HCMR Re-Imaging Study
Unique Protocol Identification Number:
National Clinical Trial (NCT) Identified Number:
Principal Investigator: Christopher Kramer
IND/IDE Sponsor:
Funded by: Cytokinetics
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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

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STATEMENT OF COMPLIANCE

Provide a statement that the trial will be conducted in compliance with the protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP) and applicable state, local and federal regulatory requirements. Each engaged institution must have a current Federal-Wide Assurance (FWA) issued by the Office for Human Research Protections (OHRP) and must provide this protocol and the associated informed consent documents and recruitment materials for review and approval by an appropriate Institutional Review Board (IRB) or Ethics Committee (EC) registered with OHRP. Any amendments to the protocol or consent materials must also be approved before implementation. Select one of the two statements below. If the study is an ***intramural*** *NIH study, use the second statement below:*

1. The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

    - United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

    National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.
    OR
2. The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the [specify NIH Institute or Center (IC) [Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), and the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, if applicable, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.
    For either option above, the following paragraph would be included:
    The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	HCMR Re-Imaging Study	
Study Description:		
Objectives:	Primary Objective:	To assess the change in biomarkers and CMR parameters including LV mass, maximal wall thickness, and LGE extent from baseline over a minimum of 7 years of follow-up extent in HCM patients who would have been candidates for clinical trials of aficamten.
	Secondary Objectives:	
Endpoints:	Primary Endpoint:	% LGE mass
	Secondary Endpoints:	LV mass, end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), ejection fraction (EF), and LV mass index (I), EDVI, ESVI, SVI RV EDV, ESV, SV, EF, EDVI, ESVI, SV, EF Maximal wall thickness LV and RV longitudinal, circumferential, and radial strain LGE – presence, mass T1 – regional and global Extracellular volume – regional and global LA volume, LAVI, and LA strain

Study Population:	Within the HCMR original cohort who have 1. Obstructive HCM and • BMI < 35 kg/m2 • LVOT-G at entry as follows: Resting gradient ≥50 mmHg OR Resting gradient ≥30 mmHg and <50 mmHg with post-Valsalva LVOT-G ≥50 mmHg NYHA Class II or III or 2. Nonobstructive HCM Same criteria as above except resting LVOT-G is <30mmHg and post-Valsalva gradient <50mm Hg • BMI <40kg/m2 • Elevated NT-proBNP > 300 pg/mL at the time of enrollment • LVEF ≥55%
Phase:	Observational
Description of Sites/Facilities Enrolling Participants:	Selected from original HCMR sites in the U.S. and U.K.
Description of Study Intervention:	Observational only. No intervention
Study Duration:	1 year
Participant Duration:	One visit

1.2 SCHEMA

1.3 SCHEDULE OF ACTIVITIES (SOA)

Study visit Day	Informed consent
	Medical history and medication review
	Vital signs
	Brief physical exam
	Cardiac MRI with and without gadolinium contrast
	Blood draw for biomarkers

2 INTRODUCTION

2.1 STUDY RATIONALE

A meta-analysis of 5 pooled studies and 2993 patients followed for a median of 3 years has demonstrated that after adjusting for baseline characteristics, the extent of late gadolinium enhancement (LGE) was associated with SCD (1.36 for every 10% increase in LGE as % of LV mass). HCMR data already show a primary event rate of 4% in patients with >10% LGE, 1.3% in patients with 1-10% LGE, and 0.4% in those without LGE. It is this type of observation that underscores the power of this cohort. Two small studies have shown progression of LGE in patients with HCM, primarily in patients with greater hypertrophy and LGE at baseline and progression is associated with a decline in ejection fraction, heart failure hospitalizations, and arrhythmias.[7,8]

2.2 BACKGROUND

Hypertrophic cardiomyopathy (HCM) has a prevalence of between 1 in 200 and 1 in 500 in the general population and is the most common monogenic heart disease. It is characterized by unexplained left ventricular hypertrophy (LVH), diffuse and patchy fibrosis, and myofibrillar disarray[1, 2]. It is an important cause of sudden cardiac death (SCD) in young individuals[3]. While many patients experience a mild clinical course, cumulative disease burden is considerable and most will experience complications, particularly heart failure (HF) or atrial fibrillation (AF)[4]. Accurately predicting prognosis and stratifying risk are important unmet clinical needs[5]. Risk scores to predict SCD using demographic, clinical, and echocardiographic markers have been developed[9] and tested[10]. However, existing risk scores fail to precisely predict risk. Furthermore, based on current guideline-based risk assessment, most patients will be deemed to be at low or intermediate risk, and yet most events occur in these patients[10, 11].
Identifying novel risk markers is required to improve upon present models. In addition, updated predictive models that focus on other clinically relevant endpoints that can be intervened upon, e.g. HF and AF, will advance the field and improve patient care. Previously available medical therapy for HCM focuses on symptom palliation and does not alter the natural history, protect against SCD, or prevent the development of AF or HF. However, novel disease-modifying therapies are now available[12].
Therefore, creating a new prognostic model will identify patients at increased risk for SCD, AF or HF, and will foster the evaluation of novel therapeutic strategies aimed at altering phenotypic expression and natural history. In turn, this would lead to improved survival and quality of life and reduced healthcare costs in HCM.
Our group has set out to redefine risk markers for critical cardiovascular outcomes in HCM through *HCMR, Novel Markers of Prognosis in Hypertrophic Cardiomyopathy*, U01HL117006-01A1.[6] In this unique and carefully designed study, we have recruited 2750 patients from 44 sites in 6 countries and collected comprehensive demographic, clinical, imaging, biomarker, and genetic data from each. This is the largest systematic prospective study of this disease performed to date. Recruitment was completed in

April 2017. To date, mean follow-up is at 6.3 years. Baseline data analysis was completed and published.[13] The principal findings are summarized in the Figure below.

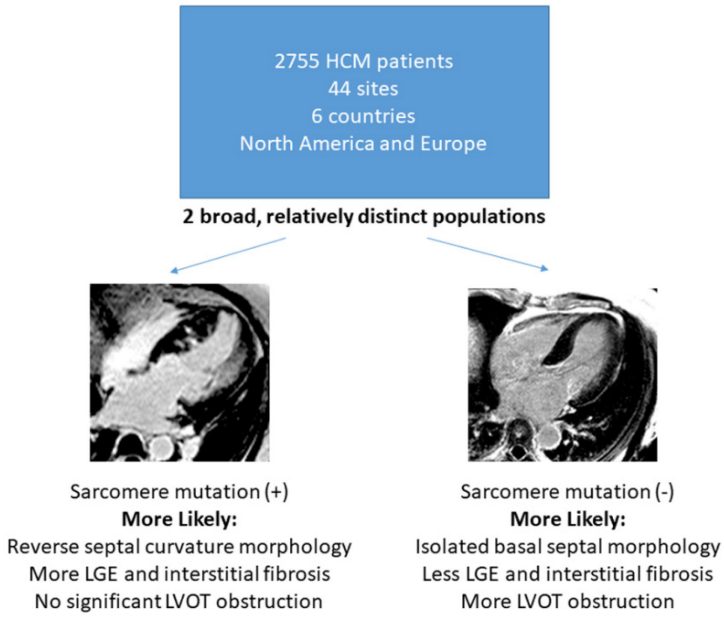

Figure Legend: 2755 patients from 44 sites in 6 countries were recruited. Two relatively distinct populations were identified as depicted. Left – 4 chamber inversion recovery gradient echo LGE image in a patient with reverse curvature asymmetric septal hypertrophy. Patchy LGE is noted in mid-septum. Right – similar orientation and image type in a patient with reverse curvature asymmetric septal hypertrophy. No LGE is noted. One group was sarcomere mutation positive, and more likely had reverse septal curvature morphology, more fibrosis, and less obstruction whereas the other was sarcomere mutation negative, and more likely had isolated basal septal hypertrophy with obstruction and less fibrosis.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Blood Draw and IV placement

The risk of IV line placement and blood draw are of bruising, bleeding, and local infection. A vagal reaction and fainting due to either procedure is quite rare (<1%).

CMR

CMR uses strong magnetic fields to obtain images. During the switching (slewing) of the magnetic fields, the MR scanner makes loud banging sounds that may cause discomfort to patients being scanned. Earplugs will be provided to minimize this discomfort. In addition, the switching of the magnetic field gradients can, under some circumstances, cause peripheral nerve stimulation, which may be

experienced as a mild twitching reaction in certain muscles. Such effects are rare and the switching rates are kept well below the levels where such effects are known to occur frequently. All magnetic field gradient slewing will be within FDA-approved parameters and have not been reported to have adverse health effects. To generate MR images, radio waves are used that can cause a mild warming sensation similar to exposure to hot weather or tanning on the beach. Body temperature may increase slightly (less than 1°C). The total CMR scanning protocol will be accomplished within 60 minutes. ECG leads or fiber-optic detectors will be placed on the subject's body to obtain a triggering signal for the purpose of cardiac gating. ECG leads under very rare circumstances have caused local skin irritation during MR scans. The technical staff has been trained as per standard-of-care to place leads in such a manner as to avoid such burns. There are risks of IV catheter placement that include tenderness, swelling, warmth at the injection site, extravasation of the contrast agent and, rarely, infection. Should the patient experience any of the above discomfort to an intolerable degree, the CMR examination can and will be stopped at any time upon the request of the subject.

Gadolinium

There are rare reports of allergies to gadolinium. With the use of cyclic gadolinium chelates, nephrogenic systemic fibrosis, which was reported with linear chelates before 2010, is no longer an issue. All of the patients recruited will have received gadolinium with their intake CMR in HCMR and have not had a problem with it. Gadolinium is xx in pregnancy

2.3.2 KNOWN POTENTIAL BENEFITS

There are no definite benefits of participating in this study. However, the patient's physician may receive information from the CMR that may be of benefit in the patient's care.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risks of this study are extremely low as are the potential benefits.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To assess the change in LGE extent from baseline over a minimum of 7 years of follow-up extent in HCM patients who would have been candidates for clinical trials of aficamten.	Change in % LGE mass	LGE extent is a risk factor for SCD. The progression of LGE over time is incompletely understood.
Secondary		
To assess the change in CMR parameters including LV mass, volumes, and maximal wall thickness, from baseline over a minimum of 7 years of follow-up extent in HCM patients who would have been candidates for clinical trials of aficamten.	LV mass, end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), ejection fraction (EF), and LV mass index (I), EDVI, ESVI, SVI RV EDV, ESV, SV, EF, EDVI, ESVI, SV, EF Maximal wall thickness LV and RV longitudinal, circumferential, and radial strain LGE – presence, mass T1 – regional and global Extracellular volume – regional and global LA volume, LAVI, and LA strain	Prior f/u CMR studies in HCM are short-term and with a small n. This would be the largest f/u study to date with the largest n.
Tertiary/Exploratory		
To assess the change in biomarkers from baseline over a minimum of 7 years of follow-up extent in HCM patients who would have been candidates for clinical trials of aficamten.	NTproBNP and hsTNT and change in these measures from baseline	Changes in biomarkers over time are also important to understand in HCM

4 STUDY DESIGN

4.1 OVERALL DESIGN

A total of 314 patients from 9 sites (187 with oHCM, 127 with nHCM) will be approached to consent for re-imaging and repeat blood draw. Patients will be approached by the individual site PI and/or CRC and all studies will be performed at that site. Patients who consent will undergo a repeat CMR with similar a protocol to that performed as per the initial study in 2014-17. The only substitution would be a wideband sequence for LGE imaging in patients with devices, as available.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This would represent the largest f/u CMR study to date in HCM and the largest n.

4.3 JUSTIFICATION FOR DOSE

n/a

4.4 END OF STUDY DEFINITION

When the last patient has had a study visit for CMR and blood draw

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Patients in the original HCMR cohort with:

1) Obstructive HCM

- Males and females between 18 and 65 years of age
- BMI < 35 kg/m2
- LVOT-G at entry as follows:

Resting gradient ≥50 mmHg OR
Resting gradient ≥30 mmHg and <50 mmHg with post-Valsalva LVOT-G ≥50 mmHg

- NYHA Class II or III

or

2) Non-obstructive HCM

- Same criteria as above except resting LVOT-G is <30mmHg and post-Valsalva gradient <50mm Hg

- BMI <40kg/m2
- Elevated NT-proBNP > 300 pg/mL at the time of enrollment
- LVEF ≥55%

5.2 EXCLUSION CRITERIA

- Paroxysmal atrial fibrillation or flutter documented prior to entry.
- Paroxysmal or permanent atrial fibrillation requiring rhythm restoring treatment (eg, direct-current cardioversion, ablation procedure, or antiarrhythmic therapy) ≤6 months prior to entry. (This exclusion does not apply if atrial fibrillation has been treated with anticoagulation and adequately rate-controlled for >6 months.)

- History of syncope or sustained ventricular tachyarrhythmia with exercise within 6 months prior to entry.
- Pregnancy due to potential risk of gadolinium to the fetus
- Patients with a pacemaker that are pacer-dependent as they cannot undergo MRI

5.3 LIFESTYLE CONSIDERATIONS

n/a

5.4 SCREEN FAILURES

Patients who have died or been lost to follow-up since entry into the original study

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Phone calls to prospective patients will be made by site study coordinators who have been in touch with these same patients through the original HCMR study. All studies will be performed at the site that the patient was enrolled at in the original HCMR study.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

A limited physical examination will be performed including heart rate and blood pressure
Results of recent testing will be recorded including ECG, exercise testing, Holter monitoring, and echocardiography.

- **Intravenous access will be obtained**
- **Blood draw (80 cc or approximately 5 tbsp.) for biomarkers, specimen banking and Hematocrit. No genetic testing will be performed.**

Blood (80 cc or approximately 5 tablespoons) will be collected by peripheral venipuncture at enrollment as a source of serum and plasma for biomarker analysis. Fasting samples are requested but if this is not possible logistically, non-fasting samples can be acquired and noted as such.

A urine sample will be collected, as applicable, to determine pregnancy status.

Full details of the protocol will be in the Blood Draw Manual

- **CMR**

A CMR will be performed and will take approximately one hour. 0.15mM of gadolinium contrast will be infused through an intravenous line during the MRI.
Full details of the protocol will be in the Imaging Manual.

6.1.2 DOSING AND ADMINISTRATION

n/a

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

n/a

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

n/a

6.2.3 PRODUCT STORAGE AND STABILITY

n/a

6.2.4 PREPARATION

n/a

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

n/a

6.4 STUDY INTERVENTION COMPLIANCE

n/a

6.5 CONCOMITANT THERAPY

6.5.1 RESCUE MEDICINE

n/a

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

n/a

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

The patients are able to withdraw from the study at any point in time.

7.3 LOST TO FOLLOW-UP

Patients lost to f/u will be accounted for. They will be considered lost to follow-up if they do not respond to 3 phone calls and a certified letter. Should there be substantial losses additional sites can be added, as only a fixed number of patients per site can be recruited based on the strict entry criteria.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

n/a. No therapy is being studied and thus efficacy is not addressed.

8.2 SAFETY AND OTHER ASSESSMENTS

The patient will be monitored by MRI staff and the CRC during the CMR from the control room. Blood pressure and heart rate will be monitored during the MRI. A few patients will have devices (pacer or implantable cardioverter-defibrillator) and this will increase the needed ECG monitoring by device nurse or MRI staff. These devices will need to be interrogated by a device nurse prior to the MRI scan, adjusted to the proper setting for MRI, and then reset after the scan.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

AN AE IS ANY UNTOWARD MEDICAL OCCURRENCE IN A SUBJECT UNDERGOING THE INITIAL STUDY PROCEDURES.8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An SAE is any untoward medical occurrence that:

- Results in death.
- Is life-threatening. Any adverse experience that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that, had it occurred in a more serious form, might have caused death).
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly/birth defect.
- An event that required intervention to prevent permanent impairment or damage..

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

Mild, moderate, severe

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

Related or unrelated to the study

8.3.3.3 EXPECTEDNESS

Expected or unexpected

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

During and immediately after the CMR and blood draw

8.3.5 ADVERSE EVENT REPORTING

Adverse events that are not serious will not be reported in this study.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Adverse events that are deemed to be serious, related and unexpected will be reported to each site's local IRB.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Reporting events to participants will occur on necessary basis.

8.3.8 EVENTS OF SPECIAL INTEREST

n/a

8.3.9 REPORTING OF PREGNANCY

pregnancy testing will be required for women of childbearing potential as pregnant patients will be excluded.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Any other adverse event that is not expected

8.4.2 UNANTICIPATED PROBLEM REPORTING

To the IRB

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

As necessary

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

n/a

- Secondary Efficacy Endpoint(s):

9.2 SAMPLE SIZE DETERMINATION

n/a

9.3 POPULATIONS FOR ANALYSES

All patient data collected

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

CMR, echocardiographic parameters and biomarkers will be described by means and standard deviations, medians and interquartile ranges for continuous variables, minimum and maximum values and counts and percentages for categorical variables.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Change from baseline to follow-up CMR, echocardiographic and biomarkers will be described by absolute difference (follow-up value minus baseline value) and percent change from baseline((follow-up value – baseline value)/baseline value x 100). Associations with baseline values will be examined.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The association between changes in collected CMR, echocardiography and biomarker measures and clinical outcomes (as collected as part of the HCMR study) will be examined.

9.4.4 SAFETY ANALYSES

n/a

9.4.5 BASELINE DESCRIPTIVE STATISTICS

CMR, echocardiographic parameters and biomarkers will be described by means and standard deviations, medians and interquartile ranges for continuous variables, minimum and maximum values and counts and percentages for categorical variables.

9.4.6 PLANNED INTERIM ANALYSES

n/a

9.4.7 SUB-GROUP ANALYSES

n/a

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

n/a

9.4.9 EXPLORATORY ANALYSES

n/a

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

To be performed by PI or research coordinator. All questions will be answered and concerns will be addressed. Each subject will receive a copy of the signed consent form. Consent will be documented as completed in local EMR system used.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

By PI or CRC

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Consent will be obtained and signatures documented

10.1.2 STUDY DISCONTINUATION AND CLOSURE

n/a

10.1.3 CONFIDENTIALITY AND PRIVACY

All patient data will be de-identified and their previous site-specific code will be applied to imaging data and blood samples. All will be HIPPAA compliant.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Biomarker specimens will be stored at the Brigham and Women's Core laboratory for potential future biomarker analysis

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Christopher M. Kramer MD (overall PI) University of Virginia Health, ckramer@virginia.edu	
Stefan Neubauer MD (co-PI) University of Oxford, Stefan.Neubauer@cardiov.ox.ac.uk	
Carolyn Ho MD (biomarker core lab director) Brigham and Women’s Hospital, cho@bwh.harvard.edu	
Raymond Kwong MD, (CMR core lab director) Brigham and Women’s Hospital, rykwong@partners.org	
William Weintraub MD, (data coordinating center) MedStar Research Institute, william.s.weintraub@medstar.net	

10.1.6 SAFETY OVERSIGHT

By the overall PI's and site PI's

10.1.7 CLINICAL MONITORING

Will be performed by site CRC's during the blood draw and MRI as described above. The CRC will be observing the subject during and immediately after the blood draw. The CRC will be present in the MRI control room and will monitor the vital signs (BP and HR) at least twice during the scan.
Medstar will monitor incoming data on a regular basis for queries and clarification of data. Brigham and Women's will be responsible for reviewing image quality

10.1.8 Quality Assurance and Quality Control
Each site will ensure quality of CMR acquisition. UVA site investigator will review MRI images before the patient is taken off the scanner to ensure adequate image quality. After images are sent to the core lab at Brigham and Women's Hospital, CMR quality will be assessed by Raymond Kwong MD and core lab assistants).

Data will be evaluated for compliance with protocol and accuracy in relation to source documents. The study will be conducted in accordance with procedures identified in the protocol.

Each site will use their individual SOPs at all clinical and laboratory sites. Regular monitoring and an independent audit will be performed according to GCP/ICH (e.g., data monitoring).

Medstar will assure protocol compliance, ethical standards, regulatory compliance, data quality and proper storage and handling of samples at each site.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

By site PI and CRC's. CRC's will be responsible for sending CMR to the Brigham core lab and blood specimens to the Brigham core lab. Imaging and biomarker data will be analyzed at the respective core labs. They will in turn send data to the Data Coordinating Center at MedStar Research Institute where statistical analysis will be performed. All patient data will be collected via source documentation on site by the CRC and sent to Medstar in a manner compliant with the current institutional and local regulations.

10.1.9.2 STUDY RECORDS RETENTION

By site for 5 years

10.1.10 PROTOCOL DEVIATIONS

Reported to IRB

10.1.11 PUBLICATION AND DATA SHARING POLICY

Publication will be overseen by the HCMR Executive Committee. Data will be shared as abstracts and manuscripts as it becomes available.

10.1.12 CONFLICT OF INTEREST POLICY

The Executive Committee will track any COI by its members and site PI's.

10.2 ADDITIONAL CONSIDERATIONS

n/a

10.3 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure

ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	**Date**	**Description of Change**	**Brief Rationale**
1.0	1/13/25	N/A	
2.0	2/6/25	• Added missing physical exam, vital signs, medical history and medication review to study visit. • Updated eligibility to exclude those that are currently pregnant.	IRB Compliance Reviewer requests

		• Clarified amount of blood drawn • Clarified that there is no genetic testing in this study. • Clarified when subjects would be considered “Lost to Follow Up” • Added details to adverse events and serious adverse events section • Added details to consent procedures and documentation. • Clarified that data is coded and de-identified. • Added personnel and information regarding key roles and study governance. • Added additional information about clinical monitoring. • Clarified quality assurance and control. • Updated Data handling and record keeping • Added references	

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