Cardiovascular Inflammation Reduction Trial (CIRT) Inflammation Imaging
Dr. Zahi A. Fayad
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Mount Sinai	Protocol Title:	Cardiovascular Inflammation Reduction Trial (CIRT) Inflammation Imaging Study
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	Date Revised:	March 7, 2019
	Study Number:	GCO# 14-1382; IF2430508; HS# 14-00185

MSSM Protocol Template HRP-503a

Instructions:

1. *Prepare a document with the following sections. Note that, depending on the nature of your research, certain sections below may not be applicable. Indicate N/A as appropriate, explaining where possible.*
2. *For any items described in the sponsor's protocol, grant application or other source documents submitted with the application, you may reference the title and page numbers of these documents rather than cutting and pasting into this document.* ***Do NOT refer to any derived documents, such as the Sample Consent document, or other internal documents required with the submission.***
3. *If you reference page numbers, attach those pages to this protocol.*
4. *When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.*

Brief Summary of Research (250-400 words):

Vascular inflammation, a central feature of atherosclerosis, participates in the initiation, perpetuation and instability of plaques. Multiple clinical trials of cholesterol lowering therapy with statins have demonstrated that reductions in atherosclerotic cardiovascular disease (CVD) events are associated with reductions in both LDL cholesterol (LDL-C) and the systemic inflammatory mediator C-reactive protein (CRP). The Cardiovascular Inflammation Reduction Trial (CIRT) investigates if an anti-inflammatory agent commonly used in rheumatoid arthritis (low dose methotrexate (LDM)) can reduce CV morbidity and mortality among patients with a prior myocardial infarction or angiographically demonstrated multivessel coronary artery disease (GCO#13-1467).

In this ancillary CIRT imaging study, we propose to use this well validated approach by non-invasive serial FDG-PET/CT imaging in a subset of patients enrolled in the main CIRT trial to directly visualize vascular inflammation. Once the subjects are enrolled in the main CIRT trial, baseline imaging will be done and follow up imaging will be done approximately 8 months after the baseline imaging. To clarify, we anticipate on having the randomization visit to follow closely after the baseline imaging visit, which means that subjects will be coming approximately 8 months after the randomization visit in the main CIRT Trial.

^{18}FDG-PET imaging data will be acquired, analyzed centrally and results incorporated into the main CIRT database. We hypothesize that LDM treatment will result in a significant decrease in plaque inflammation as measured by 18-FDG-PET/CT after 8 months as compared to placebo.

1) Objectives:

Research Question:

To determine the impact of anti-inflammatory treatment with LDM on arterial

inflammation, as assessed by FDG-PET/CT imaging in patients with stable coronary artery disease who are at increased risk. We will determine the effect of LDM on the change from baseline in the target (plaque) to background (blood) ratio (TBR) based on 18-FDG uptake measured with PET/CT after 8 months of weekly dosing with LDM (primary endpoint).

To evaluate changes in imaging endpoints in relation to changes in systemic inflammatory biomarkers (especially high sensitivity C-reactive protein (hs-CRP).

2) Background

The NHLBI funded (Ridker 5U01HL101422) Cardiovascular Inflammation Reduction Trial (CIRT) provides a unique opportunity to investigate whether a commonly used anti-inflammatory agent used in rheumatoid arthritis (low dose methotrexate (LDM)) can reduce CVD morbidity and mortality among patients with stable coronary artery disease. CIRT, is a randomized, double-blind, placebo-controlled, multi-center trial among 7,000 men and women with prior myocardial infarction or angiographically demonstrated multivessel coronary artery disease. Eligible participants will be randomly allocated over a three to four year period to usual care plus placebo or usual care plus LDM (average dose of 15-20 mg po/weekly. CIRT proposes that the reduction in CVD events with methotrexate derives from its effect on vascular inflammation, thus it is crucial to incorporate a measure of vascular inflammation imaging for confirmation of the primary mechanism of action underlying CIRT. As such, the direct evaluation of arterial inflammation would enhance the scientific value of the CIRT trial.

The inclusion of the proposed vascular inflammation imaging substudy has widespread implications that will allow this imaging modality to serve as a surrogate measure of disease, and thereby provide an opportunity for stratification in individuals at risk for CVD and evaluation of other interventions with presumed anti-inflammatory effects.

(Please see Protocol NIH CIRT imaging for more details -pages 104).

Current protocol for the Main CIRT trial as well as CIRT imaging sub study are provided as an Appendix

3) Setting of the Human Research

The total study duration is 38-40 weeks which includes a pre-randomization phase (up to 8 weeks), and a double-blind treatment phase (approximately 32 weeks). There will be four imaging centers (Mount Sinai Medical Center, New York, NY, University Health Network, Ontario, Canada, Massachusetts General Hospital, Boston, MA, and University of California San Francisco (UCSF), San Francisco, CA), which will perform all the imaging for the surrounding referring centers. There will be recruiting centers in each region (New York, Toronto, and Boston) for 17 centers in total. For the NY region, the 7 recruiting centers where the subjects will be identified and recruited will be Montefiore Medical Center (Dr. Bortnick-PI), Winthrop University Hospital (Dr. DeLeon - PI), NewYork-Presbyterian Queens (Dr. Ramnauth-PI), Weill Cornell Medical Center (Dr.

Pena-PI), Mount Sinai (Dr. R. Rosenson-PI), University of California San Francisco Medical Center (UCSF) (Dr. P. Hsue-PI), and Clinton, Maryland (Dr. Hakim-PI). For the Boston region, the 5 recruiting centers are Massachusetts General Hospital (Dr. Tawakol-PI), Lahey Clinic (Dr. Draper-PI), South Shore Internal Medicine (Dr. Cronin-PI), MGH-Chelsea Health Care (Dr. Benzaquen-PI) and Southern New Hampshire Medical Center (Dr. Schwartz-PI). For the Toronto region, the 5 recruiting centers are UHN/Toronto General Hospital (Dr. Farkouh-PI), Scarborough General Hospital Cardiology Research Associates (Dr. Roth-PI), Brampton Research Hospital (Dr. Gupta-PI), Humber River Regional Hospital (Dr. Singal-PI) and Sewa Ram Singal Professional Corp.-Finch site (Dr. Singal-PI). . Additional recruitment centers may be added in the future.

The Imaging Center at Mount Sinai will also act as the Imaging Data Coordinating Center for all 3 Imaging Centers. (*Protocol NIH CIRT imaging -page 111).* All imaging scans will be sent to Mount Sinai for Data Analysis. UCSF will also be an imaging center for their own site and will send all data to Mount Sinai.

(Please see Protocol NIH CIRT imaging for more details -pages 107-108).

Current protocol for the Main CIRT trial as well as CIRT imaging sub study are provided as an Appendix

4) Resources Available to Conduct the Human Research

The Mount Sinai research group has had excellent success in recruiting this type of patients in the New York area. There will be four major recruiting centers in the New York region. The Imaging Center at Mount Sinai has collaborated with all the recruiting centers in the past on both NIH and pharmaceutical funded studies. All personnel involved in the study are PPHS accredited and composed of experienced researchers.

5) Study Design

a) Recruitment Methods

The recruiting centers will be responsible for identifying suitable subjects for the study, recruiting the subjects into the study, informed consent, blood work and arranging for transportation of the subjects to the imaging centers as part of the CIRT imaging substudy. This is a sub study of the parent NHLBI funded CIRT trial (Ridker 5U01HL101422). Only subjects that are part of the main CIRT study and have consented to being approached for ancillary studies will be approached for recruitment into this CIRT imaging substudy. In the main CIRT trial, patients are recruited from 300 to 400 clinical sites (average of 20 randomized participants per site) in the US and Canada, all of whom have demonstrated experience in the identification, randomization, and long-term follow-up of patients with cardiovascular disease. In CIRT, as of August 14th, 2015, 4,559 subjects have answered the question regarding being contacted for ancillary study participation in the ICF. Taking out those who have withdrawn, 2,662 subjects have answered the question. Of these 2,662 subjects, 2,192 have consented to be contacted and 470 have not consented to be contacted.

The total subjects to be recruited for the CIRT Imaging substudy will be 170 (56 to 57 subjects are planned to be imaged in each of the three Imaging Centers). Only subjects recruited to the main trial will be recruited to the imaging substudy. The imaging study team will support main CIRT recruitment by using study flyers and postcard distributed at the Cardiac units, inpatients and outpatients clinics inside the Mount Sinai Health System, within the New York metropolitan area.

(Please see Protocol NIH CIRT imaging for more details -pages 111-112, 121).

Subjects will be consented for the imaging substudy by the clinical PI at the main CIRT trial centers during their initial study visit for the main CIRT trial. Subjects will also sign a consent form for the imaging sub study at the imaging center unless the PI obtaining consent is affiliated with the institution where the imaging center is located; in which case, the subjects will only sign one consent form for the imaging substudy. More details are provided in the "consent process" section.

b) Inclusion and Exclusion Criteria

The FDG-PET/CT imaging study will be performed as a substudy of CIRT, the inclusion/exclusion criteria for this imaging sub-study will include all of those of the main trial.

(Please see protocol NIH CIRT Imaging for more details -pages 117-118)

Inclusion Criteria include the following:

a. Age ≥ 18 years at screening
b. Documented MI in the past or past evidence of multivessel coronary artery disease by angiographymust have completed any planned coronary revascularization procedures associated with the qualifying event, and must be clinically stable for at least 60 d before screening; the qualifying prior MI must be documented either by hospital records or by evidence on current electrocardiogram of Q waves in 2 contiguous leads and/or an imaging test demonstrating wall motion abnormality or scar; the qualifying documentation of multivessel coronary disease must include angiographic evidence of atherosclerosis in at least 2 major epicardial vessels defined either as the presence of a stent, a coronary bypass graft, or an angiographic lesion of 60% or greater. Left main coronary artery disease that has been revascularized with a stent or bypass graft will qualify as multivessel disease, as will the presence of a 50% or greater isolated left main stenosis.
c. History of type 2 diabetes or metabolic syndrome at the time of study enrollment
d. Willing to participate as evidence by signing the study informed consent

Exclusion Criteria include the following:

1. Prior history of chronic infectious disease, including tuberculosis, severe fungal disease, or known HIV positive
2. Chronic hepatitis B or C infection

3. Interstitial pneumonitis, bronchiectasis, or pulmonary fibrosis. Chest x-ray evidence in the past 12 months of interstitial pneumonitis, bronchiectasis, or pulmonary fibrosis.
4. Prior history of non basal cell malignancy or myeloproliferative or lymphoproliferative disease within the past 5 years
5. White blood cell count <3,500/mm^3, hematocrit <32%, or platelet count <75000/mm^3
6. Liver transaminase levels (AST/ALT) greater than the upper limit of normal or albumin less than the lower limit of normal
7. Creatinine clearance (CrCl) <40 mL/min as estimated by the Cockcroft-Gault equation
8. History of alcohol abuse or unwillingness to limit alcohol consumption to <4 drinks per week
9. Women of child bearing potential, even if currently using contraception, and women intending to breastfeed
10. Men who plan to father children during the study period or who are unwilling to use contraception
11. Requirement for use of drugs that alter folate metabolism (trimethoprim/sulfamethoxazol) or reduce tubular excretion (probenecid) or known allergies to antibiotics making avoidance of trimethoprim impossible
12. Current indication for methotrexate therapy
13. Chronic use of oral steroid therapy or other immunosuppressive or biologic response modifiers
14. Known chronic pericardial effusion, pleural effusion, or ascites
15. New York Heart Association class IV congestive heart failure
16. Life expectancy of <3 years

The study population for the ancillary study will be the same as the main trial with the following additional exclusion criteria

a. Subjects with a history of multiple imaging studies associated with radiation exposure

b. If subject is Type 2 diabetic, hemoglobin A1c greater than 8% as determined by patient medical record review in the one year prior to the date of consent to this study.

c. BMI greater than 37 kg/m^2 or weight greater than 350 pounds

c) Number of Subjects

The total subjects to be recruited for the CIRT Imaging will be 170 (56 to 57 in each of the three Imaging Centers).

(Please see Protocol NIH CIRT imaging for more details -pages 111-112).

d) Study Timelines

Table 3: Timeline of the study

Timelines	Year 1				Year 2				Year 3				Year 4			
Month	0-3	3-6	6-9	9-12	12-15	15-18	18-21	21-24	24-27	27-30	30-33	33-36	36-39	39-42	42-45	45-48
Task																
Study Startup	■															
Patient recruitment	■	■	■	■	■	■	■	■	■							
Baseline Imaging		■	■	■	■	■	■	■	■							
Follow up Imaging					■	■	■	■	■	■	■	■				
Image Analysis									■	■	■	■	■	■		
Statistical Analysis														■	■	
Manuscripts Publication																■

(Please see Protocol NIH CIRT imaging for more details -pages 111, 116).

e) Study Endpoints

Imaging endpoints (SA 1): The endpoints (relative change (LDM vs. placebo, through 8 months)) in arterial inflammation based on PET imaging are as follows:
Primary endpoint used to evaluate vascular inflammation is most diseased segment (MDS) of the index vessel. The MDS is defined as the 1.5 cm segment within the carotid artery (right or left carotid) that demonstrates the highest PET/CT activity, and is calculated as a mean of maximum TBR values derived from 3 contiguous axial segments. The index vessel in turn is defined as the vessel (either aorta, right, or left carotid) with the greatest mean TBR at baseline.

Secondary endpoints will include: i) The mean of max TBR within the carotid arteries as an average of the slices from the left and right carotid) or ii) as combined (carotid and aorta); iii) the mean of the maximum TBR of all of the slices that compose the index vessel, and iv) Standardized uptake value (SUV) of each vessel analyzed (left carotid, right carotid and ascending aorta)

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	Primary Contact Name/Contact Info	Catherine Ma: Catherine.ma@mssm.edu; Renata Pyzik: ext. 5-8484
	Date Revised:	March 7, 2019
	Study Number:	GCO# 14-1382; IF2430508; HS# 14-00185

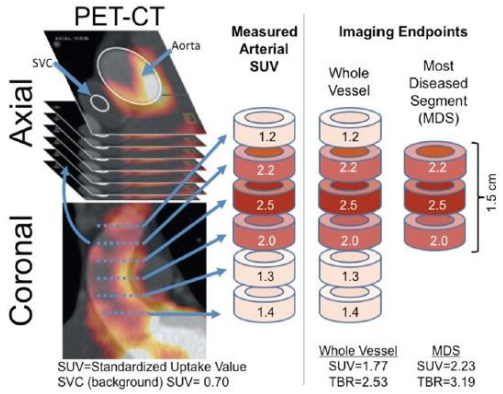

Figure 3: Sample images of aorta obtained using 18-FDG PET/CT and corresponding imaging endpoints determined

(Please see Protocol NIH CIRT imaging for more details-page 114).

Current protocol for the Main CIRT trial as well as CIRT imaging sub study are provided as an Appendix.

f) Procedures Involved in the Human Research

Table 1: Workflow for each imaging visit

Time (minutes)	Action
Before imaging visit	Subject is consented for CIRT imaging trial at main CIRT clinical site
-360	Subjects begins fast (only oral hydration permitted)
0	Subject arrives at imaging facility
5	Subject changes into hospital clothing(gown) and prepared for study
10	IV inserted for injection of FDG and for drawing blood
12	10 ml of blood is drawn for biomarker assessments
13	Blood glucose measurements for determining eligibility for FDG injection
15	10milli Curie of FDG injected into subject
105	Subject rests in a relaxed position to allow FDG circulation
120	Aorta PET/CT scans acquired
135	Carotid PET/CT scans acquired
140	Subject prepped for leaving (miscellaneous, instructions for future visits)
150	Imaging visit completed, subject leaves imaging center

(Please see Protocol NIH CIRT imaging for more details *-pages 112 - 113 (Table 1), 116)*

Timing of imaging visits as part of the CIRT imaging substudy: The first (baseline) imaging will take place prior to the open label run in of Low Dose Methotrexate in the CIRT main trial (between V1 and V2 of main CIRT). The second (follow up) imaging visit will take place 8 months after randomization into the main CIRT trial (close to V6 of main trial).

Due to early closure of the main CIRT Trial, subjects who have not reached the 8 months final imaging timepoint will be asked to go to their Imaging Center by the end of May 2018 and/or till all final imaging visits are completed, as advised by NHLBI. Subjects who have been on the Imaging substudy for 5 months or less after their baseline scan will need to be seen within this new time period.

Subject will be asked to verify with a physician insulin regiment for fasting and dieting needed prior to each imaging visit and provide study team with physician's recommendations whether to continue with our imaging study. On the day of the visit, the subject will be able to proceed with the imaging only when fasting glucose is equal or less than 170 mg/dL and equal or greater than 80 mg/dL. This will be verified at our site prior to the scan by finger stick or i.v. If the fasting blood glucose is less than 80 mg/dL each subject will be instructed to eat a snack or we will provide sugar cubes. Once fasting blood glucose is above 80 mg/dL, we will proceed with the imaging.

g) Specimen Banking

Ancillary Study Data Collection. This ancillary proposal will additionally collect the following data from each study subject participating in the imaging ancillary study
1) PET/CT Imaging data in the form of DICOM images.
2) Blood draw for evaluation of inflammatory biomarkers. These samples will also be stored in a coded fashion. The blood will only be stored for the purpose of the trial.
3) Blood draw for evaluation of pre scan glucose. This is an instant test and the data are not stored. This information is used only to determine if the subject is eligible for FDG injection at the time of imaging or if the imaging test needs to be postponed. Patients with a fasting glucose of >170 mg/dl will need to be rescheduled for an on-trial FDG-PET scan at a later date (p. 112 of other protocol)
4) Only the PIs of the imaging sub study and the main CIRT trial and their authorized representatives will have access to the code that links the imaging and blood data back to each individual subject. The linking files will be stored securely on a hard disk in Co-investigator's office.

(Please see Protocol NIH CIRT imaging for more details-page 119).

h) Data Management and Confidentiality

Image identifiers (blinded data) will be removed by the imaging site investigators and prepared for transfer to the Mount Sinai PET/CT Core Laboratory using either secure FTP or by mailing CDs with DICOM data. All Images will be coded and be identified only by a study ID number. All coded image data will also be stored at the central laboratory for imaging (Mount Sinai) on encrypted hard disks specific to this trial (CIRT image data repository). Only study personnel authorized to evaluate images, the imaging data manager and the PI will have access to imaging data. All imaging data and meta-analysis files are also stored on the same encrypted hard disk (image data repository). The image data repository has access controls and an audit trail feature built in using Mac Hg version control. This system is 21 CFR Part 11 compliant.

(Please see Protocol NIH CIRT imaging for more details -page 113).

i) Provisions to Monitor the Data to Ensure the Safety of subjects

Data for the substudy will be linked to the parent database by subject identification number only. The Mount Sinai imaging data coordinating center has programs, policies and procedures in use at all times to ensure the security and confidentiality of the data. Direct identifiable variables such as name, address, DOB, MRN, SSN, that can link the data to a person's identity will not be sent to us from the imaging sites. Only coded data is received at the core laboratory and is identifiable only by the subject ID). Research data files will be stored using this ID as the unique identifier. The linking code file which contains the linking information between the unique identifier and the direct identifiable variables will be stored in a different location than the de-identified and identifiable information and is available only to the PI and select individuals.

Part I: Elements of a Data and Safety Monitoring Plan

MSSM Principal Monitor:

Last Name: Rosenson

First Name: Robert

Academic Title: Professor

Department: CVI

Mailing Address: [redacted]

Phone: [redacted]

Email: robert.rosenson@mssm.edu

MSSM Additional Monitor:

Last Name: Heiba

First Name: Sherif

Academic Title: Associate Professsor

Department: Radiology

Mailing Address: [redacted].

Phone: [redacted]1

Email: sherif.heiba@mountsinai.org

2. Justify your choice of principal monitor in terms of the assessed risk to the research subject's health and wellbeing. In high risk studies when the principal monitor is independent of the study staff, indicate the individual's credentials, relationship to the PI, and the rationale for selection.

The investigators and research team are experienced in conducting clinical trials, trained (having met the IRB's educational requirements) and knowledgeable about the protocol, and are therefore qualified to review safety updates, monitor subjects for adverse events and assess their health and well-being during the trial. The additional monitor is also an expert in imaging and will be responsible for the safety of the subjects during their imaging visits. The co-investigators and the research team are responsible for the safety and welfare of the subjects and for conducting the trial as outlined in the protocol.

3. List the specific items that will be monitored for safety (e.g., adverse events, subject compliance with the protocol, drop outs, etc.).

Additional items that will be monitored during their imaging visit will be a chance of swelling, pain, bruising, infection or redness during blood draw; subject compliance which will also be monitored by the subject's main site and subjects will also be monitored for reactions during the injection of the 18-FDG radiotracer although there are no known side effects with the use of the agent.

*4. Indicate the frequency at which **ACCUMULATED** safety and data information (items listed in number 3 above and interim analysis of efficacy outcomes) will be reviewed by the monitor(s) or the Data Monitoring Committee (DMC). Although this information must be reviewed at least annually, the higher the study risks, the more frequently reviews must be scheduled.*

Subjects with IDDM should consult with their physician prior enrolling in our imaging sub-study. The visit preparation form called "Getting ready for your visit" includes all details as to fasting, low carbohydrate diet restriction as well medication and insulin requirements.

Subjects will have regularly scheduled visits with their main site during which the research staff will carefully assess subjects for any signs or symptoms of drug toxicity, in addition to the occurrence of any trial endpoints. A questionnaire designed to capture information about drug toxicity (including symptoms of a pulmonary, infectious, gastrointestinal, hematologic, dermatologic, and other toxicities), intercurrent hospitalizations, and elective or planned surgical procedures will be administered to all subjects.

Study algorithms will combine data from recent laboratory safety evaluations with subject's reported symptoms to determine study drug dosing and/or cessation, including sham placebo dose adjustments. Responsible physicians will be informed of any changes in the study medication dosing. Adverse events, patient symptoms, laboratory abnormalities, or other reasons for discontinuation of or reduction in dose of study drug will be collected through electronic case report forms and monitored centrally by the DCC. A Medical Monitoring program will be developed and will help identify potential adverse drug reactions to the study medication. Study coordinators will be given instructions to contact the Medical Monitor for symptoms or signs that raise the possibility of drug toxicity. The Medical Monitor will be on call 24 hours a day 7 days each week.

5. Where applicable, describe rules which will guide interruption or alteration of the study design.

The principal features of the study design and of the plan for statistical analysis of the data are outlined in the protocol. Any changes in these principal features will require a protocol amendment.

6. Where applicable, indicate dose selection procedures that will be used to minimize toxicity.

Risks associated with 18-FDG-PET/CT:

There are no known side effects with the use of the 18-FDG radiotracer. The procedure involves a single vein puncture for FDG administration. PET/CT scanning is widely used in oncology and cardiology. The metabolic tracer FDG is very safe with no potential for allergy. The radiation dose for the PET/CT scan would be the same as the background exposure of living in New York City for 1 year. The total effective whole body dose (TEDE) from a single PET study is 700 mRem. The whole body CT portion of the PET scan adds another 70 mRem to the TEDE. The resulting effective total body dose is 770 mRem, which compares with a 100 mRem yearly recommended limit for exposure for the general public and 5,000 mRem yearly limit for persons who work with radiation, established by the Nuclear Regulatory Commission (NRC). The critical organ, which is the organ which will receive the maximum dose and exceed the TEDE for FDG is the urinary bladder, which will receive 5900 mRem. This dose is well within the 50,000 mRem limit for a single organ, established by the NRC. While at this level, this kind of radiation exposure has not been shown to cause malignancies, this possibility can never be excluded. There are no other known side effects with the use of FDG as a PET agent.

7. List any specialized grading system that will be used to evaluate adverse events (e.g., National Cancer Institute Common Toxicity Criteria).

To ensure safe and effective use of nuclide imaging, a rigorous quality assurance (QA) protocol of the imaging tools and integration of the imaging data is currently in place under the guidance of the respective radiation safety offices of the participating institutions. Overall, the goal of this QA program is to identify and minimize the sources of uncertainties and errors, taking into consideration the economic, medical, legal, and regulatory implications. The PET-CT scanners will comply with all The National Electrical Measurement Association (NEMA) standards and will be tested on a routine basis for compliance. The minimum dose of 18-FDG for adequate image quality will be used in all subjects.

8. Describe procedures that will be used to assure data accuracy and completeness.

A Data and Safety Monitoring Plan (described below), including pre-specified stopping rules has been defined by an NIH appointed, independent, Data Safety Monitoring Board (DSMB) for CIRT. This DSMB will ensure conduct of the parent study in a manner suited to optimal research subject safety. In addition, the DSMB will review and approve ancillary study proposals and will on an ongoing basis review summary data pertaining to

subject participation and information collected in ancillary studies in order to ensure subject safety and to ensure that subject and site burden is minimized.

9. Should a temporary or permanent suspension of your study occur, in addition to the PPHS, indicate to whom (NIH, FDA, sponsor, IRB) will you report the occurrence.

Temporary or permanent suspension would be reported to the NHLBI and to all the sites.

Data Safety Monitoring

For the Imaging substudy, communication with the collaborating Mount Sinai co-investigators will be conducted via bi-weekly teleconferences and quarterly meetings. Confidentiality of subject data will be protected as previously described.

Unanticipated problems from the other study sites will be discussed at the teleconferences. Urgent problems will be immediately addressed by direct communication between the research teams. Plan for reporting unanticipated events that cause risk of harm to subjects or others will be reported to the PPHS in accordance with PPHS policies on reportable information.

The DSMB was constituted by the NHLBI and will be composed of members from the following areas: 1) physicians with specific expertise in the clinical management of cardiovascular disease 2) a biostatistician with specific expertise in the design, analysis, and safety monitoring of multi-center clinical trials 3) a medical ethicist, and 4) a physician with specific expertise in rheumatologic disease. The DSMB will oversee the main CIRT trial as well as the CIRT Imaging Study and the physician with expertise on rheumatologic disease will be from the Brigham and Women's Hospital site which will also provide the overall programmatic and statistical support for the CIRT Imaging Study. Dr. Fayad who is the PI of the CIRT Imaging Study and Dr. Rosenson who is the co-investigator of the CIRT Imaging Study will take part in the semiannual review.

The Committee members will collect and review the safety data every 6 months and be responsible for review of:

a) study recruitment goals and tracking of enrollment;

b) presentation of spreadsheets for data analysis;

c) adverse and reportable events as defined by the investigators;

As of 4/2/18, enrollment has ended due to early termination of the main CIRT Trial. There will no longer be any DSMB meetings.

(Please see Protocol NIH CIRT – imaging for more details: pages 120-122).

j) Withdrawal of Subjects

Participation in this imaging study is voluntary. The subjects can withdraw at any time by informing the PI and/or the study coordinators. Although the subjects can withdraw from the imaging study, they can still continue to participate in the CIRT main trial.

6) Risks to Subjects

Risks associated with 18-FDG-PET/CT:

There are no known side effects with the use of the 18-FDG radiotracer. The procedure involves a single vein puncture for FDG administration. PET/CT scanning is widely used in oncology and cardiology. The metabolic tracer FDG is very safe with no potential for allergy. The radiation dose for the PET/CT scan would be the same as the background exposure of living in New York City for 1 year. The total effective whole body dose (TEDE) from a single PET study is 700 mRem. The whole body CT portion of the PET scan adds another 70 mRem to the TEDE. The resulting effective total body dose is 770 mRem, which compares with a 100 mRem yearly recommended limit for exposure for the general public and 5,000 mRem yearly limit for persons who work with radiation, established by the Nuclear Regulatory Commission (NRC). The critical organ, which is the organ which will receive the maximum dose and exceed the TEDE for FDG is the urinary bladder, which will receive 5900 mRem. This dose is well within the 50,000 mRem limit for a single organ, established by the NRC. While at this level, this kind of radiation exposure has not been shown to cause malignancies, this possibility can never be excluded. There are no other known side effects with the use of FDG as a PET agent.

Risks associated with venipuncture and blood draw: During the collection of the blood samples, there is a chance of swelling, pain, bruising, infection, or redness at the site where the blood is drawn. Also, there is chance that the subject may feel faint.

(Please see Protocol NIH CIRT imaging for more details-page 120-121).

Risks of Fasting: If the subjects feel disoriented or dizzy, the coordinator will ask the subject to lie down until they regain their composure and will be given water. Their vital signs will be monitored until they have stabilized. If no improvement is seen, the subjects will be referred to the Co-PI, Dr. Rosenson who is the MD in this study for further management and the scan will be rescheduled.

To prevent such occurrences from happening, the coordinator will make sure of the following: 1) Remind subjects to come on time or enough time for the preparations before the scan; 2) That there is no delay in the scheduled imaging scan and that the dose is available and ready; 3) A coordinator be present with the subject to monitor the overall condition of the subject to undergo the scan. Once injected with the FDG and before the scan, the coordinator will periodically check on the subject to check his overall status.

7) Provisions for Research Related Injury

If subjects are injured or made sick from taking part in this research study, medical care will be provided. Generally, this care will be billed to their insurance and will be responsible for all treatment costs not covered by insurance. In the event of injury, the subjects can contact the Co-Investigator, Dr. Rosenson who is an MD in this study.

8) Potential Benefits to Subjects

This CIRT imaging sub study has the potential to provide valuable information with regard to the inflammatory status of the vessel walls of the subjects participating in this trial. This may provide mechanistic insights into the role of methotrexate in reducing cardiovascular inflammation and thereby provide additional data on future CV risk. There may however not be any direct benefit to the subject.

(Please see Protocol NIH CIRT imaging for more details -page 122-123).

9) Provisions to Protect the Privacy Interests of Subjects

The subjects will be recruited at several different hospitals. After the recruitment, they will be referred to the Imaging center in their geographic area for their imaging. The imaging centers will not be directly involved in recruiting the subjects. When patient consents to the study, his/her name, address, phone numbers, date of birth, medical record number will be collected and kept with the informed consent form in their respective recruiting centers. The subject will also sign a consent form at the imaging centers for the imaging and other study related procedures. Once the subjects are recruited and referred to the imaging center for imaging, the following measures will be taken to ensure subject privacy. The study treatment and procedures will be thoroughly explained to them in a private office/area, at a time of mutual convenience to both subject and investigator, by appointment. All their questions will be addressed in a simple language so that the interested subjects can adequately understand the rationale for the study as well as potential risks and benefits prior to consenting. Once the subject has agreed to participate in the study, they will be asked their preferences regarding mode of contact and limitations if any to contact by phone. Their wishes will be respected by study coordinators and investigators. All conversations will be held in a professional manner and in a manner that maintains subject privacy.

If subject requests the research images, they could be provided. However, these images will contain their private information and they will be responsible for protecting them and any future use of them.

10) Economic Impact on Subjects

Subjects will also receive [redacted] per imaging visit for a total of [redacted] for two visits for their time. In the case that subjects do not complete their scan, but do have blood drawn, they will still be compensated the [redacted]. Subjects' travel will be arranged by coordinator. If subjects use their own form of transportation, they will be reimbursed for the transportation cost for the imaging visit upon providing receipts, either by cash or check.

11) Payment to Subjects

Subjects will receive [redacted] for Baseline visit, and [redacted] for follow-up visit by cash or check.

12) Consent Process

Once the subject has agreed to participate in the main study and signed the main consent form, and has agreed to be approached for ancillary studies, the PI or the designated research staff of their respective main study site will introduce the imaging substudy to the subjects. If the subjects agree to participate in imaging substudy, the research staff of the main clinical site will consent the subject for the imaging substudy at their center. This will be done prior to reviewing the subjects' medical records to ensure eligibility for the imaging substudy. If the subject meets the eligibility criteria for the imaging substudy, staff at the recruiting center will contact the research staff of the Imaging center and inform of the new subject recruited. The research staff of the imaging center will then contact the subject and in conjunction with the staff at the recruitment center schedule the subject for their imaging visits. The consent form from the imaging center may be sent to the subject either by email or regular mail if the subjects requests for it so the subject can review it thoroughly. The imaging center research staff will also over the phone go over any questions on the consent form and verify that the subject would be willing to participate in the imaging substudy. Consent at the imaging center will be obtained by the co-Investigator and/or designated research staff in a private office on a date or time prior to baseline scanning being performed. A consent form from the imaging center for this study will be given to the subject if it has not been given previously. Subjects can read the form on the day of the scan. All questions will be answered and the consent form will be signed if the subject wishes to participate. To ensure participant understanding, the consent form will be thoroughly discussed with the subject, section by section. If any questions arise, the coordinator or principal/ coinvestigator will answer their questions until they have a clear understanding of what is expected of them if they participate. Subjects will be asked to provide in their own words a statement of their understanding of the risks and procedures of the study, and the general concept of the study. Subjects must clearly understand the potential risks and benefits before signing the consent.

Prior to collecting study data, the following details will be explained to the participant: (1) that the study represents a research effort, (2) that participation is voluntary, and there is no penalty for withdrawal, (3) there are no costs to the patient for participation, (4) potential risks and benefits for participation and (5) contact information for additional concerns. Patients will be informed of the purpose of the study, the need to be available for questionnaires and medical tests, and of their options to accept or refuse entry into the study without affecting their clinical care. All sources of research materials will be in the form of medical records, blood work, and imaging studies. The consent form at the recruitment center and the imaging center describe the same procedures and are essentially similar but will be approved by the respective institutional review boards.

Non-English speaking subjects may also be enrolled since there is a large population of Spanish-speaking patients as well as some other non-English speaking patients in the area. During the consent process, an approved Spanish consent will be provided to those subjects. A short form of the consent is available, in English and in Arabic for a single use.

13) Process to Document Consent in Writing

The standard PPHS consent template will be used to document consent.

14) Vulnerable Populations

Include	*Exclude*	*Vulnerable Population Type*
	x	*Adults unable to consent*
	x	*Individuals who are not yet adults (e.g. infants, children, teenagers)*
	x	*Wards of the State (e.g. foster children)*
	x	*Pregnant women*
	x	*Prisoners*

15) Multi-Site Human Research (Coordinating Center)

The Imaging Center at Mount Sinai will also act as the Imaging Data Coordinating Center for all 4 Imaging Centers in the CIRT imaging substudy. All imaging scans will be sent to Mount Sinai Imaging Center for Data Analysis via secure FTP or in CD rom in DICOM format.

16) Community-Based Participatory Research

N/A

17) Sharing of Results with Subjects

The research results of the study will not be shared with the subject and the subject's physician. However, any incidental findings or gross abnormalities read by the radiologist will be shared with the subject's physician involved in research. The research team will notify the primary care physician of the subject or the PI of the recruitment center of the subject for any incidental findings.

18) IRB Review History

5/7/2014, 11/3/2015, 2/2/2016, 4/22/2016 approval, 6/30/2017 – new flyers approved; 6/30- 7/27/2016 – insulin amendment; 4/19/17 continuation approval; 9/9/17 modification approved; 11/17/17 short form (English/Arabic) approved

19) Control of Drugs, Biologics, or Devices

Note: The IDS has its own forms that must be completed and a review process that must be followed before the IDS representative will sign off on Appendix B for submission to the PPHS.