

TARGET Clinical Protocol Synopsis

Study Title	Treatments Against RA and Effect on FDG PET-CT: The TARGET Trial
Clinical Phase	Phase IV
Study Rationale	This study seeks to answer the fundamental but as yet unproven hypothesis guiding most CV-related research in RA that chronically elevated levels of inflammation (either systemic, vascular or both) in RA patients compared to the general population is the main risk factor predisposing increased rates of CVD. The most critical unanswered question about CV risk in RA populations is whether anti-inflammatory DMARDs for RA also reduce CVD, which this study will assess using a surrogate measure of CV inflammation.
Study Objectives	<p><u>Primary:</u> To compare the effects on vascular inflammation of TNF antagonists (TNFi) + methotrexate (MTX) versus triple therapy (MTX + sulfasalazine [SSZ] +hydroxychloroquine [HCQ]) in patients with RA who are inadequate responders to MTX monotherapy, using FDG PET/CT as a tool for detecting vascular (arterial) inflammation.</p> <p><u>Secondary:</u> To compare the effects on vascular inflammation of achieving low disease activity or remission (LDAR) vs moderate-high disease activity (MHDA).</p>
Outcome Measures	<p>Primary: Change in vascular inflammation, as assessed by two PET/CT parameters:</p> <ol style="list-style-type: none"> 1. The maximum of the mean total to background ratio (TBR) of the most diseased segment (MDS). The MDS TBRmax is calculated as a mean of maximum TBR values derived from 3 contiguous axial segments. 2. The MDS of the index vessel, defined as the vessel with the highest average TBR at baseline, either aorta or carotid arteries. <p>Secondary: Mean TBR of the index vessel.</p>
Study Design	Phase IV, Randomized, parallel group (triple therapy vs. MTX + TNFi), multi-center, single-blind (blinded: joint assessors, image readers, bioassay technicians)
Study Population	Subjects for this trial will be RA patients who are deemed methotrexate-inadequate responders (MTX-IRs, DAS28>3.2) by their treating rheumatologist, and who have not yet started treatment with a biologic DMARD and are currently not receiving any other DMARD than MTX. In order to enrich our trial subjects for atherosclerosis, male RA patients must be at least 45 years old, and women at least 50 years old.
Eligibility: inclusion/ Exclusion Criteria	<p>Inclusion:</p> <ul style="list-style-type: none"> • Written informed consent signed by the subject; • Fulfill ACR/EULAR 2010 criteria for RA; • Men \geq 45 years and women \geq 50 years; • MTX monotherapy for \geq 12 weeks at \geq 15mg weekly; • DAS28 score $>$ 3.2; • Able to swallow pills at randomization; • Males and females with reproductive potential must agree to practice effective measures of birth control; • If taking prednisone (or equivalent corticosteroid), the dose must be \leq 10 mg/day and stable for at least four weeks prior to randomization. (If subjects are taking steroids every other day, divide dose by 2 to evaluate

	<p>eligibility.); and</p> <ul style="list-style-type: none"> • Willing to comply with all study procedures and be available for the duration of the study. <p>3.3. Exclusion Criteria</p> <ul style="list-style-type: none"> • Prior use of biologic DMARD; • Non-biologic DMARDs other than MTX for two months prior to Screening; • Current use of > 10mg per day of prednisone; • Use of a statin lipid lowering drug within the past year; • Prior patient reported, physician diagnosed clinical CV event: myocardial infarction, angina, stroke, prior vascular procedure (coronary artery angioplasty or stenting, carotid endarterectomy, coronary artery bypass surgery, valve replacement, ilio-femoral bypass surgery); • Uncompensated heart failure, demyelinating disease; • SLE or other autoimmune and chronic inflammatory diseases (i.e. inflammatory bowel disease, sarcoidosis) • Cancer treated in last five years (except basal and squamous cell) or any lymphoma or melanoma; • Diabetes mellitus or fasting blood glucose >120mg/DL; • Known pregnancy, HIV, hepatitis B, hepatitis C, active (or untreated latent) TB; • Known sulfa allergy or other known hypersensitivity to any of the trial agents or G6PD deficiency; • Known macular disease (If other pre-existing non-macular eye disease, a baseline ophthalmology screening exam should be performed.); and • Baseline blood count, renal or liver abnormalities as follows: WBC < 3.0 x 10³/ul, Hemoglobin < 9.0 g/dL, Platelet count < 90,000/ul, estimated glomerular filtration rate < 50 ml/min, liver function tests (AST or ALT) above upper limits of normal.
Study Duration	Total study duration will be 4-years, inclusive of 6 months of start-up, 2 years for recruitment, 6 months of continued follow-up, and 1 year of image and biomarker analyses, and manuscript preparation.
Subject Participation Duration	Enrolled subjects will each receive treatment and follow-up for a period of 6 months.
Site Requirements	<p>All participating sites will have met feasibility requirements that indicate their ability to recruit and retain the necessary number of subjects:</p> <ul style="list-style-type: none"> • Adequate number (minimum n=150) of RA patients; • prior clinical trial experience and successful enrollment ; • access to FDG-PET/CT; • access to standard clinical laboratory assessments; and • availability of trial staff (coordinator, nurse, trained joint count assessor).
Recruitment/ Enrollment	Site Coordinators will query their site’s medical record database to generate and maintain a list of potentially eligible RA patients on MTX monotherapy, who are not excluded by further chart review. Site rheumatologists will notify the Site Coordinator as soon as any of these patients have been deemed MTX-IR, at which point the Site Coordinator will approach the patient for potential recruitment.

Pre-screened patients who provide informed consent will then undergo screening procedures as part of the enrollment process. The screening procedures include patient questionnaires and review of medical history, as well as screening labs that determine whether the subject can safely participate in the trial.

Subjects who are found to be eligible following the screening procedures as described and are still interested in participating will proceed to randomization and baseline FDG PET/CT measurements, as described in the visit schedule.

Visit Schedule

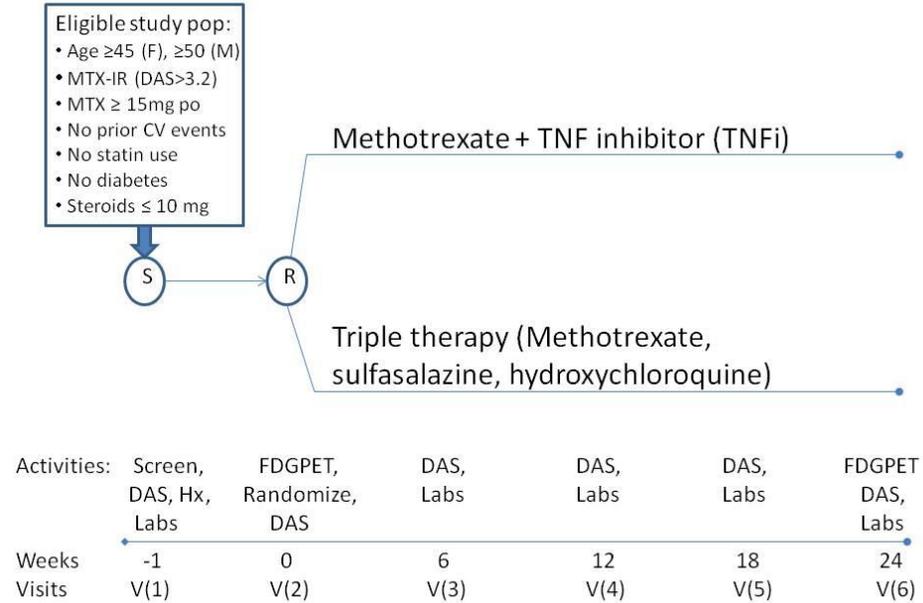
Table 1: Visit Schedule	Screen V ₁ [Wk -2]	Baseline V ₂ [Wk 0]	V ₃ [W6]	V ₄ [Wk12]	V ₅ [Wk18]	V ₆ [Wk24]
Eligibility & consent	x					
CRP	x					
PPD or Quantiferon	x					
CXR, HBV, HCV	x					
Randomize		x				
FDG PET/CT		x				x
Pregnancy test and glucose testing		x				x
Blood pressure/Clinical Parameters	x		x	x	x	x
CBC, LFTs*, BMP*	x		x	x	x	x
Biospecimen collection		x	x		x	x
Joint count	x	x	x	x	x	x
Questionnaires	x	x	x	x	x	x

Consent will be obtained at the beginning of the Screening Visit (Visit 1). Patients who meet eligibility criteria and provide informed consent will undergo the additional screening procedures outlined above in Table 1, including completion of questionnaires, screening laboratory tests including hepatitis B and C screens (if none in the past six months), and chest x-ray (if none in past 12 months). Patients found on Screening to have active hepatitis or active infection (including tuberculosis) or interstitial lung disease will be excluded. If these additional laboratory- and imaging-based eligibility criteria are met and eligibility is confirmed, the FDG PET/CT scan will be scheduled and the Baseline Visit (Visit 2) conducted. Eligible patients will be randomized via the EDC. For the Baseline Visit, the patient will be given instructions for an overnight fast for the purposes of the PET/CT scan and for the research biospecimens. The patient will complete additional questionnaires. All subsequent study visits are performed at six week intervals and should be conducted within 7 days prior to or after the designated date. Blood will be drawn at each visit for safety monitoring; additional fasting blood specimens will be drawn at Visits 2, 3, 4 and 6 for the research biospecimen repository. Visit 6 (week 24) will include acquisition of the second FDG PET/CT.

Intervention

This study will randomize enrolled patients to one of two treatment arms: triple therapy (methotrexate [MTX], sulfasalazine [SSZ], and hydroxychloroquine [HCQ]) or a tumor necrosis factor inhibitor (TNFi) plus MTX.

Study Design



The chosen study treatments are considered standard of care options for the treatment of RA in this patient population. Furthermore, the dosages, frequencies, and administration will adhere to the recommended usage guidelines.

Dosage, Frequency, and Administration

TNFi: Subjects randomized to the TNFi treatment arm will receive either etanercept 50 mg SC weekly or adalimumab 40 mg SQ every other week. The choice will be made by the patient in conjunction with his/her treating rheumatologist, taking into consideration any third party payor restrictions. Patients will continue the same dose of their concomitant background MTX.

- If a EULAR good response (DAS28 < 3.2 and absolute improvement in DAS-28 of > 0.6 and < 1.2) is not achieved by 12 weeks, then treatment will be increased if on adalimumab from 40 mg every other week to every week. If the patient is receiving etanercept, this medication will be discontinued and switched to adalimumab 40 mg every other week. Patients will remain on this new dose or new medication until the end of the study at 24 weeks.

Triple therapy: Subjects assigned to the triple therapy arm will begin SSZ 1 gm bid and HCQ 200 mg twice daily [(not to exceed 6.5 mg/kg HCQ), in addition to background MTX].

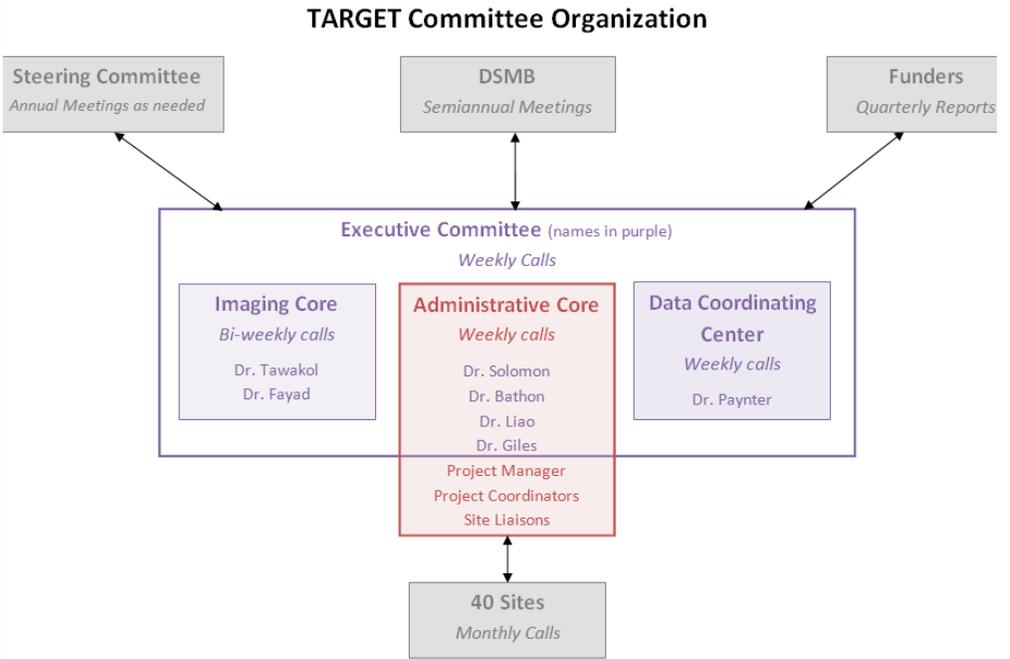
- At 6 weeks if the participant has not achieved a good EULAR response, SSZ will be increased to 1.5 gm bid.
- At 12 weeks, if a good EULAR response has not been achieved, MTX will be

switched to a SQ route and/or the dose increased to 20 or 25 mg weekly (if current dose is < 25 mg/week).

- At 18 weeks, if a good EULAR response has not been achieved, MTX will be switched to leflunomide 10 or 20 mg daily (at the discretion of the study rheumatologist). The participant will remain on leflunomide (and concomitant SSZ + HCQ) for the remaining six weeks of the study.

Blinding Joint assessors performing joint counts will be blinded to treatment assignment, as will the FDG PET/CT imaging readers. Subjects will be instructed to not discuss treatments with the joint assessors. As well, the joint assessors cannot be part of the subject’s regular patient care team. Laboratory staff who run bioassays on biospecimen samples will also be blinded to treatment assignment.

Study Organization



The proposed organizational structure is well-suited for the successful administration of this multi-site trial, and will allow for appropriate oversight and collaboration where needed.

Administrative Core:

- Consists of the TARGET PIs- Drs. Bathon and Solomon, Drs. Giles and Liao, Ms. Wohlfahrt (Project Manager) and Ms. Anne Donnelly (Senior Grants Administrator, BWH).
- Will be the central point of contact for all other entities and is responsible for overseeing study administration including the following:
 - Development and maintenance of the MOOP;
 - Assuring the study is conducted according to the protocol and MOOP;
 - Communications with clinical sites, scheduling of meetings and training sessions, responding to and documenting ad hoc communications;
 - Distribution of all changes, updates and policies of reports and documents to all participating clinical sites;
 - Maintaining the study binder (regulatory and clinical documents); and

- Participating in protocol finalization and preparing study materials.

The Executive Committee :

- Consists of the co-PIs- Drs. Bathon and Solomon, Drs. Giles and Liao, as well as Dr. Paynter, who leads the DCC, and Dr. Tawakol and Dr. Divgi of the Imaging Core;
- Will meet weekly for the first six months of the trial, then monthly thereafter;
- Will review any concerns voiced by other study staff members and resolve issues as needed;
- Will review the progress of the study;
- Will be responsible for making strategic decisions regarding study protocol, resource allocation, recruitment, and protocol adherence. They will have final say on decisions for the entire trial; and
- If conflicts arise between the Co-PIs, issues will be brought to the entire Executive Committee for resolution.

The Steering Committee:

- Will meet quarterly to discuss progress of the trial and provide critical feedback regarding clinical, conceptual, methodological, and feasibility issues that arise through the duration of the trial.

The Data & Safety Monitoring Board (DSMB):

- Will be appointed by the NIH. We anticipate that its membership will include a trial biostatistician, a cardiologist with trial experience, several rheumatologists with trial experience, and a bioethicist.

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The Funders:

- Will have a responsibility in the oversight of the trial; specific arrangement may differ by funding agency.
- Will be updated at regular timepoints with reports of trial progress such as recruitment status, unforeseen problems, and updates to specimen collection.

The Imaging Core:

- Will be co-led by Dr. Tawakol (Massachusetts General Hospital) and Dr. Fayad (Mt. Sinai School of Medicine).
- Will be responsible for overseeing all matters related to collection and assessment of the FDG PET/CT readings including training of imaging sites in standardized protocol techniques, monitoring consistency and quality of the scans, managing transmission and assessment of scans, and facilitating corrective actions for imaging sites as needed.
- Will conduct interpretation of the articular FDG uptake.
- Drs. Tawakol and Divgi will both sit on the Executive Committee to ensure communication between the radiologists and cardiologists and to ensure seamless resolution of any technical and quality assurance issues.

The Data Coordinating Center (DCC):

- Will be run by Nina Paynter, PhD of the Division of Preventive Medicine at

	<p>Brigham and Women’s Hospital. Robert Glynn, PhD, ScD will serve as Senior Biostatistician.</p> <ul style="list-style-type: none"> • Will be responsible for oversight of data collection and analysis. The responsibilities of the DCC include: <ul style="list-style-type: none"> ○ Randomization scheme and procedures; ○ Development and implementation of the data flow, schedules for transferring data from sites, and data tracking; ○ Development of procedures for data entry, error identification, and error correction; ○ Adverse event monitoring and reporting; ○ Site monitoring via the Electronic Data Capture (EDC) to ensure adherence to the protocol and procedures; ○ Quality control procedures; ○ Creating reports - enrollment, adverse events, participant status (e.g., withdrawals) by site; and ○ Trial analyses.
<p>Clinical, Laboratory, and Imaging Study Procedures</p>	<p>Clinical:</p> <ul style="list-style-type: none"> • <u>Joint count</u>: Assessment of the number of painful and swollen joints by a trained joint count assessor (an investigator or a trained research coordinator/nurse) is a standard element of all RA trials and of rheumatology clinical practice. A joint count, which helps to calculate disease activity score, will be measured at all 6 study visits. • <u>RA Disease activity</u>: The DAS-28 is a combined index to assess disease activity in RA and is used routinely in clinical trials and clinical practice. It includes 28 of the total peripheral joints (shoulders, elbows, wrists, MCPs, PIPs and knees), the acute phase response (measured either by erythrocyte sedimentation rate or CRP), and general health into one continuous measure. We will calculate the DAS-28-CRP at each visit to determine whether the patient has achieved a ‘good’ EULAR response. • <u>CV Risk Factors</u>: It will be confirmed during the Screening Visit that the patient has no self-reported, physician diagnosed prior clinical CV events, including history of myocardial infarction, stroke, uncompensated heart failure, or prior vascular procedure (coronary artery angioplasty or stenting, carotid endarterectomy, coronary artery bypass surgery, valve replacement, ilio-femoral bypass surgery). In addition, patients with diabetes and patients on statins are excluded. Once a patient is enrolled however, the following conventional CV risk factors will also be assessed: 1) at each visit - blood pressure, serum glucose; 2) at the Baseline Visit – detailed smoking history, patient reported history of hyperlipidemia (if on statins for this, patient would have been excluded), physical activity, menopausal state, family history of heart disease, anthropomorphic measurements (weight, height, waist and hip circumference). <p>Laboratory:</p> <ul style="list-style-type: none"> • <u>Usual care safety laboratory measures</u> at each visit are: complete blood count (CBC), basic metabolic panel (BMP), CRP, hepatic panel.

	<ul style="list-style-type: none"> • <u>Research laboratory measures- biorepository:</u> At the completion of the study, several analytes will be measured in the <u>Harvard CTSA lab</u> on batched patient samples from visits 2, 3, and 6. These include rheumatoid factor (RF), anti-cyclic citrullinated peptide antibody (anti-CCP), high sensitivity CRP, lipids (total-, LDL-, HDL-cholesterol and triglycerides), and insulin and glucose. The latter two analytes will be used to assess level of insulin resistance. Measurement of these values in our research lab will ensure assay consistency across sites and patients. • <u>Crescendo/Myriad:</u> an aliquot of serum from each of Visits 2, 3 and 6 will be sent to Crescendo Sciences for the MBDA (Vectra-DA) assays. <p>Imaging:</p> <ul style="list-style-type: none"> • The <u>FDG PET/CT scans</u> will assess arterial FDG uptake in the ascending aorta and in the bilateral carotid arteries. Patients will undergo FDG PET/CT scans at baseline and at 24 weeks at their local facility. A detailed draft protocol prepared by the PIs of the Imaging Core in conjunction with our articular PET/CT analysis team will be followed.
<p>Central IRB: Identification and Qualifications</p>	<p>The Central IRB for sites that do not have a local IRB will be the Partners Healthcare IRB. They have substantial multi-site clinical trial experience, with both NIH and Industry funding.</p>
<p>Subject Withdrawal</p>	<p>Study treatment may be discontinued and the subject withdrawn for any of the following:</p> <ul style="list-style-type: none"> • Cautionary laboratory value • Malignancy other than basal or squamous cell • Repeated subject non-compliance or loss to follow-up. • The subject withdraws consent • The investigator or DSMB believes it is in the best interest of the subject • The study is terminated <p>If study treatment is discontinued (e.g., for an adverse event) and there is no safety issue precluding it, the patient will be asked to return for the follow-up FDG PET/CT scan if he/she has received at least eight weeks of the randomized treatment prior to withdrawal.</p> <p>If the subject withdraws consent, all study related visits, exams, procedures and data collection are terminated.</p>