Columbia University Human Subjects Study Description Data Sheet

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Principal Investigator: Joan Bathon (527)

Study Description

1. STUDY PURPOSE AND RATIONALE

Patients with Rheumatoid Arthritis (RA) are at increased risk for developing heart failure (HF) compared to matched non-RA controls. In addition, HF is one of the main causes for premature death and a major contributor to the reduced - compared to the general population - lifespan of RA patients.
Preliminary data show that patients with RA have a lower LV mass than non-RA controls, and that this decrease in LV mass is associated with a lower cardiac output. Assuming that the decrease in the cardiac output could be indicative of pre-clinical HF, this is in contrast with what is observed in the non-RA patients, where the development of HF is preceded by an increase in LV mass. The reasons for a decreased LV mass in RA, and how this may be linked or lead to a compromised LV function are not known. Furthermore, based on preliminary data that associate the presence of specific RA characteristics (such as the presence of CCP antibodies) with a decrease in the LV mass, we can hypothesize that RA related inflammation within the myocardium may be causing myocardial cell death or apoptosis. In addition, based on data showing diffuse subendocardial hypoperfusion in patients with RA we can hypothesize that inflammation may affect the endothelium of the myocardial microvasculature, and interfere with myocardial perfusion leading to myocardial atrophy.

The first aim of this study is to evaluate and identify factors that are associated with the phenotype of low LV mass. We will enroll 150 RA patients in the study. Some of the potential low LV mass predictors to be studied include: RA associated characteristics (e.g., anti-CCP antibody titers), duration of articular disease, the degree of systemic and myocardial inflammation, and alterations in myocardial perfusion. LV structure and function will be assessed by cardiac PET-CT scan and 3-dimensional echocardiography (3D ECHO).

TNF inhibitors are an FDA approved class of medications indicated for the treatment of RA when initial treatment (usually with methotrexate) has failed to achieve remission of RA disease activity. TNF inhibitors are part of the standard of care management of RA. It is estimated that currently up to 20% of patients with RA are being treated with TNF inhibitors. More than 10 years of experience with these agents support the use of these agents for RA patients who do not respond to initial treatment. While TNF inhibitors have revolutionized the treatment of articular RA, their effects on heart failure (HF) has not been elucidated. Clinical trials in non-RA patients with advanced HF showed that these medications are not beneficial and may even be detrimental. Even though similar robust studies have never been performed in RA patients, product information sheets for all of the TNF inhibitors warn against their use in RA patients with advanced HF. However, their use is allowed for the treatment of RA in patients with moderate or mild HF with careful monitoring. Animal data, recent RA cohort data, and our preliminary data in RA patients suggest that TNF

inhibitors may prevent HF and/or improve LV function in RA. So far, no studies have investigated the direct effect of this class of drugs on myocarcial function and structure. The hypothesis that TNF inhibitors may have a differential effect on the failing myocardium - depending on whether patients have RA or not - would reconcile the contradictory literature. Assuming that systemic or myocardial inflammation may be the primary force leading to HF in RA, we hypothesize that TNF inhibitors may be beneficial in preventing or improving HF in patients with RA. We will address this hypothesis first by examining the effect of TNF inhibitor treatment in RA patients without heart failure. If safe, further studies can direct attention to RA patients with heart failure.

The second aim of the study will target 50 of the 150 RA patients enrolled in aim 1, and will evaluate the effect of treatment with TNF inhibitors on left ventricular (LV) structure and function, and also myocardial inflammation and perfusion. In this aim we will investigate the effect on TNF inhibitor treatment directly on the myocardium in patients without HF, or other known cardiovascular disease. Thus we will not enroll any patients with HF, but only patients free of any cardiovascular disease. Participants in need of treatment to control their disease activity despite methotrexate will be randomized to receive treatment with either a TNF inhibitor or other equivalent FDA approved treatment. The direct effect on the myocardial function, structure, LV mass, and subendocardial hypoperfusion will be evaluated over 6 months of observation. In this aim as already noted above - we will utilize only FDA approved drugs for RA, and the study will be conducted and monitored in the context of usual care.

2. STUDY DESIGN AND STATISTICAL PROCEDURES

2a. Study Design
(this section includes references)

For aim 1, the proposed studies will be performed in 150 patients with RA and 15 subjects without RA who will function as controls. The 150 patients will be recruited from the rheumatology clinics at New York Presbyterian Hospital of the Columbia University. The 15 control subjects will be recruited from the internal medicine clinics at the same institution or among friends of the recruited RA patients.

The 150 participants should have RA fulfilling established diagnosed criteria and not have a history of cardiovascular disease as indicated in the section for inclusion/exclusion criteria

These patients (150) will undergo the evaluations shown in the table below - and in more detail in Appendices I, II and III - during an initial visit (Visit I).

Evaluations	Visit I September/2011 - August/ 2014
Cardiac PET-CT scan*	X
3D Echocardiogram	X RA
& CV Questionnaires	X
Joint examination	X
Phlebotomy	X
Anthropometry	X
DEXA scan (body composition)**	X

*including 3 transverse CT slices (mid-chest, L4-L5, mid-thigh) and cardiac CT for evaluation of coronary artery calcification (CAC).
**only for the 50 participants who will be recruited for aim 2. (see below)

During the first PET scan a cardiac CT scan will be obtained in order to quantify coronary artery calcium (Agatston Score). Three additional CT Slices will be obtained (mid chest, lumbar, and mid thigh) to evaluate for visceral fat

accumulation as a risk factor for cardiovascular disease.

Controls will undergo only the PET-CT scan, 3D Echo, anthropometry evaluations, phlebotomy, and will complete abbreviated cardiovascular related questionnaires as outlined in Appendices I, II and III.

The PET-CT scan will occur on the same day or within one week of Study visit I.
We expect that the vast majority of the 150 enrolled patients will already be on treatment with methotrexate at the time of enrollment. Methotrexate is the cornerstone of treatment for RA and almost all patients are started on methotrexate upon diagnosis of RA as part of standard of care. However only approximately 50% of patients reach a state of RA remission or low disease activity with methotrexate. The other 50% of patients with RA do not respond adequately to methotrexate and need treatment with additional agents in order to reach remission or low disease activity. In usual care patients who do not respond to methotrexate are frequently prescribed medications such as sulfasalazine and plaquenil in addition to methotrexate (triple therapy) or a TNF inhibitor in addition to methotrexate. Whether a patient receives one (TNF inhibitor) or the other (triple therapy) treatment is a matter of physician and patient preferences most of the time. Published guidelines provide only initial treatment recommendations (for example: methotrexate for all RA patients once diagnosis is established) and do not comment on whether one therapeutic agent should be preferred over an other for patients who do not respond to methotrexate (1).

For aim 2, we will identify 50 of the patients enrolled in aim 1 who are in need for further treatment due to increased RA activity despite methotrexate treatment. These patients will be recruited to continue in the study for an additional 24 (+/- 2) weeks (6 months). The patients will be randomized to receive one of the FDA approved options in an open label protocol for increased disease activity; either a TNF inhibitor or triple therapy and in the context of standard of care as already noted above. For more information regarding inclusion/exclusion criteria please refer to the appropriate IRB/RASCAL application section below.

Although treatment with TNF inhibitor and methotrexate is slightly superior in slowing radiographic joint damage, triple therapy has comparable efficacy and multiple clinical trials (COBRA and Best) robustly support the ability of the regimen to effectively reduce disease activity and slow radiographic damage (2,3).

After the escalation in their treatment at baseline (Study Visit I) these patients will return for a second (24 weeks) study visit respectively and the set of evaluations shown in the table below - and in more detail in Appendices I, II and III - will take place. A window of +/- 2 weeks will be allowed in scheduling the study visits.

Evaluations	Visit II Mar/2012-Jan/2015
Cardiac PET-CT scan*	X
3D Echocardiogram	X RA &
CV Questionnaires	X
Joint examination	X
DEXA scan (body composition)	X
Phlebotomy	X
Anthropometry	X

*including 3 transverse CT slices (mid-chest, L4-L5, mid-thigh) and low dose radiation chest CT

During PET-CT scans a low dose CT imaging of the chest is always obtained for attenuation correction as part of the usual PET-CT protocol. Although we will not need a repeat coronary artery calcium score at visit 2, low dose radiation CT imaging of the chest is always obtained for attenuation correction as part of the usual PET protocol. During this CT imaging acquisition 3 additional slices (CT cuts) will be again obtained (mid chest, lumbar, and mid thigh) to evaluate for change in visceral fat following treatment initiation.

The 3-dimensional Echocardiogram (3D Echo) will be performed to provide a measure of LV mass and will be performed in every study visit.
The 15 controls will also be asked to have a repeat set of evaluations 6 months (24 +/- 2 weeks) after their first evaluation without any therapeutic or other intervention in between the two visits. The inclusion of non-RA controls will provide important data on the normal variation of cardiac PET-CT and 3D Echo parameters over time. Further evaluations for the control participant visits are outlined in appendices I, II and III.

Every subject (RA patient or non RA control) will have a urine pregnancy test prior to tests involving radiation exposure (PET-CT scan and DEXA) and on the same day.

The screening and consent process of a patient to receive randomized escalation of treatment will be made at the time they are consented for the first study visit. It is possible that all 150 patients will qualify for randomization of their treatment but only the first 50 of those will be selected to return for study visit II. The rest of the patients will exit the study and will continue their regular care with escalation of their treatment by their treating rheumatologist outside the study.

Standard of care entails that patients who undergo escalation of their treatment need to be evaluated every 6-8 weeks to evaluate response to treatment, the need for further treatment escalation, and toxicity monitoring. Thus in between Study Visits I and II patients will return every 6-8 weeks for safety visits which will mirror standard of care management and which will be focused on toxicity monitoring as it would happen even if the patients did not participate in the study. An exit safety visit will occur 6-8 weeks after visit II. The incorporation of safety visits in the study and the related procedures/tests are shown in Appendices I and II.

It is possible that patients randomized to receive either the triple therapy or treatment with a TNF inhibitor and methotrexate may not respond to treatment. Disease activity will be evaluated using the Clinical Disease Activity Index (CDAI) score at the time of every safety and study visit and treatment will be modified until they reach the state of low disease activity or remission as defined by a CDAI score of less than or equal to 10. CDAI score takes into account the number of swollen and tender joints and the evaluation (using a Visual Analog Scale) of disease activity by both the patient and the physician. CDAI is an extensively validated disease activity tool.

The treatment algorithm followed in this study is described below. A study flow chart describing the algorithm is provided in appendix XXI.

i. Randomization to the non TNF inhibitor arm: Patients on triple therapy will be started on 1 gram of sulfasalazine (SSZ) twice daily along with weight adjusted daily Hydroxychloroquine (Plaquenil). Methotrexate treatment will be continued. It takes approximately 6 weeks before an effect of this therapeutic regimen is experienced. In the first safety visit (which will happen approximately 8 weeks after the first study visit) the need to increase the SSZ to 3 grams daily will be evaluated based on whether the patient has reached low disease activity status or remission. In the subsequent safety visit (safety Visit 2) which will occur 8 week after Safety Visit 1, if disease activity remains moderate or high, SSZ and Hydroxychloroquine will be stopped and patients will be switched to Leflunomide (Arava) 10 mg plus methotrexate.

Patients will then return at 24 weeks for their second Study Visit (Study Visit 2) for completion of the study and further management as per standard of care.

An additional Safety Visit (Safety Visit 3) will take place at 32 weeks and will serve as an exit safety visit.

ii. Randomization to the TNF inhibitor arm: For patients randomized to receive treatment with a TNF inhibitor, disease activity will also be evaluated at the time of every visit. The effect of TNF inhibitors on arthritis activity may be observed as early as in 2 weeks but sometimes may take up to 14 weeks (approx. 3 months). At the time of the first safety visit tolerability and safety will be evaluated. At the time of Safety Visit II if CDAI is still >10 (indicative of moderate disease activity) an increase in the dose or frequency of the TNF inhibitor (in the case of agents such as infliximab or adalimumab where escalation of dosage is an option) or a switch to treatment to an alternative TNF

inhibitor will take place.

Patients will then return at 24 weeks for their Second Study Visit (Study Visit 2) for completion of the study and further management as per standard of care.

An additional Safety Visit (Safety Visit 3) will take place at 32 weeks and will serve as an exit safety visit.

The treatment algorithm described above is similar to the care patients would receive even if they did not participate in the study. The only difference is that patients will be randomized to receive one of the two standard of care treatments. The need for prednisone to temporarily control disease activity will be decided by the investigators according to usual standards of care.

As already mentioned decisions to escalate treatment will be based on CDAI score which is a composite disease activity score consisting of counts of swollen and tender joint counts and evaluation of disease activity by both the patient and the physician using a visual analog scale. The joint counts will be performed by a blinded trained joint assessor. Either a faculty member or a senior rheumatology fellow, also not aware of the patient treatment will perform the joint examinations and the assessment of disease activity. The same joint assessor will perform the joint counts for a given patient throughout the study. Every time CDAI is >10, then a change in the treatment according to the algorithm described above will be mandated to ensure patients' well being.

As already mentioned, the goal of this study is to investigate the "low LV mass phenotype" in patients with RA and its contributors in an attempt to elucidate the pathophysiology pathways that may connect RA with alterations in the myocardium and the evolution to heart failure. 3D-Echo will be used to measure the LV mass. Cardiac PET-CT imaging will be used to evaluate myocardial function (cardiac output, ejection fraction), microvasculature function (myocardial perfusion) and myocardial inflammation (F18-FDG uptake).

The research questions to be addressed with the study visit I are the following:

i) Are anti-CCP antibodies or other RA-specific characteristics (e.g., disease duration, activity, severity) associated with lower LV mass (or other LV parameters of structure/function)?

ii) What is the prevalence, the degree and correlates of microvascular dysfunction in RA? Is it associated with low LV mass or reduced global or regional contractility? Is it associated with systemic, articular and/or myocardial inflammation?

iii) What are the prevalence, patterns, distribution and severity of inflammation as measured by F18-FDG uptake in myocardial PET imaging? Are intensity and/or distribution of F18-FDG uptake correlated with low LV mass or global or regional contractility? Does the severity/distribution of F18-FDG uptake correlate with levels of systemic and/or articular inflammation?

For the second aim of this study the goal is to evaluate the effect of TNF inhibitors on the myocardium. For the 50 patients undergoing randomization and the controls the questions to be addressed will be the following:

i) Are global measures of LV structure (e.g., mass) or contractility (e.g., ejection fraction) affected (reduced or increased) by treatment with TNF antagonists? Is there a different effect compared to alternative therapy?

ii) If microvascular dysfunction and/or inflammation are present before treatment, do they improve with treatment with TNF compared to alternative treatment? If parameters improve only with TNF inhibitor, this would suggest that TNF inhibitors exert a local anti-inflammatory effect on the myocardium mechanistically different compared to alternative treatment.

iii) If treatment-induced improvements in microvascular dysfunction and/or inflammation (F18-FDG uptake) are

observed with TNF inhibitor treatment and not with alternative treatment, do they correlate with (or mediate) global (or regional) changes in LV structure or function? If so, this would suggest a causal relationship between regional myocardial vasculopathy and/or inflammation with LV dysfunction.

iv) Do treatment-induced improvements in systemic inflammation (e.g., CRP) and RA disease activity correlate with changes in myocardial microvascular perfusion and/or inflammation If so, this would suggest a relationship between systemic and myocardial inflammation.

In preliminary exploratory data analyses, summary statistics for the continuous and categorical variables will be calculated, including means, standard deviations, quartiles and ranges, and for the categorical variables, counts and percentages. In initial analyses, statistical comparison of continuous variables will be conducted using the t-test or nonparametric method, as appropriate. The comparisons of the prevalence of categorical CV risk factors will be conducted using the Chi-square test or the Fisher's exact test, as appropriate. All comparisons will be conducted at the alpha=0.05 level of significance using two-tailed tests, unless otherwise noted. To account for the potential for multiple comparisons artifact: a) First, significance testing will be based on a priori hypotheses and not spurious significant p-values; b) Second, if multiple comparisons are undertaken, adjustments in the threshold for statistical significance will be made as necessary. If multiple and collinear variables are detected, appropriate techniques will be utilized to minimize the impact of collinearity on the statistical efficiency of the derived parameter estimates.

To explore the associations of anti-CCP antibody, which can be analyzed as a dichotomous or continuous variable, other characteristics of RA (e.g. duration; activity; severity), and myocardial FDG uptake with continuous measures of global LV structure (e.g. LV mass) and function (e.g. ejection fraction, end-systolic volume stroke volume), we will perform descriptive analyses and potential data transformation as needed required to meet the requirement for statistical tests involved. LV structural and functional outcomes for those with presence/absence of anti-CCP antibody, longer/shorter RA duration, or more/less severe RA will be compared using t-tests or an appropriate non-parametric test. Association between LV structural and functional outcomes and anti-CCP antibody level and other RA characteristics as continuous predictors will be examined using nonparametric approach such as Loess plots to explore the natural form of the associations. Multivariate regression models (linear, polynomial, or piecewise regression, as appropriate) will be used to evaluate whether associations are independent of potential confounders. This will include explicitly adjusting for conventional CV risk factors in the investigation of associations of LV mass/contractility with RA characteristics to studying the degree in which these associations are independent of these risk factors.

Linear mixed effects (MIXED) regression models will be used to assess trends in LV structure and functional outcomes over time between the two visits for the patients who will undergo randomization reevaluation with PET-CT and 3D Echocardiogram, while controlling for potential confounders. The data will include PET-CT studies for 25 RA patients receiving TNF antagonists and 25 RA patients receiving alternative treatment, and PET-CT studies for 15 non-RA patients. The data are longitudinal since LV outcomes are measured for each person at 2 different time points. Since repeated measures tend to be correlated within a person, mixed models with both fixed and random effects will be used to adjust for this correlation. We will use unstructured correlation structure given that each visit will occur roughly around a fixed time since study visit I, and use robust standard error estimates to conduct statistical inferences. To study the TNF inhibitor effects on LV structure or functional outcomes, visit-specific indicators, RA status, TNF treatment status, and visit x TNF treatment interaction will form the bases for the mean model. The visit-specific indicators will capture the time trend of LV outcomes over the study period, the RA status will delineate the overall mean difference in LV outcomes between RA and non-RA, with the TNF treatment status indicator and its interaction with visit indicators capturing the baseline difference in LV outcomes between TNF treated and non-treated groups and the potential TNF treatment effect on LV outcome over time, respectively. Actual TNF inhibitor dosage could be used in place of TNF status indicator in the model if necessary, and other potential covariates could be added into the model for confounding adjustment. For example, inflammation markers could be added into the model to examine whether any TNF treatment effect is mediated through the change in systemic inflammation. Similar modeling approaches can be used to study all research questions of interest using the corresponding outcomes and their hypothesized predictors listed in those questions to be addressed. For any binary outcomes in this type of regression analysis, e.g. indicator of whether a LV outcome exceeding certain critical value, generalized linear mixed effects models (GLIMMIX) can be used to study the odds of such outcome as a function of the independent variables.

All analyses will be performed with STATA statistical software, version 9.0 (STATA Corp, College Station, TX) and PLINK (http://pngu.mgh.harvard.edu/ purcell/plink). In all tests, a two-tailed alpha error of 0.05 will be defined as the level of statistical significance.

References:
1. Saag KG, Teng GG, Patkar NM, et al: American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum. 2008,59 (6):762-84.
2. Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allart CF, et al: Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): A randomized, controlled trial. Arthritis Rheum. 2005, 52:3381-3390
3. Van Tuyl LH, Lems WF, Voskuyl AE, et al. Tight control and intensified COBRA combination treatment in early rheumatoid arthritis: 90% remission in a pilot trial. Ann Rheum Dis. 2008, 67(11):1574-7

2b. Sample size and power calculations

To investigate the dose-response association between two continuous variables in cross-sectional analyses, we will first categorize the sample into 4 equal sized groups based on the quartiles of the continuous predictor and study the dose response association pattern using one-way ANOVA. With a total sample size of 150 for study Visit I, thus N=37 per group, in such a one-way ANOVA we will have 80 % power to detect a dose response pattern with a difference of 0.25 SD or high in any two adjacent quartiles. When linear association is a good measure to characterize the dose response association between a continuous outcome and a continuous predictor, we will have 80% power to detect a correlation level of 0.227 or higher, in either direction, with a total N=150 and a two-sided alpha error of 0.05.

We will obtain valuable information on LV structure/function outcomes for the cross-sectional visit, as well as for change in these outcomes over 6 months, for 3 groups of study participants, 25 RA patients treated with TNF-antagonist, 25 RA patients treated with triple treatment or alternative, and 15 non-RA participants with otherwise similar characteristics. For continuous outcomes we will obtain mean, standard deviations, and skewness (to inform us whether certain variables may need transformation before analyses so that sample size/power evaluation for future studies may need to be based on transformed data) for cross-sectional as well as the change over time measurements, and the correlations between two consecutive measurements over time. For binary variables we will obtain prevalence estimates and odds ratios as estimates of association between two repeated binary measures over time. Even accounting for a possible 15% drop out rate of participants, the correlation estimate will have precision ranged approximately between within +/- 0.33 for a correlation of 0.50 and within +/- 0.09 for a correlation of 0.90. For prevalence of binary outcomes, our estimate will be ranged approximately from within +/- 17.9% for a prevalence of 50% to +/-10.7% for a prevalence of 90%. To estimate the power of detecting a 24 week (6 month) change in an LV myocardial outcome within the TNF treated RA group, with a 2-sided alpha of 0.05 and N=22 (accounting for possible drop out), we calculated the minimal detectable change based on cross-sectional SDs and various values for within person correlation between outcome measures at subsequent visits based on data from previous studies performed by the same investigator group. For example with a conservative SD of 1.8 L/min for cardiac output (CO) and 4.2 mL/m2 for stroke volume (SV) and the correlation between subsequent visits being 0.2 we will have 80% power to detect a 24 week (6 month) change of 1.47 l/min for CO or 3.42 ml/m2 for SV or more in the TNF inhibitor treated RA group. Similarly in order to estimate power for comparing changes between the TNF inhibitor treated group, the triple therapy treated group and the normal control group we based our calculations with comparing the changes between those groups with one way ANOVA assuming a 15% drop out and a 2-sided alpha of 0.05. We will have 80% power to detect any set of 3 group differences/changes if the SD of the changes is 0.444 or greater. We will have 80% power to detect a difference through the 3 group-one-way-ANOVA if the mean 24 week (6 month) change in SV for the TNF inhibitor group is 5.2ml/m2 or higher while the mean change for the other two groups is 0. To provide a context regarding the number used above as an expected change in SV we would like to mention here that in our pilot data we observed a change in SV of 12.5mL/m2 or higher with TNF inhibitor treatment in patients with RA.
Based on preliminary data RA patients had an LV mass of 120± 27 grams while normal people had an LV mass of 147

±40 gram. For a change in left ventricle mass from 120 to 147 grams over the 6 month period we will have an 80% power to detect this improvement of LV mass in 25 patients treated with TNF inhibitor with a one sided alpha of 0.05 assuming a correlation of 0.35. We will have more than 85% power to detect a difference of 27 grams of mass between the TNF inhibitor treated group and the triple therapy treated group.
For changes in FDG uptake indicative of myocardial inflammation we assume that according to AHA guidelines a significant change in the intensity of FDG uptake would be equal to a decrease of 50%. We will have more than 80% power to detect such a difference between the TNF inhibitor treated group and the triple therapy treated group after 6 months of treatment with a 2 sided alpha of 0.05.

3. STUDY PROCEDURES (See Appendices I,II and III)

Study procedures that are done outside the context of usual care for patients with RA are the following:

i.

Cardiac PET-CT imaging will be used to evaluate myocardial perfusion, myocardial inflammation and myocardial function.

(this section includes references)

PET Perfusion Imaging:

The demonstration and quantification of myocardial hypoperfusion/ischemia with nuclear imaging techniques is a well-established method to predict cardiovascular disease progression risk in cardiac patient populations (1). Myocardial hypoperfusion is a powerful predictor of cardiac endpoints such as nonfatal myocardial infarction and death. Myocardial blood flow determined by quantitative PET is an independent predictor of the coronary circulatory dysfunction in cardiac clinical events and shows superiority to conventional methods. In a recent review, Schindler et al report that functional alterations in cardiac circulation measured by PET imaging appear to be prognostically superior to structural assessments of coronary vessel disease (i.e. coronary angiography, calcification) in predicting future cardiac events. PET measurement of coronary flow reserve provides a sensitive index for evaluating changes in coronary disease severity. A review of a series of seven studies involving more than 1000 patients indicates that perfusion imaging with PET is a sensitive and specific method to diagnose severity of coronary disease (1). These studies found an average sensitivity and specificity of approximately 90% (1,2).
PET measurement of myocardial perfusion is an ideal measure of coronary and microvascular involvement for the purposes of this study, and is preferable to other available techniques. In addition to prognostic significance, there are several reasons for the choice of quantitative PET for myocardial perfusion. The use of PET addresses common limitations of other methods such as coronary angiography. That is, percent diameter stenosis of coronary vessels obtained by means of coronary angiography is poorly related to flow capacity or coronary flow reserve of the coronary arteries. Gould and colleagues have reported that progression or regression of coronary vessels stenosis may involve complex changes in which the integrated hemodynamic effects, absolute arterial lumen area, and length are not accounted for by any single geometric measurement such as percent stenosis. Furthermore, quantifying single focal stenoses on coronary arteriograms does not account for multiple stenoses, diffuse anatomic lesions, or disorders of arterial vasomotion. Therefore, coronary angiography, including quantitative coronary angiography, does not reflect the perfusion capacity of the integrated coronary artery circulation that is diseased in atherosclerosis. It has thus been suggested that the measurement of size and severity of myocardial perfusion abnormalities by PET-CT better reflects changes in the integrated flow capacity of the coronary circulation that are more relevant to long-term clinical outcomes and more sensitive to modest changes in lifestyle modification interventions than other diagnostic methods (1,2). PET-CT imaging also provides accurate information about microvascular blood flow and endothelial dysfuction.

PET Imaging Protocol:

PET utilizes radiolabeled agents (such as [13N] ammonia) for the measurement of myocardial blood flow at rest and during pharmacological stress using agents such as the vasodilator adenosine. The percent increase in blood flow from

rest to stress provides a measure of coronary blood flow reserve, including microvascular flow. Normal subjects without cardiovascular disease or risk factors have a coronary flow reserve on the order of 4. They are capable of a 4 fold increase in blood flow with pharmacological stress, while patients with coronary artery disease demonstrate attenuations in coronary flow reserve.
We will perform PET myocardial perfusion imaging using [13N] ammonia for the measurement of myocardial blood flow at rest and during pharmacological stress using the vasodilator adenosine. PET imaging will be performed in a blinded procedure in all subjects under the supervision of Dr. Bokhari, Investigator and Director of the Columbia University Medical Center Cardiac Positron Emission Tomography Center. Dr Bokhari will otherwise have no contact with the study subjects and will not be aware of participants' clinical info collected during the study. The PET data will be acquired on the Siemens Biograph Truepoint 40 PET/CT scanner. The camera has 4mm resolution and scan time performance superior to the prior generation of PET imaging devices. The Siemens biograph uses computed tomography (CT) acquisition for attenuation correction as well as co-registration with the emission image. PET data are collected in 47 planes 3.375 mm thick that cover a range of 16 cm. A dose of 10 mCi of [N13] ammonia is injected and a 10 min dynamic acquisition is started. The process is repeated, including a second attenuation scan, for the stress study. The injections of ammonia are separated by at least 40 minutes to allow the first injection to decay to a level where it will not interfere with the second study. All scanning is performed in 2D gated mode and reconstructed with filtered back projection using a Hann filter cutoff at 1 cycle/cm.

PET-CT Flow Measures:

To calculate coronary flow reserve, measurements of regional myocardial blood flow at rest and during adenosine stress will be obtained. For this purpose, list mode data will be formatted into dynamic frames of variable length (12 frames x 5 sec, 3 frames x 20 sec, 1 frame x 300 sec). The last frame is used as a template for sectorial region of interest (ROI) analysis of the dynamic images. The input function is generated by drawing an ROI in the LV chamber on a mid-ventricular slice. This procedure yields PET absolute flow measurements in dL/min per 100 gms. The left ventricle is sampled radially from 40 different angles and 40 samples of flow are obtained for each short axis slice. The resulting hundreds of samples are grouped into 17 segments. Since the number of slices is variable, the total number of final samples will vary. Thus, for each segment we will obtain between 520 samples, from which means and standard deviations will be computed for each of the 17 regions. This procedure of repeated sampling allows a greater precision in the flow data. Coronary flow reserve is the ratio of maximum flow during stress to flow at rest. An overall measure of coronary flow reserve for the entire myocardium (across all the 17 regions) will be calculated. Secondarily, regional flow reserve will be calculated according to vascular territories designated by standard techniques, i.e., left anterior descending (LAD), left circumflex (LCX), and right coronary artery (LCA). Additionally, base to apex myocardial perfusion gradients will also be quantified according to methods described by Gould and colleagues. From territorial areas, additional segmentation dividing mid and mid to apical circumferences of the left ventricle will be assigned within each polar map. Within each area, relative myocardial tracer concentrations will be quantitated by comparison to a normal database.

Myocardial Perfusion Defect Score:

In addition to the flow measures described above, we will construct a quantitative summed stress and rest score describing the extent and the severity of the perfusion defects across 17 segments of the myocardium. In each region, the defect severity is quantified on a 4 point scale from normal to absent perfusion. The regional severity scoring is then summed up across the 17 segments yielding a total score. Separate total scores are obtained for the rest and stress conditions, with the rest score assessing fixed or irreversible defects. A reversible defect score will be obtained by subtracting the rest score from the stress score (i.e., summed difference score). For each of the summed rest, stress, and difference scores, each patients score will be divided by the highest possible score to yield a % myocardial involvement. These scores will represent secondary outcome for statistical analysis.

PET for inflammation:

F18 fluorodeoxyglucose (FDG) is a glucose analog that is taken up in metabolically active cells including myocytes and tumor cells. It is also taken up in regions of inflammation. Uptake into myocytes depends on substrate, insulin

levels and GLUT4 transporter. Uptake by tumor and by regions of inflammation presumably uses GLUT1, a non insulin dependent transporter. Positron emission tomography will be performed on all patients from the base of the skull to the chest cavity after injection of F18 FDG and CT scan for neck and chest will be performed. Images will be obtained one to two to three hours after injection. Glucose levels will be checked at the time of injection using a standard clinical protocol. Uptake of tracer will be reported as global or focal and scored. Intensity of uptake will be scored according to a scale from 0 to 3. Level 0 will be no myocardial uptake. Level 1 will be myocardial uptake less than the mediastinal uptake. Level 2 will be uptake in the myocardium equal to mediastinal uptake. Level 3 will be uptake in the myocardium that is greater than mediastinal uptake. Extent of uptake will be assessed as number of specific regions of increased intensity.
A computerized program will also be utilized to assess for the standardized uptake value (SUV) which will give a continuous variable based on quantitative uptake.

CT scan images of the neck and/or chest will be fused with PET scan images to correlate the regions with regions of increased uptake.

PET-CT for the evaluation of ventricular function:

PET assessment of ventricular function is performed during gated myocardial perfusion imaging. With gated PET, accurate measurements are made of LV end-diastolic and end-systolic volumes as well as of LV ejection fraction. Additionally this method allows for assessing regional and global ventricular function both at rest and stress.

Reliability of Cardiac PET Image Reading:

The analysis of cardiac PET scans is largely automated and subject to minimal operator input. Nevertheless, we will monitor reliability of the analysis process. Inter rater and test retest reliability for analysis of cardiac PET scans will be performed prior to the start of the study with two research physicians; using 20 prior scans from previous imaging procedures. These scans will be analyzed independently while blinded to subject identity and diagnosis. For inter rater and test retest reliability, an intra-class correlation coefficient (ICC) >.9 will be considered acceptable. The process will be repeated until this threshold is met. These readings will not be used in the final data analysis. All scans will be analyzed at the conclusion of the study by one of the physician raters blinded to subject identity and treatment group who will not have had contact with the study subjects or involvement in any clinical aspect of the study. Having scans read by a single rater ensures consistency of the measurement. The PET scans will be randomly sequenced for reading by subject group and treatment phase.

3 transverse CT images for the distribution of visceral fat:

Adipose tissue distribution provides an assessment of risk for the development of cardiovascular disease depending on whether is predominantly accumulated as visceral fat or not. Since patients will undergo CT imaging of the chest as part of the cardiac PET-CT imaging protocol we will take the opportunity to obtain 3 additional transverse CT images at the level of the liver, lumbar region and mid-thigh. These images will be obtained within seconds while the patient is having the PET-CT cardiac evaluation and with minimal additional exposure radiation. Fat distribution will be used in our analyses as a potential mediator or confounder of alterations in myocardial perfusion and structure.

CT imaging for Coronary Artery Calcification (CAC):

Coronary artery Calcification (CAC), a subclinical measure of atherosclerosis measured by Computer Tomography (CT) is associated with the degree of atherosclerotic plaque, and is strongly predictive of cardiovascular events including those at low risk. Coronary arterial calcification is part of the development of atherosclerosis, occurs almost exclusively in atherosclerotic arteries, and is absent in the normal vessel wall. Coronary artery calcification occurs in small amounts in the early lesions of atherosclerosis that appear in the second and third decades of life, but it is found more frequently in advanced lesions and in older age.
All subjects (RA patients and controls) will undergo cardiac CT scanning at the same time as the PET examination during study visit 1 only. Electron-beam computed tomography (EBCT) and multi-detector computed tomography

(MDCT) are the primary fast CT methods for CAC measurement at this time. Both technologies employ thin slice CT imaging, using fast scan speeds to reduce motion artifact. Thirty to 40 adjacent axial scans usually are obtained. A calcium scoring system has been devised based on the X-ray attenuation coefficient, or CT number measured in Hounsfield units, and the area of calcium deposits. For our study we will quantify CAC using the Agatson method, with a phantom of known calcium density scanned along with the participant to ensure standardization across scans. A CT study for coronary artery calcium measurement is completed within 10 to 15 min, requiring only a few seconds of scanning time.
The methodology to be used used has been extensively described and standardized and can be reviewed in the reference literature below (3-5).

References:

1. Klocke, FJ, Baird, MG, Lorell, BH, Bateman, TM, Messer, JV, Berman, DS, O'Gara, PT, Carabello, BA, Russell, RO, Jr., Cerqueira, MD, St John Sutton, MG, DeMaria, AN, Udelson, JE, Kennedy, JW, Verani, MS, Williams, KA, Antman, EM, Smith, SC, Jr., Alpert, JS, Gregoratos, G, Anderson, JL, Hiratzka, LF, Faxon, DP, Hunt, SA, Fuster, V, Jacobs, AK, Gibbons, RJ , Russell, RO, ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging-executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). Circulation 2003; 108: 1-15 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14522503
2. Schindler, TH, Zhang, XL, Vincenti, G, Mhiri, L, Lerch, R , Schelbert, HR, Role of PET in the evaluation and understanding of coronary physiology. J Nucl Cardiol 2007; 14(4): 589-603 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17679069
3. Carr JJ, Nelson JC, Wong ND, McNitt-Gray M, Arad Y, Jacobs DR Jr, Sidney S, Bild DE, Williams OD, Detrano RC: Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk
Development in Young Adults (CARDIA) study. Radiology 2005, 234:35-43.
4. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R: Quantification of coronary-artery calcium using ultrafast computed-tomography. J Am Coll Cardiol 1990, 15:827-832.
5. Nelson JC, Kronmal RA, Carr JJ, McNitt-Gray MF, Wong ND, Loria CM, Goldin JG, Williams OD, Detrano R: Measuring coronary calcium on CT images adjusted for attenuation differences. Radiology 2005, 235:403-414.

ii.

3-Dimensional Echocardiography (3D Echo) will be used to evaluate LV mass.

(this section includes references)

3D Echo for evaluation of LV mass

3D Echo has demonstrated incremental value about LV mass over conventional echocardiographic modalities (M-mode, 2D Echo) in different patient populations [1,2]. The major strength of 3D Echo is the accurate imaging of cardiac structures avoiding the need for geometric assumptions in order to calculate outcomes such as the mass of the left ventricle.
Conventional echocardiographic modalities are limited mainly by inaccuracies and variations caused by use of geometric assumptions in case of asymmetric LV geometry and unintended use of oblique planes. 3D Echo, based on the assessment of a larger number of tomographic views, resolves these limitations. 3D Echo correspondingly has the advantage of reducing dependence on geometric models and reducing error based on angulated images [3, 4]. Thus, 3D Echo offers LV mass determination substantially comparable to cardiac magnetic resonance (CMR) imaging, as for global LV volumes [5]. This correlation between 3D Echo and CMR has also been stronger than that has been between conventional echocardiography and CMR [6]. Interobserver variability of real-time 3 dimensional echocardiography

(RT3DE) was additionally reported to be significantly lower than that of 2D Echo, supporting its superiority [7]. 3D Echo accuracy, has been verified using autopsy findings [4]. 3D Echo and CMR also produce comparable results in terms of LV mass with similar interobserver variability [8]. Moreover, 3D Echo is less dependent on operator practice and help to compensate operator inexperience when compared to conventional echocardiography.
3D Echo is feasible in the clinical setting and provides fast and accurate assessment of LV mass, which is superior to conventional echocardiographic methods, especially in distorted hearts. This leads to greater sensitivity and reduced sample size. As 3D Echo is less costly than CMP, it is modality of choice for the proposed study.

References:

1. Gottdiener JS, Bednarz J, Devereux R, Gardin J, Klein A, Manning WJ, Morehead A, Kitzman D, Oh J, Quinones M, Schiller NB, Stein JH, Weissman NJ: American Society of Echocardiography. American Society of Echocardiography recommendations for use of echocardiography in clinical trials. J Am Soc Echocardiogr 2004, 17:1086-119.
2. Yao J, Cao QL, Masani N, Delabays A, Magni G, Acar P, Laskari C, Pandian NG: Three-dimensional echocardiographic estimation of infarct mass based on quantification of dysfunctional left ventricular mass. Circulation 1997, 96:1660-6.
3. Natori S, Lai S, Finn JP, Gomes AS, Hundley WG, Jerosch-Herold M, Pearson G, Sinha S, Arai A, Lima JA, Bluemke DA: Cardiovascular function in multiethnic study of atherosclerosis: normal values by age sex and ethnicity. AJR Am J Roentgenol 2006, 186(6 Suppl 2):S357-65.
4. Qin JX, Jones M, Travaglini A, Song JM, Li J, White RD, Tsujino H, Greenberg NL, Zetts AD, Panza JA, Thomas JD, Shiota T: The accuracy of left ventricular mass determined by real-time three-dimensional echocardiography in chronic animal and clinical studies: a comparison with postmortem examination and magnetic resonance imaging. J Am Soc Echocardiogr 2005, 18:1037-43.
5. Jenkins C, Marwick TH: Baseline and follow-up assessment of regional left ventricular volume using 3-Dimensional echocardiography: comparison with cardiac magnetic resonance. Cardiovasc Ultrasound 2009, 7:55.
6. Nikitin NP, Constantin C, Loh PH, Ghosh J, Lukaschuk EI, Bennett A, Hurren S, Alamgir F, Clark AL, Cleland JG: New generation 3-dimensional echocardiography for left ventricular volumetric and functional measurements: comparison with cardiac magnetic resonance. Eur J Echocardiogr 2006, 7:365-72.
7. Caiani EG, Corsi C, Sugeng L, MacEneaney P, Weinert L, Mor-Avi V, Lang RM: Improved quantification of left ventricular mass based on endocardial and epicardial surface detection with real time three dimensional echocardiography. Heart 2006, 92:213-9.
8. Pouleur AC, le Polain de Waroux JB, Pasquet A, Gerber BL, Gérard O, Allain P, Vanoverschelde JL: Assessment of left ventricular mass and volumes by three-dimensional echocardiography in patients with or without wall motion abnormalities: comparison against cine magnetic resonance imaging. Heart 2008, 94:1050-7.

iii. Phlebotomy - laboratory examinations (See Appendix II)

Participants will undergo laboratory testing and related procedures according to standard of care for monitoring of patient with Rheumatoid arthritis on arthritis medications. Part of the blood obtained will be for usual patient care and part for research purposes as shown in the list below. The exact distribution of testing according to the visit can be viewed in Appendix II.
For study visit I standard of care tests and procedures will not be duplicated if they have already been performed prior to study entry and if results are available in patients records.

LABS TO BE PERFORMED AS PART OF REGULAR CARE
Rheumatoid factor
CCP antibodies
Complete blood count with differential (CBC)
Comprehensive metabolic panel (CMP)
CRP (CRP), ESR
Fasting lipid panel
G6PD

HCV Ab
HBVsAg and HBVsAb

LABS FOR PURELY RESEARCH PURPOSES
Blood for processing, storage, and future biomarker evaluation

OTHER PROCEDURES THAT ARE CONSIDERED STANDARD OF CARE

(this section includes references)

Urine pregnancy test during every study visit involving radiation exposure (prior to the imaging and on the same day)
PPD placement (1) for latent tuberculosis
Pneumococcus vaccination (1)
Influenza (seasonal and H1N1) vaccination (1)
Opthalmologic examination prior or within one year from initiation of treatment with Plaquenil (hydroxychloroquine) according to standard of care, as Plaquenil may rarely cause retinal toxicity (1)

As noted earlier this procedures will not be duplicated if they have taken place as part of usual care prior to participation in the study.
The total volume of blood for the purely research tests is 65 ml in study visits. In addition labs as part of usual care will add 21.4 ml of blood draw volume in Study Visit I and 9.4 ml in study visit II. The maximum amount of blood to be drawn including both research and usual care tests (at visit I) will be 86.4 ml in study visit I and 74.4 ml in study visit II. 9.4 ml of blood will be drawn in safety visits.
Blood samples for research purposes will be stored in Rheumatology divisional freezers at Columbia University in a de-identified manner indicated only by a numeric patient ID.

References:
1. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, Paulus HE, Mudano A, Pisu M, et al: American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum. 2008,59(6):762-84.

iv. Clinical examination including joint examination, anthropometry and vital signs (See also Appendix I)
A musculoskeletal comprehensive examination to obtain counts of swollen and tender joints will take place in every visit. In addition as shown in appendix I other evaluations including seated blood pressure, waist circumference and height and weight will be obtained.

v. DEXA scan
A whole body DEXA scan will be performed on the 50 RA patients who will be randomized to escalation of treatment. As shown in appendix I it will be performed at the time of Study Visit I and II. The purpose will be to evaluate the amount and the pattern of adipose tissue distribution in the body which is an important parameter and risk factor for atheromatous and cardiovascular disease. Radiation exposure is minimal (0.001 rem) per study per patient and there are no risks associated with this study. Pregnancy test as noted earlier will be performed prior to DEXA for every female participant with child bearing potential.

vi. Questionnaire completion (See also Appendix III)
Patients will be asked to complete questionnaires at the time of their study visits as indicated in Appendix III. The questionnaires will be administered in English and Spanish and with the assistance of a research coordinator. The questionnaire list is included below

SF36
HAQ
Health and life questionnaire
Physical activity questionnaire

Medical history
Prednisone history
RA history
Oral Health
Medication history
RA medication history
Joint Count
Personal history
RA LTRC respiratory symptoms
RA LTRC Occupational and environmental exposures
400m Walk Test

4. STUDY DRUGS OR DEVICES

The drugs that will be prescribed to subjects in this study, listed below, are FDA approved for the indicated use, at the prescribed dose(s), and in the patient populations being studied.
TNF INHIBITORS
ENBREL® (etanercept)
REMICADE® (infliximab)
SIMPONI® (golimumab)
HUMIRA® (adalimumab)
CIMZIA (certolizumab)

OTHER RA MEDICATIONS
PLAQUENIL® (Hydroxychloroquine sulfate)
ARAVA® (leflunomide)
Methotrexate
Sulfasalazine
Folic Acid
Prednisone

5. STUDY INSTRUMENTS

SF 36 (Appendix IV): The SF 36 questionnaire is the most widely used tool for measuring patient-reported quality of life. It captures practical, reliable, and valid information about functional health and well-being from the patient's point of view. This surveys is for adults 18 years of age and older, and can be self-administered or interview-administered. Is extensively validated and standardized.

HAQ (Appendix V): The Health Assessment Questionnaire (HAQ) was developed originally in 1978 by James F. Fries, MD, and colleagues at Stanford University. It was designed to represent a model of patient-oriented outcome assessment. The HAQ has been administered and validated in patients with a wide variety of rheumatic diseases, including rheumatoid arthritis.
It is one of the first self-report functional status (disability) measures, and is widely used throughout the world. Although it measures functional status it was found to be the best predictor of mortality in patients with RA. The HAQ has become a de facto mandated outcome measure for clinical trials in rheumatoid arthritis and some other diseases. Is extensively validated and standardized.

Health and life questionnaire (Appendix VI): This questionnaire includes several instruments designed to measure psychosocial characteristics that may be important in understanding the causes of cardiovascular disease. These psychosocial factors may themselves lead to increased risk of cardiovascular disease or may interact with other traditional risk factors, such as diet or sedentary lifestyle. The areas assessed as part of this questionnaire include neighborhood, characteristics, depression, stress, and social support. This is a self-administered form. The terms used in the questionnaire should require no explanation, because they are used in the way they tend to be used by most

people in everyday life. This questionnaire has been extensively used in research before and also during the Multi-Ethnic Study of Atherosclerosis (MESA).

Physical activity questionnaire (Appendix VII): The International Physical Activity Questionnaires (IPAQ) is a standardized questionnaire that will be used to evaluate levels of physical activity. It can be used for either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health related physical activity. The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Medical history, Prednisone history, RA history, Medication history (Appendices VIII, IX, X, XI): these questionnaires only collect history information from the patient, do not require a scoring system and do not need to be standardized or validated as they are used only as history taking tools. However they have been used in our previously federally funded study (ESCAPE I) in the context of MESA (Multi-Ethnic Study of Atherosclerosis)

Oral Health Assessment (Appendix XII): this questionnaire collects information about oral conditions, dental and periodontal disease. RA can affect the oral cavity causing xerostomia (dry mouth) which may predispose to dental disease. In addition a theory linking RA pathogenesis with periodontal disease is under investigation by the research community. This questionnaire does not provide an "oral health score" and is not a standardized data collection tool. It is a symptom and personal history collection form.

RA medication (Appendix XIII) and Joint count (Appendix XIV) questionnaires: these questionnaires only collect history information from the patient, do not require a scoring system and do not need to be standardized or validated as they are used only as history taking tools. Appendix XIII collects information on medications for the treatment of rheumatoid arthritis (not other medications). Appendix XIV collects information about the number of joints that are affected by RA since numbers of affected joints inform therapeutic decisions.

Personal history (Appendix XV): The Personal History questionnaire is used to collect information on socio-economic status (SES) and smoking and drinking habits, all of which are related to an individuals risk of cardiovascular disease. It has been used in previous studies such as in ESCAPE I and in the Multi-Ethnic study of atherosclerosis (MESA)

Lung Tissue Research Consortium (LTRC) respiratory symptom questionnaire (Appendix XVI) and LTRC occupational and environmental exposure (Appendix XVII): Respiratory involvement is the second cause of mortality in patients with RA and symptoms overlap with those from cardiovascular disease. We will use these questionnaires to investigate the risks for respiratory involvement and the prevalence of respiratory symptoms in our research subjects. This questionnaires are used extensively in pulmonary disease related research by entities such as the Lung Tissue Research Consortium (LTRC) and the American Thoracic Society.

400m Walk Test (Appendix XVIII)): Participants will be asked to walk a short distance (400m). This will happen under supervision by the research coordinator and after cardiovascular contraindications have been ruled out by the attached questionnaire. Vital signs will be recorded prior to and after the completion of the test. All information will be recorded in the attached questionnaire. The purpose of this test is to evaluate the tolerance to mild exercise and the response of the cardiovascular system (Heart Rate and Blood pressure) to brisk walking. This test has been used in several studies including MESA.

6. STUDY SUBJECTS

(this section includes references)

Subjects fulfilling the 2010 ACR-EULAR diagnostic criteria for RA (1) but without any history of previous self reported or physician diagnosed cardiovascular events will be eligible for participation in the study. The goal is to

enroll 150 patients for the purposes of this protocol. Subjects will be recruited from the arthritis clinics at the Columbia University.

Among the subjects above, patients with RA who have moderate to high disease activity as defined by a CDAI higher than 10 will be given the opportunity to consent for randomization in treatment with either a TNF inhibitor or alternative treatment and return for follow up visits as indicated in earlier sections. 50 patients will be randomized to this aspect of the study.

15 subjects without RA and without prior cardiovascular disease will also be recruited. These subjects will be recruited among patients in the internal medicine clinics at the Columbia University or from friends of the recruited patients.

Inclusion Criteria
For patient participation in Study Visit I (150 participants):

Diagnosis of RA
Age>18 years old
For patient participation in the randomized treatment and subsequent visits (50 of the initially recruited 150 participants):

Moderate to high RA disease activity defined by a CDAI of >10

Stable dose of Methotrexate for 6 weeks prior to enrollment;

Stable doses of NSAID and prednisone (if already taking these medications) for 2 weeks prior to study

For control participation (15 controls):
Age>18 years old
Absence of diagnosis of RA.

Major Exclusion Criteria

For patient participation in Visit I (150 participants):
Prior self-reported physician diagnosed CV event (MI; angina; stroke or TIA; HF; prior CV procedure (e.g., coronary artery bypass graft, angioplasty, valve replacement, pacemaker);
Contraindications to having a PET-CT scan or receive adenosine or FDG.
Active treatment for Cancer

For patient participation in the randomized treatment and follow up visits (50 of the 150 initially enrolled participants):

Uncontrolled hypertension
Diabetes
Smoking
Treatment with a TNF inhibitor or other biologic currently or within the last 6 months
Treatment with any non-biologic DMARD other than MTX in the past two months;
Untreated positive PPD or active tuberculosis
History of Lymphoma and Melanoma
Ejection Fraction (EF) < 40% (if not known in advance then the Study Visit I Echocardiogram results will be used to exclude the patient in this part of the study)
Change with NSAID/Prednisone dosage in last 2 weeks
Participation in other research studies involving imaging/radiation exposure

A copy of the Patient Screening Form is attached to the protocol as Appendix XXV.

For controls :

Prior self-reported or physician diagnosed CV event (MI; angina; stroke or TIA; HF; prior CV procedure (e.g., coronary artery bypass graft, angioplasty, valve replacement, pacemaker);
Contraindications to having a PET-CT scan or receive adenosine or FDG.
Uncontrolled hypertension.
Participation in other research studies involving imaging/radiation exposure

A copy of the Control Screening Form is attached to the protocol as Appendix XXVI and a copy of the Radiation Screening Form is attached as Appendix XXVII.

RA subjects and controls who do not consent to any aspect of the study such as to the blood draws or to evaluation with PET-CT will be excluded from this study.

In addition patient and controls who are receiving treatment for cancer, with cognitive inability will be excluded from the study.

Patients and controls on statin treatment for hyperlipidemia should ideally stay on a stable dose and the same statin agent for the duration of the study. We will encourage but not require the participants and their treating physicians to do so. The reason is that statins are known to have an anti-inflammatory effect and may interfere with analysis/ interpretation of the amount of myocardial inflammation as measured during PET-CT imaging. Recognizing however, that some patients will be newly diagnosed with hypercholesterolemia during the clinical trial portion of the study and require treatment with a statin, we will allow for this medication initiation, anticipating that the number of new statin starts will be balanced between the two groups due to randomization.

References:

1. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS, et al: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988, 31:315-324

7. RECRUITMENT

Rheumatology colleagues in the CUMC Division of rheumatology will be informed about the current study during regular divisional research meetings where ongoing research projects in the division is reviewed and also during day to day discussions among faculty and fellows.

150 adult patients with RA will be recruited from the patient population seen in the rheumatology private practices and clinics at New York Presbyterian Hospital and Columbia University Medical Center. A letter (attached to the protcol as Appendix XXIX) will be sent on behalf of the Columbia rheumatology physicians to all the patients with Rheumatoid Arthritis followed by the above rheumatologists inviting them to participate in the study. A follow-up phone call by the study coordinator may also take place within a week of mailing out the letters to answer any questions the patients may have.

Flyers (see Appendix XIX) will be available in the waiting area of the rheumatology clinics informing the patients about the ongoing study.
For the enrollment of the controls the following process will be followed: Every RA patient enrolled in the study will be asked whether they could notify and refer friends without RA who may be willing to participate in the study. Referred friends will be asked to communicate by telephone with our research coordinator in order to review eligibility and then arrange the first visit if eligible and willing to consent.

In addition flyers describing the study and tailored for recruitment of non-RA controls will be available in the waiting

rooms of the internal medicine clinics of the New York Presbyterian Hospital (see Appendix XX). Non-RA subjects who are interested in participating will use the contact information provided on the flyers to contact our research coordinator and undergo review of eligibility before proceeding to the consent process.

8. INFORMED CONSENT PROCESS

As noted above, patients will be informed of this study by their treating physician and, if the patient expresses an interest in participating, the Principal Investigator or Co-Investigator or the Study Coordinator will explain the study and review the IRB approved consent form in detail. Each potential subject will have the opportunity to ask questions. Each potential subject will reiterate in his or her own words the purpose of the study, the risks, the benefits, and the alternatives to participating. Individuals who decide to participate in the study will provide written consent. The investigator will also sign and date the consent form. One copy of the consent form will be given to the subject and the original will be filed in the study's research file. Those who want to sign the consent form immediately will be allowed to do so, but will be encouraged to take the consent form home and discuss the study with their family and/or significant other before deciding whether or not to participate.

Patients who are not fluent in English will be provided with an appropriate IRB approved translation of the IRB approved English consent form. The consent form discussion will take place with the assistance of a translator or bilingual member of the study team. Due to the demographics of our local population, we anticipate the need for a Spanish translation and will obtain a certified Spanish translation of the consent form as soon as the English version is approved by the IRB. We have accessibility to Spanish translators to assist with consent form discussions and other study visits and at least two member of our study team are bilingual. Translators are also available through the hospital should the need arise.

9. CONFIDENTIALITY OF STUDY DATA

All data and specimens collected during this study will be assigned a unique code number and will be separated from the patient's name and any other information that could identify the patient. The data file and the file that links the unique code number to patient identity will be maintained in separate password protected files on password protected computers in a locked office in the Division of Rheumatology. Only the Principal Investigator and key study personnel designated by the Principal Investigator will have access to these files. Those with access are held to the strictest standards of confidentiality. The results of this research may be published in scientific journals or presented at medical meetings, but patient identity will not be disclosed.

10. PRIVACY PROTECTIONS

The consent form discloses to potential participants the individuals and/or agencies that are able to look at and copy research records, namely:

- The investigator, study staff and other medical professionals who may be evaluating the study
- Authorities from Columbia University and New York Presbyterian Hospital, including the Institutional Review Board ('IRB')
- The Office of Human Research Protections ('OHRP')
- The Food and Drug Administration ('FDA')
- The sponsor of this study, the National Institutes of Health, including persons or organizations working with or owned by the sponsor

Information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

In addition to confidentiality disclosures described in the consent form, potential participants will also sign the

attached study specific HIPAA Form before participating in this study.

11. POTENTIAL RISKS

A risk exists that despite all provisions to maintain participants confidentiality, confidentiality nonetheless may be compromised. As mentioned above every effort will be made to secure the data collected and separate identifying from deidentified information.

Phlebotomy is associated with minor discomfort and occasional patients may experience a more severe vaso-vagal reaction and light-headedness. A minor risk of a skin infection at the site of phlebotomy also exists but may be treated with a short course of antibiotics should it occur.

The mortality of the PET-CT imaging is low and associated mainly with the stress phase and administration of adenosine. In patients with established coronary artery disease, mortality is reported to be 2/10000 patients. The risk for an acute myocardial infarction is also reported to be 2/10000. These numbers will not be applicable to our participants as candidates with prior cardiovascular events will be screened out.

In addition the mortality at the Columbia university PET center has been 0% for PET-CT stress tests for the last 11 years with over 11000 PET-CT stress tests performed. Research participants with contraindications or risk factors for complications to PET-CT imaging and its stress phase (i.e., patients with cardiac blocks, or severe bronchospastic disease) will be excluded from the study.

The radiation exposure/dosimetry with PET-CT imaging is within FDA guidelines for research of this type. The radiation obtained during each PET examination in our protocol would be equivalent to few months of natural and cosmic radiation.

The additional 3 CT transverse images described above, the cardiac CT for CAC evaluation, and the DEXA are also associated with a small radiation exposure but no other significant risks. Female patients will be tested with a pregnancy test the morning of the day of each test associated with radiation exposure.

In addition the patients will have to be fasting overnight when they present for their study visits and this may cause mild discomfort.

In every study visit participants will be asked if they received radiation from imaging procedures outside the current protocol (for their clinical care). If other imaging studies have taken place the cumulative radiation exposure will be calculated and if it exceeds the level of 50 mSv which is considered to be the maximum acceptable radiation exposure per year then the subject will not continue with further participation in the study.

The testing performed in this study may unmask conditions that have been silent (asymptomatic). If a significant medical finding is noted during participation in this study, the P.I. will be notified immediately by study personnel, PET-CT or Echocardiography centers. Findings will be handled as "alerts" , need for "urgent" or "immediate" referral. An "alert" refers to a medical finding that may have adverse health consequences if untreated. An "urgent referral" is made for abnormalities that require medical attention but not on an emergency basis. An "immediate referral" is a medical emergency that requires immediate notification of both the participant and his/her primary care physician. Examples of "immediate referrals" for PET-CT scans or echocardiography will include, pericardial effusions or pulmonary tumors.

If cause for an "immediate referral" is identified by clinical personnel or PET-CT or echocardiography personnel, the cardiologist or technicians will notify Dr Bathon immediately. Dr. Bathon will then take appropriate medical action which will include informing the patient's primary care provider immediately. The less urgent "alerts" will be transmitted back to the PI from the Reading Centers within two weeks after receiving the scan. Dr. Bathon will take appropriate action, which again will include notification of the patient's primary care physician. A record of all this

events will be maintained.

12. DATA AND SAFETY MONITORING

This study is a single site study employing FDA approved medications for an FDA approved indication. Furthermore, the study is of short duration and does not involve vulnerable populations. Therefore, it is considered low risk and in discussions with the NAIMS program officer requires a safety monitoring committee but not an external DSMB. Our proposed safety monitoring plan for this study consists of:

i. Continuous, close monitoring by the Principal Investigator in conjunction with a named Safety Officer during the first meetings of a Safety Monitoring Committee (see below); and

ii. Twice yearly meetings of a Safety Monitoring Committee (SMC).

There will be prompt reporting of all adverse events to the Safety Officer as well as prompt reporting of unanticipated problems, serious adverse events as well as other risk-related events to the Columbia University Medical Center IRB, in accordance with their reporting policy. This plan is deemed appropriate because study drugs are FDA approved and are used for FDA approved indications; it does not involve high risk or vulnerable populations; and it is a single site study of short duration.

The Safety Officer and Safety Monitoring Committee (SMC) will act in an advisory capacity to monitor patient safety and evaluate the efficacy of the interventions described in this study.

Safety assessments
Toxicity monitoring, joint examination, general clinical examination vital signs (including blood pressure) will be assessed at every visit. In between Study Visits I and II patients will return every 6 to 8 weeks for safety visits per standard of care and which will be focused on toxicity monitoring. Interim safety visits will include the following laboratory assessments: CBC with differential, comprehensive metabolic panel, CRP, and ESR. An exit safety visit will take place approximately 8 weeks after the completion of study visit II and the evaluations mentioned above will take place as well. Study visits including radiation exposure (PET-CT, DEXA, x-rays) will include a urine pregnancy test for all female participants of childbearing potential. Disease activity will be evaluated using the CDAI score at the time of every safety and study visit and treatment will be escalated according to standard of care until they reach the state of low disease activity or remission as defined by a CDAI score of less than or equal to 10.

A copy of the Safety Visit Check Off Sheet is attached as Appendix XXVIII.
Definitions of Adverse Events
An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (or therapy). Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment.

A serious adverse event is an undesirable sign, symptom or medical condition which: (1) is fatal or life-threatening, (2) required or prolonged hospitalization, (3) results in persistent or significant disability/incapacity, (4) constitutes a congenital anomaly or a birth defect, (5) is medically significant, in that it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

In this study, we will utilize a mild, moderate, and severe scale to grade adverse events.

- Mild adverse events will include common side effects with these and other medications, transient laboratory test alterations; discomforts noted but no disruption of daily activities; no therapy, or only symptomatic therapy required.
- Moderate adverse events will include persistent mild events that cause significant impairment in quality of life, laboratory test alterations indicating injury without long-term risk; discomfort sufficient to modify normal daily activity; specific therapy required (i.e. more than symptomatic).

- Severe adverse events prompting immediate withdrawal from the study include laboratory test indicating a serious health threat or permanent injury; incapacity, inability to work, inability to perform normal daily activity; hospitalization required or prolonged; emergency treatment required; life-threatening events; death.

An "unanticipated problem" is any incident, experience or outcome during the study that:
- is serious adverse event or suggests that the study may be placing subjects at a greater risk of harm than was previously known or recognized, and
- is related or possibly related to participation in the research and
- is unexpected given the study procedures and the characteristics or the subject population being studied

All unanticipated problems will be reported promptly to the IRB. All unanticipated problems will also be reported to the safety officer, the SMC, and the funding source for this study (NIH/NIAMS).

In addition all adverse events regardless of whether they constitute unanticipated problems as well as adverse events thought to be related or possibly related to study procedures will also be reported to IRB and to the safety officer, the SMC, and the funding source for this study (NIH/NIAMS).

SMC Responsibilities
The SMC will evaluate the progress of this study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial site, and other factors that can affect study outcome. They will also consider factors external to the study when interpreting the data, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study.

The SMC will make recommendations to the investigators concerning continuation or conclusion of the study.

The SMC will protect the confidentiality of the trial data and the results of monitoring.

Membership
The SMC will consist of three voting members who are not investigators in the study
- A Cardiologist at Mt. Sinai Hospital NY, NY, (Roxana Mehran, MD)
- A Rheumatologist at Cornell University/Hospital for Special Surgery (Steven A. Paget, MD)
- A Columbia University Rheumatologist (Laura Geraldino, MD)

The members will have no financial or scientific conflict of interest with this study. Written documentation attesting to absence of conflict of interest will be available upon request.

The Chairperson for the SMC will be decided during the first meeting and will be responsible for overseeing the meetings and developing the agenda. He/She is the contact person for the SMC.

A Safety Officer will be identified by the PI and committee members at the first meeting. This person will be the contact person for severe adverse event reporting. Procedures for notifying the Chair of the SMC will be discussed at the first meeting.

Committee Process
The first meeting will take place before the study is initiated to discuss the protocol, any modifications, and to establish guidelines to monitor the study. The SMC Chairperson and the PI will prepare the agenda to address the review of modification of the study design, initiation of the trial, identification of a Safety Officer, reporting of adverse events, stopping rules, interim analysis plan, etc.

Meetings of the SMC will be held twice yearly at the call of the Chairperson but additional meetings will be held if the need arises. In addition to committee members, the meetings are attended by the principal investigator and

members of the study team, when appropriate. Meetings may be convened as conference calls as well as in person, although the initial meeting and meetings to discuss interim analysis will be face-to-face. An emergency meeting of the SMC may be called at any time by the Chairperson should questions of patient safety arise - such as at the time of any adverse events or unanticipated problems.

Meeting Format
SMC meetings will consist of an open and a closed session. The open session may be attended by the principal investigator and/or members of the study team. Issues discussed at open sessions will include conduct and progress of the study, including patient accrual, compliance with protocol, and problems encountered. Patient-specific data and treatment group data may not be presented in the open session.

The closed session will be attended only by voting SMC members. The SMC may request others to attend by part or all of the closed session as appropriate. All safety and efficacy data will be presented at this session. The discussion at the closed session is completely confidential.

Should the SMC decide to issue a termination recommendation, full vote of the SMC will be required. In the event of a split vote, majority vote will rule and a minority report will be appended.

Reports
i. Interim Reports: Interim reports will be prepared and distributed by the principal investigator to the SMC during the week preceding the meeting. Additions and other modifications to these reports may be directed by the DSMC on a one-time or continuing basis. Interim data reports generally consist of two parts:
- Part 1 (Open Session Report) provides information on study aspects such as accrual, baseline characteristics, and other general information on study status.
- Part 2 (Closed Session Report) may contain data on study outcomes, including safety data, and depending on the study, perhaps efficacy data. The Closed Session Report is considered confidential and should be destroyed at the conclusion of the meeting.
ii. Reports from the SMC: A written report containing the recommendations for continuation or modifications of the study, signed by the SMC Chairperson, will be sent to the Principal Investigator within one week following the meeting.

It is the responsibility of the PI to distribute the SMC recommendation report to all co-investigators and to assure that copies are submitted to the IRB associated with the study.

Confidentiality
All materials, discussions and proceedings of the SMC are completely confidential. Members and other participants in SMC meetings are expected to maintain confidentiality.

13. POTENTIAL BENEFITS

No direct benefit to study subjects should be expected from this study. Treatment is the same as is provided in standard of care. Rheumatoid arthritis may improve, remain the same, or worsen. Although subjects may not personally benefit from participating in this study, by taking part they may contribute new information that may benefit RA patients in the future.
In addition incidental abnormalities in any of the tests performed in this study will be communicated to the patient with the advice to follow up with the primary care physician as appropriate and as described earlier.

14. ALTERNATIVES

Subjects do not have to take part in this study to receive treatment for Rheumatoid Arthritis. Alternatives to participating in this study include continuing on their current treatment or other standard of care treatment from their primary Rheumatologist, which may or may not be the same as the treatment received during participation in this study. Prospective participants should discuss treatment options with the study doctor to obtain enough information to

decide if they want to join the study.

15. RESEARCH AT EXTERNAL SITES: Not applicable.

16. COLUMBIAAS LEAD INSTITUTION: Not applicable.