic cart. Blood pressure will subsequently be obtained 4.5 minutes into the rest period, then during the last 30 seconds of every 2-minute increment during exercise (i.e. between 3.5 and 4.0 minutes into exercise). It should be noted if data is collected outside of this 30 second window. Heart rate and O_2 saturation should be recorded each minute. Peak exercise heart rate, blood pressure, and O_2 saturation should also be recorded. See **Figure 2 and 3**.

	Rest					Unloaded Exercise			Loaded Exercise							Recovery				
Min	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15+	12	13	14	15	16
Watt	0	0	0	0	0	0	0	0	15	30	45	60	75	90	105+	0	0	0	0	0
HR	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
O2 Sat	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
BP					x			x		x		x		x		x		x		x
RPM	0	0	0	0	0	60	60	60	60	60	60	60	60	60	60	60	0	0	0	0

Figure 2. Schematic representation of exercise protocol



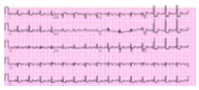
DEVICE	PRIMARY	DERIVED
Metabolic cart		
CO_2 O_2 Flow	$PETCO_2$, VCO_2 $PETO_2$, VO_2 RR, V_T, V_E	V_E/V_{CO2} RER, AT O_2 pulse
	Blood pressure	Double product
Pulse Oximeter	SpO2 saturation	~O_2
	Heart rate Rhythm	Pattern changes
Treadmill 15 W/min ramp		

Figure 3. Measuring devices, primary, and derived measurements obtained during CPET. ET indicates end tidal, *f* breathing frequency, RER respiratory exchange ratio.

<u>Key Protocol points</u>:

- **Subjects must meet all inclusion and exclusion criteria before performing CPET**
- **The CPET must be completed within three weeks but not less than one week prior to randomization.**
- **Baseline tests: Send Screening tests to MGH CPET Core Laboratory as soon as possible for review for CPET criteria eligibility. Once reviewed, a CPET eligibility email will be received from the MGH. Once subjects have passed all inclusion and exclusion criteria, randomization can take place. <u>Sites will use the MGH CPET Core Lab adjudicated exercise measurements (Peak VO_2, RER) for all randomizations</u>. See Appendix II for sample email. Please file all CPET eligibility emails received from the MGH CPET Core Laboratory appropriately within the site study binder.**
- **Site personnel must indicate on the supplemental worksheet the patient's reason for cessation.**

- **Whenever possible, patients should perform exercise testing between three and ten hours after taking beta blocking agents.**
- **The Week 24 CPET should be performed at approximately the same time of day (e.g., morning, mid-day, afternoon) as the baseline CPET at screening, at a consistent time after the last dose of beta-blocker.**
- **For the Week 24 CPET, Investigational Product should be administered on site, prior to CPET.**
- **Sites should contact patients shortly before the Week 24 visit and confirm their ability to perform CPET.**
- **If a patient is temporarily unable to exercise on the treadmill or bicycle (whichever modality was used at baseline) due to an adverse event (e.g., ankle sprain, upper respiratory infection, migraine), but not due to HCM symptoms, or if the site is unable to perform CPET (e.g., equipment malfunction), then the Week 24 visit may be postponed by up to 4 weeks. The patient should continue to receive IP until the visit.**

3.4 TABULAR CPET DATA DISPLAY

Table 6. Tabular data displays for cardiopulmonary exercise testing.

Time min	Speed (mph)	Grade (%)	VO_2 (ml/kg/min)	VO_2 (ml/min)	VCO_2 (ml/ min)	RER	RR (min^{-1})	Vt (ml)	V_E (L/min)	$P_{ET}CO_2$ (mm Hg)	$P_{ET}O_2$ (mm Hg)	HR (min^{-1})	O_2 sat (%)	SBP (mm Hg)	DBP mm Hg)

Unshaded cells represent standard metabolic cart output. The shaded regions of this table may be automatically populated during the study or may need to have data entered depending on the degree to which other measurement equipment is interfaced with the metabolic cart. To aid in data recording for post-test completion of these data fields, please see printable data entry form (Section 7, pages 19-22). This information will need to be entered into the above tabular format either during or after the CPET, prior to transmission of the study to the core laboratory.

4.0 DATA RECORDING AND TRANSMISSION TO THE CORE LABORATORY

Please transmit the test to the CPET Core Lab immediately upon completion of the study. The MGH CPET Core Lab will be able to determine eligibility based on CPET parameters within three business days of receipt of the tests. Sites will be informed of subject CPET related eligibility by email.

4.1 CPET DATA PREPARATION

For each CPET performed, the Core Laboratory requests that all information be integrated into a single CPET file that will be transmitted to the Core Lab. For each study, the following steps will be taken to ensure standardized data reporting.

1. Prior to exercise testing, enter patient data into BREEZESUITE or analogous software according to instructions outlined above (Section 3.1, #3).
2. Data recording during CPET testing
    A. Breath-by-breath data should be formatted according to Table 6, page 14.
    B. Real-time addition of heart rate every minute, and blood pressure recordings every two minutes during exercise is technically possible in the BREEZESUITE and Vmax/Encore programs but may be cumbersome during supervision of a CPET. Hence, we recommend recording of heart rates (from the ECG) and blood pressures during testing. Following completion of the CPET, this data can then be entered into the BREEZESUITE "Event Entry" screen or equivalent on other software systems. To access the Event Entry screen follow these steps:
        a. Enter the "Protocol/Log" tab, "Visit Log" section
        b. Select the clock/pencil icon to enter data at an appropriate time during the test (i.e. 10 minutes of exercise)
        c. Select the "Gas Exchange" tab with the "Event Entry" box
        d. Use the drop-down variable menu to select/enter BP, and heart rate
        e. Select "ABG" to enter current hemoglobin level
        f. Confirm that the Tabular data reporting form is updated for heart rate and blood pressure.
        g. Add "Why the patient stopped exercising/reason for cessation of exercise." A single primary reason should be specified, though addition of a secondary reason is permissible.
    C. The core lab would prefer a self-contained single file in which all data is incorporated within the CPET software program. However, if this is not possible, data may be manually entered into electronic versions of 7.0 and then transmitted to the core laboratory as a Microsoft Excel file. Files should be named as described on Section 3.1, including Protocol name/number, study ID, and test description.

4.2 CPET DATA TRANSFER TO THE CORE LAB

Copy the archived file onto a computer disk or flash drive immediately following the CPET. BREEZESUITE software requires entering the Import/Export Program from the Start Menu→Programs→Medgraphics→DBP Tools→Tools→Export, then select the patient file and the destination of the file under the Browse menu. This will enable the site's CPET lab to export the file to a local disk and to then send the file electronically as an enclosure (see below). Viasys Vmax/Encore software can be used to directly email test files using the "Special Functions" tab and selecting the "File compress/email" option. Metabolic measurement systems with software programs other that those supported by Medgraphics and Viasys/Sensormedic will be required to convert gas exchange data into Excel format for breath-by-breath data interpretation. In addition, graphical data should be generated to facilitate calculation of the ventilatory threshold by the V-slope technique. Label the computer disk with the following information: a) SEQUOIA-HCM, b) Site number (six digits) c) subject ID (three digits), and d) date of study. <u>This will serve as a back-up hard copy of the data to remain at the individual CPET lab.</u>

The MGH Core Laboratory will utilize the Accellion Secure File Transfer Service to exchange files with participating CPET laboratories via a web browser. The service is a secure web-based

application with anti-virus detection built in. Attached files are encrypted and the recipient receives an email with a link.

When the recipient clicks the link, the file is downloaded. This will enable rapid, readily traceable transfer of data between participating sites and the core laboratory. Files should be sent to the MGH CPET Core Laboratory at **cpetcore@partners.org** and the Data Analyst staff located on page 25.

The CPET laboratory contact specified on the CPET Feasibility Questionnaire will receive an invitation from a Core Lab analyst to register for the transfer service. Upon clicking on the attachment, the screen depicted in Figure 4 will appear with instructions on how to register for this free service. Participants will automatically create a login and password as part of a simple authentication process which can be used to send files back to the core lab or anyone else who is registered user with an affiliate email address. Participating CPET labs will be able to send up to 10 files at a time to the core laboratory, with an overall size limit of 2GB.

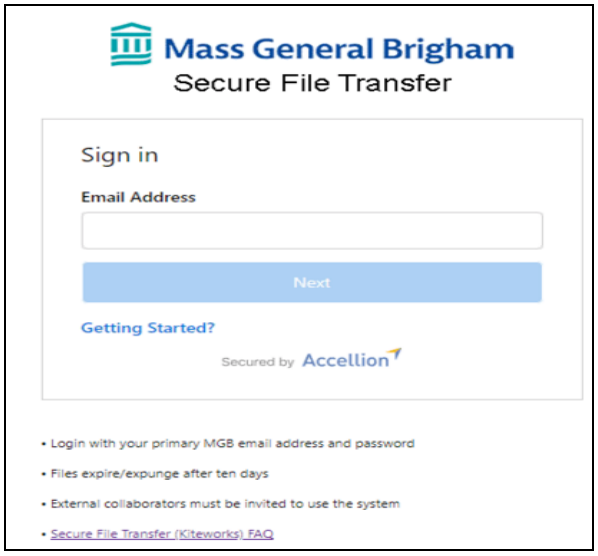


Figure 4. Mass General Brigham Secure File Transfer screen for registering for the file transfer service that will be used by the MGH CPET Core Laboratory

Participating labs can use the following website to login to the service in order to transfer files to MGH**: http://transferkw.partners.org** In addition to basic send and receive functions, the File Manager menu tab provides a File Cabinet, Inbox and Send History for keeping track of the files you have sent and received. The core laboratory will maintain this record of file transmissions and we will encourage participating labs to do the same. Further general information about how to use this file transfer service is available at **https://transferkw.partners.org/**

4.3 CORE LAB STUDY PROCESSING

Upon arrival of each study at the core laboratory the study will be logged into our database. As each study moves through the sequence of data processing, analysis, and report generation it will be logged and tracked accordingly. An email reminder will be sent to sites if studies do not arrive in a timely fashion.

Gas exchange data will be analyzed uniformly across sites. Programs will be applied to select the highest 5-breath median VO_2 during the final minute of incremental exercise. Primary breath-by-breath data will also be used to calculate ventilatory threshold by the V slope method.[13]

5.0 QUALITY ASSURANCE AND QUALITY CONTROL PRACTICES

Prior to initiation of the trial, sites will be required to conduct two initial tests on a "standard subject." These tests will serve to an indicator of appropriate calibration procedure, protocol adherence, and appropriate data compilation and transmission to the core laboratory. Individual CPETs will be expected to demonstrate a change in respiratory exchange ratio of >0.15 and demonstrate appropriate increases in ventilation, VO_2, and carbon dioxide production during exercise.

If the core lab questions the quality of data that they receive from a testing site, we may require the site to perform another certification test. In addition to recalibration of the treadmill and the metabolic cart, the core lab may request repeated studies on the "standard subject." Furthermore, if new equipment (metabolic cart or ergometer) is obtained, repeat qualification testing must be completed.

For a normal subject, VO_2 should increase at a rate of approximately 10 ml/min/watt on a treadmill ergometer. For sites that do not meet these standards, step-by-step review of each part of the exercise test, including treadmill belt speed and angle, calibration, review of potential air leaks and verification that the metabolic cart was working properly will be performed. If further quality assurance tests are required, they should be labelled alphabetically.

6.0 GENERAL INFORMATION ABOUT CPET PROCEDURES FOR STUDY PURPOSES

***If shared with patients, the below must be approved by IRB/EC/CA and translated into local language.**

Exercise Test (CPET):

- You will have a mouthpiece in place that will enable us to measure the amount of oxygen that your body uses during exercise
- You will begin with a 5-minute period of rest with the mouthpiece in place
- The treadmill will begin slowly and gradually increase its speed or the cycle will be easy to pedal then become more difficult
- You will exercise for as long as possible
- We will measure your blood pressure periodically
- You will continue to be monitored with the mouthpiece in place for 5 minutes after exercise

Pre-test instructions:

- Do not have anything to eat for 4 hours before the exercise test.
- **At Screening**, continue to take your regularly scheduled medications, especially beta-blockers, as normal.
- **At Week 24**, continue to take your regularly scheduled medications except for the trial drug. This will be taken on site.
- You may continue your usual routine of drinking coffee or tea
- Avoid medications that can make you drowsy within 8 hours prior to the test
- Wear loose fitting, comfortable clothing that will permit you to move your legs freely
- Wear athletic shoes appropriate for exercise
- Do not engage in strenuous exercise on the day prior to the test
- Do not exercise at all within 12 hours prior to the test

7.0 PROTOCOL SPECIFIC WORKSHEETS

7.1 SITE QUALIFICATION TREADMILL WORKSHEET

Qualification Testing, Normal Subject TREADMILL testing

Cardiopulmonary Exercise Worksheet
Referring Center Name and Number: _____
PI Name: _____
Date, Time, Study description (A or B): _____
Gas Exchange Equipment and Software Manufacturer: _____

Elapsed Time (min)	Work Rate (Increase 20W/min)	Grade (%)	Speed (mph)	HR (bpm)	O_2 sat (%)	SBP (mmHg)	DBP (mmHg)
-1 (Pre)	Rest	0	0				
0-5	Rest	0	0				
5-8	10	4	0.8				
8-9	30	9.5	1.1				
9-10	50	12.5	1.3				
10-11	70	14.5	1.6				
11-12	90	16.5	1.8				
12-13	110	17.5	2.1				
13-14	130	18.5	2.3				
14-15	150	19	2.6				
15-16	170	20	2.8				
16-17	190	20.5	3.1				
17-18	210	21	3.3				
18-19	230	21.5	3.5				
19-20	250	22	3.7				
20-21	270	22.5	3.9				
21-22	290	23	4.1				
>22		↑0.5/min	↑0.2/min				
Peak time: ____							
Rec. 1 min	10	0	1.1				
Rec. 2 min	Rest	0	0				
Rec. 3 min	Rest	0	0				
Rec. 4 min	Rest	0	0				
Rec. 5 min	Rest	0	0				

*Recordings should be made during the last 15 sec of each minute

7.2 Site Qualification Cycle Worksheet

Qualification Testing, Normal Subject Cycle testing

Qualification Testing, Normal Subject, CYCLE ERGOMETRY
Referring Center Name and Number: _____
PI Name: _____
Date, Time, Study description (A or B): _____
Gas Exchange Equipment and Software Manufacturer: _____
Rec. indicates recovery, W indicates watts, HR indicates heart rate, SBP indicates systolic blood pressure, DBP indicates diastolic blood pressure.

Elapsed Time (min)	Work Rate Increase at 20 W/min	RPM (min^{-1})	HR	O_2 sat (%)	SBP (mmHg)	DBP (mmHg)
-1 (Pre)	Rest	0				
0-5	Rest	0				
5-8	0 (unloaded)	60				
8-9	20	60				
9-10	40	60				
10-11	60	60				
11-12	80	60				
12-13	100	60				
13-14	120	60				
14-15	140	60				
15-16	160	60				
16-17	180	60				
17-18	200	60				
18-19	220	60				
19-20	240	60				
20-21	260	60				
21-22	280	60				
>22	+20/min	60				
Peak time: _____	**W_____**					
Rec. 1 min		60				
Rec. 2 min		0				
Rec. 3 min		0				
Rec. 4 min		0				
Rec. 5 min		0				

***Recordings should be made during the last 15 sec of each minute**

7.3A TREADMILL WORKSHEET FOR SEQUOIA-HCM SUBJECTS ≤ 80 KG

Complete for each subject and send to MGH Core Laboratory with Gas exchange tabular data

Treadmill EXERCISE DATA WORKSHEET			
Site Name and Number:		Most recent Hemoglobin	
Subject ID:		Testing Timepoint:	
Date of exercise:		Start Time of exercise:	
Technician of record:			
Reason for cessation of Exercise:			
Did patient fast for 4 hours prior to CPET?		☐Yes	☐ No**
Did patient continue usual medication routine, especially beta-blockers?		☐Yes	☐ No**
Did patient avoid medications that may cause drowsiness within 8 hours prior to the CPET?		☐Yes	☐ No**
Did patient abstain from strenuous exercise in the 24 hours prior to the CPET?		☐Yes	☐ No**
At Week 24, did patient take IP per protocol instructions?		☐Yes	☐ No**

Elapsed Time (min)	Work Rate ≈15W/min (W)	Speed (mph)	Grade (%)	HR (bpm)	O_2 sat (%)	SBP (mmHg)	DBP (mmHg)
-1 (Pre)	Rest	0	0				
0-5	Rest	0	0				
5-8	5	0.8	2				
8-9	15	1.2	5				
9-10	30	1.5	7				
10-11	45	1.7	9				
11-12	60	1.9	10				
12-13	75	2.1	11				
13-14	90	2.3	12				
14-15	105	2.5	13				
15-16	120	2.6	14				
16-17	135	2.8	14.5				
17-18	150	3	15				
18-19	165	3.2	15.5				
19-20	180	3.4	15.9				
20-21	195	3.6	16.3				
21-22	210	3.8	16.7				
22-23	225	4	17.1				
23-24	240	4.2	17.4				
24-25	255	4.4	17.7				
>25		+0.2/min	+0.3/min				
Peak time _____	**W_____**						
Rec 1min	5	1.0	0				
Rec.2min	0	rest	0				
Rec 3min	0	rest	0				
Rec 4min	0	rest	0				
Rec 5min	0	rest	0				

***Recordings should be made during the last 15 sec of each minute**
**if no, CPET must be rescheduled

7.3B TREADMILL WORKSHEET FOR SEQUOIA-HCM SUBJECTS > 80 KG

Complete for each subject and send to MGH Core Laboratory with Gas exchange tabular data

Treadmill EXERCISE DATA WORKSHEET		
Site Name and Number:	Most recent Hemoglobin	
Subject ID:	Testing Timepoint:	
Date of exercise:	Start Time :	
Technician of record:		
Reason for cessation of exercise:		
Did patient fast for 4 hours prior to CPET?	☐Yes	☐ No**
Did patient continue usual medication routine, especially beta-blockers?	☐Yes	☐ No**
Did patient avoid medications that may cause drowsiness within 8 hours prior to the CPET?	☐Yes	☐ No**
Did patient abstain from strenuous exercise in the 24 hours prior to the CPET?	☐Yes	☐ No**
At Week 24, did patient take IP per protocol instructions?	☐Yes	☐ No**

Elapsed Time (min)	Work Rate ≈15W/min (W)	Speed (mph)	Grade (%)	HR (bpm)	O_2 sat (%)	SBP (mmHg)	DBP (mmHg)
-1 (Pre)	Rest	0	0				
0-5	Rest	0	0				
5-8	5	0.7	1.4				
8-9	16	1.3	3.0				
9-10	24	1.6	4.3				
10-11	36	1.9	5.3				
11-12	44	2.2	6.0				
12-13	50	2.5	6.5				
13-14	60	2.8	7.0				
14-15	70	3.0	7.5				
15-16	82	3.2	8				
16-17	90	3.4	8.4				
17-18	98	3.6	8.8				
18-19	111	3.8	9.2				
19-20	125	4	9.6				
20-21	140	4.2	10				
21-22	155	4.4	10.3				
22-23	164	4.6	10.5				
23-24	181	4.8	10.7				
24-25	191	5.0	10.9				
>25		+0.2/min	+0.5/min				
Peak time:_____	**W_____**						
Rec. 1 min	5	1.1	0				
Rec. 2 min	rest	0	0				
Rec. 3 min	rest	0	0				
Rec. 4 min	rest	0	0				
Rec. 5 min	rest	0	0				

***Recordings should be made during the last 15 sec of each minute**

**if no, CPET must be rescheduled

7.4 Cycle 15 Ramp Worksheet for SEQUOIA-HCM Subjects

Complete for each subject and send to MGH Core Laboratory with Gas exchange tabular data

*Recordings should be made during the last 15 sec of each minute

CYCLE EXERCISE DATA WORKSHEET			
Site Name and Number:		Most recent Hemoglobin	
Subject ID:		Testing Time point:	
Date and time at start of exercise:		Seat Height	
Technician of record:		FEV1/FVC	
Reason for cessation of exercise:			
Did patient fast for 4 hours prior to CPET?		☐Yes	☐ No**
Did patient continue usual medication routine, especially beta-blockers?		☐Yes	☐ No**
Did patient avoid medications that may cause drowsiness within 8 hours prior to the CPET?		☐Yes	☐ No**
Did patient abstain from strenuous exercise in the 24 hours prior to the CPET?		☐Yes	☐ No**
At Week 24, did patient take IP per protocol instructions?		☐Yes	☐ No**

Elapsed Time(min)	Work Rate Increase 15 W/min	Target Pedal Rate (rpm)	Actual Pedal Rate (rpm)	HR (bpm)	O_2 sat (%)	SBP (mmHg)	DBP (mmHg)
-1 (Pre)	Rest	0					
0-5	Rest	0					
5-8	0	60					
8-9	15	60					
9-10	30	60					
10-11	45	60					
11-12	60	60					
12-13	75	60					
13-14	90	60					
14-15	105	60					
15-16	120	60					
16-17	135	60					
17-18	150	60					
18-19	165	60					
19-20	180	60					
20-21	195	60					
21-22	210	60					
22-23	225	60					
23-24	240	60					
24-25	255	60					
>25	15/min	60					
Peak time:_____	**W_____**						
Rec. 1 min	0	60					
Rec. 2 min	rest	0					
Rec. 3 min	rest	0					
Rec. 4 min	rest	0					
Rec. 5 min	rest	0					

Recordings should be made during the last 15 sec of each minute*if no, CPET must be rescheduled

8.0 CPET LAB CHECKLISTS

8.1 SITE QUALIFICATION PROCEDURES CHECKLIST

☐ Verify your site's compliance with equipment requirements and calibration procedures.

☐ Accept emailed invitation from Massachusetts General Hospital CPET Core Laboratory to join the Mass General Brigham Secure File Transfer Service (see Section 4 for detailed instructions).

☐ Submit two incremental symptom-limited CPET qualifying tests on the same "standard normal subject," using the Certification data worksheet, (Section 7.0, page 19, 20) via the Mass General Brigham Secure File Transfer Service.

8.2 CPET PROCEDURES CHECKLIST

☐ Print and distribute patient education form (Section 6.0) to subjects at least 48 hours prior to testing and assess compliance with instructions upon the subject's arrival to the laboratory.

☐ Obtain the subject's study ID number from your site's research coordinator.

☐ Assess CPET contraindications (Table 2, page 8).

☐ Configure gas exchange data output according to Table 6, page 14.

☐ Enter current hemoglobin level into CPET electronic file or data supplemental sheet.

☐ Complete CPET according to the appropriate protocol (Sections 3 and 7), integrate all study data into a single CPET file and name the file according to Section 4.1.

☐ Save a backup copy of the CPET file on a disk that will be maintained in individual CPET laboratories and transmit the electronic file to the core laboratory.

☐ Transmit data file to the core laboratory and await a CPET eligibility status email from the MGH Core Laboratory. Do not randomize until CPET eligibility is confirmed by the MGH Core laboratory. See Appendix II for sample emails. File email appropriately in site binder.

Subjects are eligible if they reach a RER $\geq$ 1.05 and a peak VO_2 <90% predicted.

9.0 SEQUOIA-HCM CPET CORE LABORATORY PERSONNEL

Primary Contact:

Core Laboratory Coordinator	Diane Cocca-Spofford BSN, MHA Tel: 617-726-8228 E-mail: dcoccaspofford@mgh.harvard.edu
Mailing Address:	MGH Core CPET Laboratory GRB 800, Cardiology Division Massachusetts General Hospital 55 Fruit St, Boston, MA 02114
MGH CPET Core Laboratory	Email: **cpetcore@partners.org**

Additional Laboratory Personnel Contact Information

Core Laboratory Director	Gregory D. Lewis MD Tel: 617-724-6158 Email: glewis@partners.org
Core Laboratory Chief Technician and Data Analyst	Shaina McGinnis Email: slmcginnis@mgh.harvard.edu
Core Laboratory Data Analytics Staff	Kailin Chen Email: kchen33@mgh.harvard.edu Catharine Griskowitz Tel: 617-726-5052 Email: cgriskowitz@mgh.harvard.edu Ilya Giverts Email: igiverts@mgh.harvard.edu

10.0 APPENDIX I: SAMPLE SITE QUALIFICATION RESPONSE LETTERS

10.1 SAMPLE CERTIFICATION LETTER

HARVARD
MEDICAL SCHOOL

MGH CPET Core Laboratory
Bigelow 800, 55 Fruit Street
Boston, Massachusetts 02114
Tel: 617.724-9254, Fax: 617.724-4105
Email: cpetcore@partners.org

Gregory D. Lewis, M.D.
Section Head, Heart Failure
Medical Director, Heart Transplantation
Director, MGH CPET Laboratory
Cardiology Division and Pulmonary Unit

Oct 31, 2022
Site X CPET Lab Certification

Dear Site X SEQUOIA-HCM Team,

I am pleased to inform you that the MGH Cardiopulmonary Exercise Testing (CPET) Core Laboratory has certified your site to perform Cardiopulmonary Exercise Tests for the SEQUOIA-HCM Trial. In preparation for conducting CPETs for the trial please review the specific comments below related to your qualification tests.

Your laboratory successfully completed two incremental CPETs on 26 Oct 2020 and 27 Oct 2020 that were submitted via the Mass General Brigham Secure File Transfer Service on 27 Oct 2020. The two studies demonstrate close adherence to the specified protocol in the CPET Manual of Operations. The test subject demonstrated normal resting values for gas exchange variables.

These certification tests exhibit consistency in peak gas exchange variables. There is a 7% variance in peak VO_2 (35.4 ml/kg/min vs. 37.9 ml/kg/min), 8% variance in ventilatory efficiency (25.12 vs 27.24), 4% variance in peak RER (1.16 vs. 1.18), 2% variance in peak workload (248 watts vs. 254 watts) and 3% variance VO_2/work slopes (10.2 ml/watt vs. 10.5 ml/watt). Please review the following finding:

1. **Reason for Cessation:** For trial tests, please indicate the reason for cessation of exercise (most commonly shortness of breath or leg fatigue). This can be written on the supplemental datasheet for the test or sent alongside the primary data file.

Overall, the transmitted data reflects appropriate adherence to the SEQUOIA-HCM CPET protocol and indicates your laboratory's readiness to begin testing for the SEQUOIA-HCM trial. I would like to thank you for completing the certification process and your attention to detail in doing so. Please don't hesitate to contact our core laboratory team with questions.

Sincerely,
Gregory D. Lewis MD

10.2 SAMPLE RETEST LETTER

MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

MGH CPET Core Laboratory
Bigelow 800, 55 Fruit Street
Boston, Massachusetts 02114
Tel: 617.724-9254, Fax: 617.724-4105
Email: cpetcore@partners.org

Gregory D. Lewis, M.D.
Section Head, Heart Failure
Medical Director, Heart Transplantation
Director, MGH CPET Laboratory
Cardiology Division and Pulmonary Unit

Feb 19, 2022
Site X CPET Lab Certification

Dear Site X SEQUOIA-HCM Team,

Thank you for performing qualification cardiopulmonary exercise tests (CPETs) for the SEQUOIA-HCM Trial. Based on the tests received, it will be necessary for your site to perform further qualification testing in order to be certified to perform CPETs for the SEQUOIA-HCM Trial. In preparation for conducting this further qualification testing, please review the specific comments below.

Your laboratory successfully completed two incremental CPETs on 14 Feb 2020 and 16 Feb 2020 that were submitted via the Mass General Brigham Secure File Transfer Service on 16 Feb2020.

The test subject demonstrated normal resting values for gas exchange variables. Additionally, these certification tests meet criteria for maximum volitional effort and exhibit consistency in peak gas exchange variables. There is a 9% variance in peak VO_2 (27.9 ml/kg/min vs. 30.4 ml/kg/min), 1% variance in ventilatory efficiency (27.5 vs 27.1), 3% variance in peak RER (1.04 vs. 1.01), 8% variance in peak workload (216 watts vs. 234 watts) and 9% variance in VO_2/work slopes (5.7 ml/watt vs. 5.2 ml/watt).

However, these certification tests did not include the 3 minutes warm up period as specified in the CPET MOP. Additionally, the aerobic efficiencies exhibited in these tests are below the expected physiologic range of 10.0±1.5 ml/watt. One further qualification test is requested to assure that the proper protocol is followed.

We look forward to receiving further qualification testing and completing the certification process. Please don't hesitate to contact our core laboratory team with questions.

Sincerely
Gregory D. Lewis MD

11.0 APPENDIX II: SAMPLE SUBJECT ELIGIBILITY AND INELIGIBILITY EMAILS

11.1 SAMPLE SUBJECT ELIGIBILITY EMAIL

Hello Site X SEQUOIA-HCM team,

We are pleased to inform you that subject 6031-000001-001-SCR meets CPET eligibility criteria for the SEQUOIA-HCM Trial based on:

1. Peak VO2 = 16.6 (<90% of predicted)
2. Peak RER = 1.14 (≧1.05)

Please share this information with anyone on your team who is not included on this email.

Best,

MGH Core Lab Member

Print this document and file with your study documents

11.2 SAMPLE SUBJECT INELIGIBILITY EMAIL

Hello Site X SEQUOIA-HCM team,

We regret to inform you that subject 6031-000001-001-SCR does not meet CPET eligibility criteria for the SEQUOIA-HCM Trial based on the following:

1. Peak VO2 = 16.6 (≤90% of predicted)
2. Peak RER = 0.90 (≤1.05)

Please share this information with anyone on your team who is not included on this email.

Best,

MGH Core Lab Member

Print this document and file with your study documents

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