Rationale and Design for PACE: Patients with Intermittent Claudication Injected with ALDH Bright Cells

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Peripheral artery disease (PAD) is recognized as a public health issue because of its prevalence, functional limitations, and increased risk of systemic ischemic events. Current treatments for claudication, the primary symptom in patients with PAD, have limitations. Cells identified using cytosolic enzyme aldehyde dehydrogenase (ALDH) may benefit patients with severe PAD but has not been studied in patients with claudication. PACE is a randomized, double-blind, placebo-controlled clinical trial conducted by the Cardiovascular Cell Therapy Research Network to assess the safety and efficacy of autologous bone marrow–derived ALDHbr cells delivered by direct intramuscular injections in 80 patients with symptom-limiting intermittent claudication. Eligible patients will have a significant stenosis or occlusion of infrainguinal arteries and a resting ankle-brachial index less than 0.90 and will be randomized 1:1 to cell or placebo treatment with a 1-year follow-up.

The primary end points are the change in peak walking time and leg collateral arterial anatomy, calf muscle blood flow, and tissue perfusion as determined by magnetic resonance imaging at 6 months compared with baseline. The latter 3 measurements are new physiologic lower extremity tissue perfusion and PAD imaging–based end points that may help to quantify the biologic and mechanistic effects of cell therapy. This trial will collect important mechanistic and clinical information on the safety and efficacy of ALDHbr cells in patients with claudication and provide valuable insight into the utility of advanced magnetic resonance imaging end points. (Am Heart J 2014;168:667-673.e2.)

The evaluation of the physiologic and clinical effects of cell therapy in individuals with claudication presents considerable challenges to trial design. The Cardiovascular Cell Therapy Research Network (CCTRN) has significant expertise in both cell therapy trial design and PAD therapeutic outcome assessment. This study integrates knowledge from 3 distinct fields—cell therapy, vascular medicine, and magnetic resonance imaging (MRI)—into the planning of the Patients with Intermittent Claudication Injected with ALDH Bright Cells (PACE) trial. This prospective, multicenter, placebo-controlled randomized trial will investigate the effects of a subset of bone marrow mononuclear cells (BMMNCs) on leg perfusion and limb symptoms in individuals with symptom-limiting intermittent claudication. We anticipate that these results will improve future PAD clinical trial design and ultimately lead to novel stem cell therapies for these patients.

**Background**

**Peripheral artery disease**

In the United States, at least 8 to 10 million people have PAD3,4 and up to 12% of adults with atherosclerosis risk
factors in developed nations have evidence of PAD. Five clinical presentations of PAD are recognized: asymptomatic disease (in 50% of patients), atypical leg symptoms (40%-50%), typical (classic) exercise-induced claudication (in 8%-12%), and the 2 severe manifestations (<2%-5%) of acute limb ischemia and CLI.

Individuals with lifestyle-limiting claudication symptoms may benefit from several evidence-based therapies that lower cardiovascular ischemic risk and diminish the functional limitations associated with claudication. Supervised exercise is an effective therapeutic option that is durable and cost effective. Claudication pharmacotherapy (eg, cilostazol) improves walking distance and quality of life in many low-risk individuals but is significantly underused. Invasive open surgical and endovascular revascularization techniques are useful in patients who do not improve with other options. However, each of these approaches has limitations. Supervised exercise cannot be used successfully in patients who have significant non-PAD exertional comorbidities, whose health care providers do not offer this treatment in cardiac rehabilitation programs, or who lack motivation or social support. Cilostazol is not universally tolerated, cannot be used in patients with systolic heart failure, and may not yield an adequate therapeutic response. Revascularization may not be feasible in patients with unfavorable anatomy, has associated risks to the index limb and renal function, and may increase myocardial infarction and stroke risk. Therefore, novel therapeutic options are needed for patients with PAD and claudication. Cell therapy may become an attractive treatment option for individuals with claudication if clinical benefits are proven.

Cell type

Bone marrow mononuclear cells have enhanced neangiogenesis in ischemic tissues in preclinical studies, and clinical studies have demonstrated that these cells may benefit patients with PAD and CLI. However, only 1 small nonrandomized trial has been conducted in patients with intermittent claudication. Bone marrow mononuclear cells are a heterogeneous population of cells that includes stem cells and non-stem cells with varying degrees of therapeutic potential. Selected cell populations from the bone marrow enriched for angiogenic activities may provide a superior therapeutic effect. A subtype of hematopoietic progenitor cells has been isolated based on the presence of the cytosolic enzyme aldehyde dehydrogenase (ALDH), a marker for stem and progenitor cells. This subpopulation of progenitor cells called ALDHbr cells represents about 1% of total BMNCs and contains a heterogeneous mixture of cell types thought to be needed for ischemic repair, including hematopoietic, endothelial, and mesenchymal progenitor cells. Preclinical studies have shown that ALDHbr cells promote angiogenesis and restore blood flow in hind limb ischemia, and quantitative real-time polymerase chain reaction has shown gene expression of multiple angiogenic factors, including interleukin 8, transforming growth factor β, vascular endothelial growth factor, and midkine in bone marrow–derived ALDHbr cells. Moreover, in a phase 1 trial, Perin et al demonstrated the safety and potential efficacy of ALDHbr cells in patients with CLI. In addition, in a pilot study of patients with heart failure, ALDHbr cells injected into the left ventricle showed a similar safety profile and improvement in surrogate efficacy end points.

Magnetic resonance imaging

Recent advances in MRI techniques may provide new, more accurate methods to noninvasively quantify the angiogenic response to cell administration. Both arterial anatomy and skeletal muscle perfusion may be evaluated by administering exogenous contrast media to image arterial and microvascular structures. The benefits of MRI for this study include the absence of ionizing radiation (making it safe for repeated measurements), a tomographic 3-dimensional field of view unencumbered by acoustic windows, excellent soft-tissue contrast, the ability to measure bulk vascular (and tissue) morphology and flow patterns within major vessels, and the capability to assess microvascular flow and tissue metabolism. This anatomical and physiologic evaluation of a stem cell intervention in vivo will enable clinical determination of the angiogenic effects in ischemic lower limbs. In addition, MRI can provide cross-sectional imaging of the skeletal muscle to identify and quantify pathophysiologic alterations in the skeletal muscle of patients with PAD.

Cardiovascular Cell Therapy Research Network

In its second National Institutes of Health–funded cycle, the CCTRN comprises 8 clinical research centers (University of Florida, Indiana University, University of Louisville, University of Miami, Minneapolis Heart Institute, the University of Minnesota, Texas Heart Institute, and Stanford University), a data coordinating center (DCC), a cell processing quality assurance center, and 3 core laboratories including a biorepository. The organizational structure and oversight of the CCTRN are described in the Appendix A.

Study design

PACE is a randomized, double-blind, placebo-controlled clinical trial designed to evaluate the effect of ALDHbr cells versus placebo in individuals with PAD and intermittent claudication. The investigation is funded by the National Heart, Lung, and Blood Institute (NHLBI). The hypothesis of PACE is that ALDHbr cells will increase peak walking time (PWT) in patients with PAD.
and intermittent claudication by increasing blood flow in the treated limb. Additional hypotheses to be tested are that (1) ALDH<sup>br</sup> cells increase the number of new vessels in the treated limb; (2) ALDH<sup>br</sup> cells increase hyperemic vascular flow; (3) ALDH<sup>br</sup> cells increase perfusion; and (4) changes in PWT will correlate with changes in the number of new vessels, vascular flow, or perfusion.

**Study population**
A total of 80 patients will be randomly assigned to receive either active (n = 40) or placebo (n = 40) therapy. The study group will comprise patients who have atherosclerotic lower extremity PAD with symptom-limiting intermittent claudication identified as greater in 1 leg. Patients will be selected based on their PAD anatomy to include the presence of a significant (≥50%) stenosis or occlusion of the infragenicular arteries, including the superficial femoral artery, popliteal artery, and/or infrapopliteal arteries. Patients will not have documented aortoiliac inflow stenoses and will have a resting ankle-brachial index (ABI) < 0.90 or a toe-brachial index < 0.70 (for patients with noncompressible pedal pulses) (Table I).

Patients initially considered for PACE will undergo a preliminary review of their medical records to determine if they meet the inclusion and exclusion criteria (Table I and online Appendix Supplementary Table). Once deemed eligible, patients will meet with the research team to review the possible risks of participation and informed consent documents, which will provide information regarding standard alternative claudication therapies.

**Baseline screening and randomization**
Baseline evaluations will be conducted during the screening period extending from the date informed consent is signed until the day of treatment (not to exceed 60 days before treatment).

Participants will be randomized through a Web access database created and maintained by the DCC.

**Cell processing**
To isolate ALDH<sup>br</sup> cells, we will collect 180 mL (±10 mL) of bone marrow from the patient’s posterior superior iliac spine; the level of sedation (conscious sedation or general anesthesia) for this procedure will be determined by local institutional guidelines. The final study product must meet specific release criteria before distribution to the clinical sites (Table II). If the study product does not meet release criteria, the patient will not be treated but will continue in the trial as part of the intention to treat analysis. The cell product will be delivered to the local cell-processing laboratories from either Aldagen (North Carolina) or the Center for Cell and Gene Therapy (Baylor College of Medicine, Houston, Texas) and must be administered within 96 hours of bone marrow aspiration. The placebo product comprises phenol red–free CellGro SCGM serum-free medium (CellGenix Technologie Transfer GmbH, Freiburg, Germany) supplemented with 1% human serum albumin. Both placebo and cell product are supplied in packaging identical in appearance.

**Cell delivery**
The objective of delivery is to place the cells or placebo at a depth corresponding to the muscular mass of the calf (gastrocnemius) and lower thigh (semitendinosus and biceps femoris). After the patient is made as comfortable as possible, the injection leg will be confirmed, and the 10 injection sites will be marked with a template to standardize injections across centers. Anesthetic cream will be applied, and the needle will be inserted at a 90° angle to the skin for 8 injections into the bulk of the gastrocnemius and 2 into the thigh adductors. After insertion, the syringe will be aspirated to avoid intravascular injection, and then 1 mL of study product will be slowly delivered at each injection site. After injections, gentle pressure will be applied with a bandage over each injection site, if necessary (Figure 1).
Follow-up evaluations

Follow-up will begin on the injection day (day 0). Randomized patients will be followed up for safety and efficacy for 180 days, with evaluations on days 7, 30, 90, and 180 (primary end point assessment) (Figure 2). Patients will be contacted by telephone at 12 months to assess long-term leg symptoms, physical limitations, and quality of life. Participants will be considered lost to follow-up after 3 consecutive failed telephone contacts and 1 undeliverable certified letter.

Safety monitoring

All study participants will have adverse events transmitted to each center’s institutional review board and the DCC, the Food and Drug Administration, and the NHLBI-sponsored data safety and monitoring board. The data safety and monitoring board will meet at least twice yearly to review the performance of the participating sites, assess recruitment, evaluate study progress, and report to the NHLBI. PACE will be placed on temporary hold until a thorough investigation is conducted if: 1 case of malignant tumor growth at the site of study product injection; 3 cases of cellulitis/vasculitis in a treated (index) limb; 3 cases of deep vein thrombosis (DVT); 1 case of pulmonary embolism; 1 case of disease progression to CLI; or 1 case of compartment syndrome. The DCC will oversee regulatory and safety compliance of all participating units.

Biorepository

For patients who consent to sample donation, any bone marrow that was not used to make the study product will be shipped to the biorepository. In addition, the following samples will be shipped to the biorepository for phenotyping and functional analyses: whole peripheral blood, plasma, and buffy coat obtained before bone marrow harvest, 30 minutes after product injection, and at follow-up (1 week, 1 month, and 6 months). Bone marrow from patients will be analyzed by flow cytometry for 14 cell surface markers and by 2 colony-forming assays (colony-forming unit fibroblast and hematopoietic colony-forming cell-assay) to determine functional potency.

Magnetic resonance imaging

An MRI core laboratory (Johns Hopkins University) will assess MRI quality among sites. End points were selected based on published reproducibility assessments. Lower extremity peripheral artery anatomy and function will be assessed by using time-resolved, contrast-enhanced magnetic resonance angiography (MRA) after the injection (0.05 mmol/kg) of an extravascular gadolinium-based contrast agent. For upper leg MRA, 3-dimensional contrast-enhanced MRA data acquisition will be triggered when the injected contrast bolus (0.1 mmol/kg) is seen at the target anatomy by using a real-time monitoring scan. Bulk macrovascular blood flow to the calf muscle will be assessed by using a phase-contrast magnetic resonance (MR) sequence in conjunction with cardiac gating. Peak arterial blood flow and the time-resolved flow curve across the R-R interval will be measured for the vessel of interest. Arterial flow reserve will be measured by using the flow measured at resting and hyperemic states. Reactive hyperemia will be induced in the symptomatic leg with the use of inflatable cuffs. The cuff will be inflated for 300 seconds (for 180-300 seconds for patients who cannot tolerate a 5-minute cuff inflation) at the midthigh level with suprasystolic pressures to completely occlude flow to the calf (>25-50 mm Hg above brachial systolic blood pressure). Hyperemic flow will be measured for up to 10 minutes after cuff deflation. Microvascular function will be determined in the calf musculature by performing perfusion measurements using dynamic contrast-enhanced MRI (DCE-MRI). Dynamic contrast-enhanced MRI will be preceded by the measurement of spin-lattice relaxation time ($T_1$) of the tissues of interest (ie, over the field of view of DCE-MRI measurement) using a multiple–flip angle $T_1$.
measurement. A similar cuff inflation and deflation protocol described above will be used. In addition, gadolinium-based contrast agent (0.05 mmol/kg) will be administered immediately after the cuff is fully inflated. A rapid release of cuff pressure (<1 second) will ensure a bolus infusion of contrast agent, and the DCE-MRI sequence will be run in a dynamic fashion with an effective temporal resolution of about 5 seconds per dynamic. The acquired slice orientation will be transverse to encompass both legs. A total number of 60 dynamics will be acquired (3-4 minutes) to observe the first passage of contrast bolus. The signal intensity curves will be converted to contrast agent concentration curves to quantify microvascular blood flow. After the dynamic scan, the T1 measurement sequence will be repeated to measure postcontrast T1 times. We will use the precontrast and postcontrast T1 times to calculate the extracellular volume of the calf muscle.

Statistical analysis plan

PACE will test the hypothesis that ALDH<sup>br</sup> cells improve PWT and lower limb blood flow compared with placebo. Its 4 primary end points to be assessed at 6 months (1 clinical and 3 MR end points) are (1) PWT, (2) leg collateral artery anatomy (MR), (3) macrovascular flow (MR), and (4) calf muscle perfusion (MR) (Table III). Each end point will be assessed as the difference between follow-up and baseline. The effect of therapy on each primary evaluation will be assessed at the 0.05 level with no adjustment for multiple comparisons. All primary analyses will be conducted under the “intention-to-treat” principle and an additional “as treated” analysis.

Secondary end points are change in resting ABI, change in postexercise ABI, and change in claudication onset time. Each will be obtained at baseline and at 3 and 6 months. We will also analyze changes in two quality of life measures (Walking Impairment Questionnaire and Peripheral Artery Questionnaire) between baseline and 1, 3, and 6 mo. We will formally assess the relationship between PWT and the 3 imaging-based primary end points adjusting for important baseline covariates. Specific analyses and subgroup evaluations are provided in the Appendix A.

Discussion

The PACE trial design is unique on several levels. First, the results of this study will fill a current knowledge gap by collecting efficacy data from a randomized clinical study of cell therapy in patients with intermittent claudication. Second, we are using a novel cell population that has shown promise in improving limb perfusion in a pilot study in patients with CLI. Finally, this protocol evaluates new MR anatomical and physiologic end points that may be applied more broadly in future PAD clinical trials and may provide mechanistic insights that can link anatomical arterial structure, physiologic flow, and clinical end points in cell-treated patients.
Table III. Study end points

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<tr>
<th>Multiple primary end points (reflecting change from baseline to 6 mo between groups)</th>
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<td>PWT</td>
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<td>Leg collateral artery anatomy: no. of new vessels</td>
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<tr>
<td>Vascular flow: change in peak flow (mL/sec)</td>
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<tr>
<td>Perfusion: change in peak hyperemic flow (mL/sec)</td>
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<td>Secondary end points (reflecting change from baseline)</td>
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<td>Resting ABI at 3 and 6 mo</td>
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<td>Postexercise ABI at 3 and 6 mo</td>
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<tr>
<td>COT at 3 and 6 mo</td>
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<tr>
<td>PWT at 3 mo</td>
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<tr>
<td>Walking Impairment Questionnaire at 1, 3, and 6 mo</td>
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<td>Peripheral Artery Questionnaire at 1, 3, and 6 mo</td>
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<td>Assessment of the relationship between PWT and the 3 imaging-based primary end points</td>
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Abbreviation: COT, Claudication onset time.

The typical end point of PWT (also expressed as maximal walking distance) on a graded treadmill has many physiologic determinants, including the severity of the conduit artery stenosis, the extent of arterial collaterals, microvascular function, capillary density, mitochondrial function, skeletal muscle fiber type and innervation, and neurobehavioral determinants such as motivation and alterations in gait. Measurement of PWT is a clinically relevant end point as it defines functional status, is approvable by the Food and Drug Administration, and permits comparison of the net treatment effect of cell therapy to currently approved and future investigational therapeutic approaches. However, in evaluating a novel therapy that may have differential mechanistic effects, using an end point that also assesses specific anatomical and functional flow changes due to the therapy is desirable. Thus, we considered the use of MRI end points to evaluate the changes in perfusion, flow, and the vasculature that might be induced, allowing a more direct demonstration of the biologic effect of stem cell therapy on collateral channels (arteriogenesis) or capillary density (angiogenesis). Because the use of MRI end points presents additional challenges in a traditional phase 3 clinical trial paradigm in which only 1 primary end point is appropriate, we are operating in a different type I error paradigm.

Previous PAD trials have also assessed limb perfusion with the use of imaging modalities such as digital subtraction angiography (DSA). Digital subtraction angiography has shown improvement in collateral circulation after cell therapy in patients with CLI; however, in a randomized, double-blind cell therapy trial that showed significant increase in pain-free walking distance and ABI (n = 25), 2 groups of experienced radiologists and vascular surgeons were unable to distinguish any significant difference in the arterial anatomy measured from the DSA of responders as compared with nonresponders. The authors concluded that DSA is not sensitive and reliable enough to quantify the changes in blood flow or clinical benefits that might occur after cell therapy. In considering these findings, we sought to investigate the role of a potentially more sensitive imaging modality.

The data collected in this trial can offer new insights into how lower extremity arterial structure and blood flow physiology may alter key PAD clinical outcomes. For example, the relative concordance (or discordance) between the traditional functional PAD end points (PWT) and the novel MR end points is unknown. A therapeutic beneficial PWT response may be observed in the absence of anatomical collateral or perfusion changes and would therefore imply a need to re-evaluate current mechanistic hypotheses of cell therapy benefits. Such discordance may lead to new efforts to improve the sensitivity of the MRI measurements. Alternatively, an identifiable change in imaging end points without associated changes in traditional PAD assessments would advance the field by expanding the ability to evaluate therapeutic effects and identify the mechanisms of benefit.

By combining varied network-based expertise, the PACE trial design offers significant benefits in advancing the knowledge base for PAD therapies. These results may lead to the identification of new, reliable MRI end points and increase the options for safe, effective cell treatments for patients with PAD. Our study addresses an unmet need by identifying a potentially therapeutic stem cell regimen for patients with intermittent claudication.

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**Disclosures**

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References

Appendix A
Cardiovascular Cell Therapy Research Network

The Cardiovascular Cell Therapy Research Network (CCTRN) was established by the National Heart, Lung and Blood Institute (NHLBI) to develop, coordinate, and conduct multiple collaborative protocols testing the effects of stem cell therapy on cardiovascular disease. The Network builds on contemporary findings from cell therapy studies in the basic science community, translating this newly acquired information to the clinical setting in the phase I/II study paradigm. The data coordinating center (DCC) located at the University of Texas School of Public Health provides trial management and data analysis for CCTRN studies. The Biorepository Core Laboratory (at the Texas Heart Institute) stores patient samples for studies aimed at examining the relationship between clinical outcomes of cell therapy and cell characteristics to better understand the mechanisms of cell-mediated repair. Together, the Network components provide standardization of cell therapy preparation and endpoint measurements.

All clinical centers participate in the selection and design of Network protocols, which are also reviewed by an independent Protocol Review Committee and a Gene Therapy/Cell Therapy Data Safety and Monitoring Board (DSMB) under the aegis of the NHLBI. Each clinical center and the DCC have independent Institutional Review Board approvals and oversight. The multicenter nature of this effort accelerates recruitment and provides the combined expertise of experienced researchers in designing and conducting trials and interpreting the results. In addition, the regional arrangement of CCTRN clinical centers creates the environment for a disbursed and rapid distribution of findings to the research community and ultimately the public.

Additional Details of the Statistical Analysis Plan

Secondary and safety endpoints (Table III) will be reported in descriptive terms. The MR efficacy endpoints will be assessed only at the 6-month time point. Although the stratified (by clinical center) random assignment of participants to treatment groups should ensure comparability with respect to known and unknown variables, an imbalance may still occur by chance. Descriptive statistics for baseline characteristics known or suspected to be associated with outcomes will be prepared for the treatment groups. The variables considered in such a description can be categorized as 1) demographic characteristics; 2) medical history; 3) physical examination; and 4) laboratory data. Exact testing for categorical variables and Student t testing for continuous variables will be used to evaluate the differences in baseline variables between treatment groups.

Clinical endpoints will be assessed by a standing PACE endpoints committee whose members will be blinded to therapy assignment.

The 4 primary endpoints and 5 secondary endpoints listed above are each continuous and will be assessed individually using a simple unweighted general linear model to evaluate the effect of therapy on the change from baseline to 6 months in the primary and secondary endpoints. Analyses will be adjusted for clinical center effects and important baseline covariates. Log transformations will be considered if the PWT data are not normally distributed. Clinical endpoint distributions will be assessed using a dichotomous approach.

Prospectively declared subgroups of interest are age, sex, race, baseline ABI, diabetes, hypertension, cilostazol and statin use, and characteristics of the bone marrow and study product, including function of progenitor cells (hematopoietic and mesenchymal) and the number of cells delivered. In addition, an analysis will be conducted in those patients who had resting and post-exercise ABI measurements. The effect of therapy will be assessed in patients who had a 20% decrease in ABI between rest and exercise pressures and those who did not. Additionally, the effect of therapy will be assessed in patients with suprapopliteal disease and infrapopliteal disease compared to the effect of therapy in patients with only infrapopliteal disease.
Supplementary Table

Exclusion Criteria
1. Presence of any musculoskeletal disease, cardiac or pulmonary disease, or neurological disease that limits the patient’s ability to walk to fulfill protocol requirements (claudication must be the consistent primary exercise limitation).
2. Inability to complete treadmill testing per protocol requirements.
3. Ability to walk for more than 11 minutes on the treadmill during treadmill testing.
4. Patients who identify both legs as equivocally symptomatic or alternate between symptomatic legs on the baseline treadmill tests.
5. Patients with critical limb ischemia (ischemic rest pain or ischemia-related non healing wounds or tissue loss (Rutherford categories 4, 5 or 6).
6. Recent (<3 months) infrainguinal revascularization (surgery or endovascular revascularization) or revascularization planned during study period.
7. Patients with a patent bypass graft in the index limb, with or without evidence of a hemodynamically significant stenosis or other defect (kinking, pseudoaneurysm, or fistula).
8. Patients with >2+ lower extremity pitting edema.
9. Patients with myelodysplastic syndrome (MDS).
10. Patients who are pregnant or lactating, planning to become pregnant in the next 12 months, or are unwilling to use acceptable forms of birth control during study participation.
11. CHF hospitalization within the last 1 month prior to enrollment.
12. Acute coronary syndrome in the last 1 month prior to enrollment.
13. HIV positive, active HBV or HCV disease.
14. History of cancer within the last 5 years, except basal cell skin carcinoma.
15. Any bleeding diathesis defined as an INR ≥ 2.0 (off anticoagulation therapy) or history of platelet count less than 100,000 or hemophilia.
16. Contraindication to MRI (including knee replacement hardware in the index leg) or known allergy to MR contrast media.
17. Chronic kidney disease (eGFR <30 by MDRD or Mayo or Cockcroft-Gault formula).
18. Uncontrolled diabetes (Hba1c > 8.5).
19. Planned change (join or quit) to active involvement in a supervised exercise program (e.g., with a trainer, exercise protocol, and goals, such as in a PAD, cardiac or pulmonary rehabilitation program) during study participation.
20. Plans to change medical therapy during the duration of the study, (i.e. patients who use cilostazol should remain on a stable dose for four weeks prior to enrollment and should not change doses for the 6 months of the study duration.) As always, cilostazol can be discontinued if new heart failure or intolerance occurs during study participation.
21. Any condition requiring immunosuppressant medications (e.g., for treatment of organ transplants, psoriasis, Crohn’s disease, alopecia areata).
22. History of inflammatory or progressively fibrotic conditions (e.g. rheumatoid arthritis, systemic lupus erythematosis, vasculitic disorders, idiopathic pulmonary fibrosis, retroperitoneal fibrosis).
23. Patients with any untreated stenosis > 70% of the distal aorta, common iliac, or external iliac arteries by CT, Angiography or MRI imaging will be excluded from enrollment (patients with previously successfully revascularized inflow stenoses may enroll in PACE). Subjects who were screen failures for a flow-limiting proximal lesion may be rescreened 3 months after successful angioplasty/stenting.
24. Inability to provide written informed consent due to cognitive or language barriers (interpreter permitted).
25. Concurrent enrollment in another clinical interventional investigative trial.
26. Presence of any clinical condition that in the opinion of the PR or the sponsor makes the patient not suitable to participate in the trial.