PROTOCOL TITLE: **Tel**misartan Plus **Ex**ercise to Improve Functioning in PAD: The **TELEX** Trial

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Telmisartan Plus **Ex**ercise to Improve Functioning in PAD: The **TELEX** Trial

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1.0 Objectives

1.1 Purpose, Objectives, Specific Aims

Our work and that of others shows that patients with lower extremity peripheral artery disease (PAD) have greater functional impairment, faster functional decline, and higher rates of mobility loss compared to people without PAD (1-7). PAD-related ischemia-reperfusion of calf skeletal muscle during walking activity is associated with calf skeletal muscle fiber atrophy and impaired calf muscle mitochondria function (8-12). These calf muscle abnormalities in people with PAD are associated with functional impairment and mobility disability (13-15). Yet few medical therapies are available to improve functioning or prevent disability in PAD.

Recent evidence suggests that the angiotensin receptor blocker (ARB) telmisartan may reverse the skeletal muscle dysfunction present in PAD (16-19). In normal mice, telmisartan increases Type I skeletal muscle fibers, improves mitochondrial function, and enhances exercise performance (16-18). Also in mice, ARBs reduce fibrosis and enhance satellite cell-dependent muscle regeneration after muscle injury (20-23). We hypothesize that these favorable effects of ARBs and telmisartan on skeletal muscle in mice may be particularly beneficial for the ischemia-reperfusion related calf muscle injury observed in patients with PAD. In support of our hypothesis, a small pilot trial in humans showed that telmisartan improves treadmill walking performance in people with PAD (19).

After a discussion with the Data Safety Monitoring Board on 10/31/19, it was determined that the sample size would be reduced from 240 participants to 112 participants and that the primary comparison will be comparing all participants randomized to telmisartan (with and without exercise) vs. all participants randomized to placebo (with and without exercise). The specific aims and power calculation and statistical analysis plan were revised accordingly. The reason for the change in sample size was due to difficulty with enrollment, because most people with peripheral artery disease were already taking either an ACE inhibitor or an angiotensin receptor blocker (ARB).

This study will definitively establish whether telmisartan improves walking performance in people with PAD. We will conduct a randomized clinical trial (2 x 2 factorial design) of 112 participants with PAD randomized to one of four arms: Group A: telmisartan + supervised exercise therapy; Group B: telmisartan + a “no exercise” control group; Group C: placebo + supervised exercise therapy; and Group D: placebo + a “no exercise” control group. Our primary outcome is change in six-minute walk performance between baseline and 6-month follow-up. Our secondary aims will measure change in treadmill walking performance, patient-reported walking performance (measured by the Walking Impairment Questionnaire (WIQ)), and quality of

life (measured by the Short Form-36 Physical Functioning (SF-36 PF) score). In exploratory aims, we will obtain calf muscle biopsies to delineate biologic pathways by which these therapies improve functioning.

Primary Specific Aim. Our primary specific aim for this study is as follows: We will determine whether telmisartan therapy with or without exercise improves six-minute walk distance at 6-month follow-up, compared to placebo with or without exercise. Specifically, this aim consists of a two group comparison of all participants randomized to telmisartan vs. all participants randomized to placebo.

Secondary specific aim #1. We will determine whether telmisartan combined with supervised treadmill exercise achieves greater improvement in six-minute walk distance at 6-month follow-up, compared to supervised exercise alone and compared to telmisartan alone, respectively.

Secondary specific aim #2. We will determine whether telmisartan alone improves six-minute walk distance at 6-month follow-up, compared to placebo.

Secondary specific aim #3. We will determine whether telmisartan with or without exercise improves maximal treadmill walking distance, the Walking Impairment Questionnaire, and the Short Form 36 physical functioning score compared to placebo with or without exercise Specifically, this aim consists of a two group comparison of all participants randomized to telmisartan vs. all groups randomized to placebo.

Tertiary specific aim 1. We will determine whether telmisartan therapy alone significantly improves maximal treadmill walking distance, the Walking Impairment Questionnaire (WIQ), and the Short Form 36 (SF-36) PF score at 6-month follow-up, compared to placebo alone.

Tertiary specific aim 2: We will determine whether telmisartan combined with supervised treadmill exercise achieves greater improvement in maximal treadmill walking distance, the Walking Impairment Questionnaire (WIQ), and the Short Form 36 (SF-36) PF score at 6-month follow-up, compared to supervised exercise alone and compared to telmisartan alone, respectively.

Our first exploratory specific aim is to determine the effects of telmisartan (with and without exercise) on gastrocnemius muscle biopsy measures of quantity and activity of peroxisome proliferator activator receptor delta (PPARδ), PPAR-γ coactivator-1alpha (PGC-1α), adenosine monophosphate-activated protein kinase (AMPK), relative gene expression of PPARδ, PGC-

1α, AMPK, FOXO3A, and SIRT-1, satellite cell number, and Type 1 muscle fiber composition at 6-month follow-up, compared to placebo (with and without exercise). This aim will facilitate the identification of potential biologic pathways underlying improved walking performance in people with PAD.

Our second exploratory specific aim is to determine the effects of telmisartan alone, exercise alone, and the combination of telmisartan plus exercise on gastrocnemius muscle biopsy measures of quantity and activity of peroxisome proliferator activator receptor delta (PPARδ), PPAR-γ coactivator-1alpha (PGC-1α), adenosine monophosphate-activated protein kinase (AMPK), relative gene expression of PPARδ, PGC-1α, AMPK, FOXO3A, and SIRT-1, satellite cell number, and Type 1 muscle fiber composition at 6-month follow-up, compared to placebo. This aim will facilitate the identification of potential biologic pathways underlying improved walking performance in people with PAD.

1.2 Hypotheses.

We hypothesize that:
1. PAD participants randomized to telmisartan with or without exercise (i.e. all participants randomized to telmisartan) will achieve greater improvement in six-minute walk distance at 6-month follow-up, compared to placebo with or without exercise (i.e. all participants randomized to placebo).
2. PAD participants randomized to the combination of telmisartan plus supervised treadmill exercise will achieve greater improvement in six-minute walk distance at 6-month follow-up, compared to telmisartan alone and supervised exercise alone, respectively.
3. PAD participants randomized to telmisartan alone will achieve greater improvement in six-minute walk distance compared to placebo.
4. PAD participants randomized to telmisartan (with or without exercise) will achieve greater improvement in maximal treadmill walking distance, the WIQ, and the SF-36 PF score at 6-month follow-up, compared to participants randomized to placebo (with or without exercise). Specifically, we hypothesize that all participants randomized to telmisartan will improve each outcome significantly more than all participants randomized to placebo.
5. PAD participants randomized to telmisartan alone will significantly improve maximal treadmill walking distance, the WIQ and the SF-36 PF score at 6- month follow-up, compared to placebo.
6. PAD participants randomized to the combination of telmisartan plus supervised treadmill exercise will achieve greater improvement in maximal treadmill walking distance, the WIQ, and the SF-36 PF score at 6-month follow-up, compared to telmisartan alone and as compared to supervised exercise alone, respectively.

2.0 Background

2.1 Relevant prior experience and gaps in current knowledge

A. Lower extremity peripheral artery disease (PAD) causes functional impairment, functional decline, and disability. PAD affects eight million men and women in the U.S. and more than 200 million men and women worldwide (24,25). PAD will be increasingly common as the population survives longer with chronic disease (26). Our work and that of others demonstrate that people with PAD have greater functional impairment, more rapid functional decline, and faster mobility loss than those without PAD (1-7). Recent evidence shows that chronic disability, such as that associated with PAD, accounts for more than half of U.S. health burden (26). Furthermore, therapeutic advances have not kept pace with the growing burden of disability from chronic disease (26).

B. Few therapies have been identified to improve functioning and prevent disability in PAD. Only two medications, pentoxifylline and cilostazol, are FDA-approved for treating PAD-associated walking impairment. Of these, recent data show that pentoxifylline is usually ineffective and benefits from cilostazol are modest (27-31). New therapies are urgently needed to prevent disability in patients with PAD.

C. Ischemia-reperfusion injury damages calf skeletal muscle in patients with PAD. Patients with PAD experience calf muscle ischemia during walking activity, when metabolic demands exceed oxygen supply. Patients with PAD experience calf muscle reperfusion during rest, when blood supply increases sufficiently to meet calf muscle oxygen requirements. This phenomenon of ischemia-reperfusion generates reactive oxygen species (ROS), such as superoxide anion and hydrogen peroxide, that damage muscle fibers, impair mitochondrial function, and promote apoptosis (8-12,32-34). For example, in a study of 34 participants with PAD and 21 without PAD who underwent calf muscle biopsy, PAD participants had higher protein carbonyl content (695 grayscale units $\pm$ 1.32 vs. 486 grayscale units $\pm$ 135) and higher 4-hydroxy-2-nonenal (HNE) levels (436 grayscale units $\pm$ 119 vs. 261 grayscale units $\pm$ 101, $P<.001$), indicating higher calf muscle levels of oxidative stress in the PAD participants. Higher quantities of oxidative stress were associated with fewer myofibers in participants with PAD (8).

D. Further evidence of damaged calf skeletal muscle in patients with PAD. People with PAD have smaller calf muscle mass, impaired calf muscle mitochondria function, and poorer leg strength compared to people without PAD (8,11-13,32-36). Several examples follow. First, in our Walking and Leg Circulation Study (WALCS) II cohort, we used computed tomography (CT) to image calf skeletal muscle in 439 people with PAD and 265 without PAD (13). Presence and severity of PAD were associated with

smaller calf muscle area (ABI < 0.50: 5,193 mm^2; ABI 0.50-0.90: 5,546 mm^2; ABI 0.91-1.30: 5,941 mm^2, P<0.001) and higher calf muscle percent fat (ABI < 0.50: 12.8%; ABI 0.50-0.90: 11.4%; ABI 0.91-1.30: 9.2% P=0.02) even after adjusting for known and potential confounders including age, sex, comorbidities, and physical activity (13). Second, among patients with PAD, electron microscopy of calf skeletal muscle shows pathologic changes in myofibrils, mitochondria, nuclei, and sarcolemma of calf muscle myofibers (11). Third, calf muscle mitochondria from PAD patients have a quantitative mitochondria dysfunction, with reduced energy production (33,34). One study used magnetic resonance spectroscopy to measure the efficiency with which mitochondrial oxidative phosphorylation restores levels of adenosine triphosphate (ATP) following ATP-depleting exercise in 12 men with PAD and 14 without PAD who engaged in 90 seconds of submaximal plantarflexion exercise. The PAD participants had significantly poorer phosphocreatine recovery (137 seconds $\pm$ 41 vs. 44 seconds $\pm$ 3, P=0.02) and poorer ATP recovery (60 seconds $\pm$ 10 vs. 29 seconds $\pm$ 2, P=0.02) following exercise than patients without PAD (33). These results demonstrate a defect in calf muscle mitochondrial oxidative phosphorylation in PAD that is independent of differences in blood flow between people with and without PAD. Fourth, in two separate studies, poorer mitochondrial function, measured by respirometry from muscle biopsy specimens (14) or magnetic resonance spectroscopy (34), was associated with poorer treadmill walking in people with PAD. Fifth, more adverse calf muscle characteristics, measured by CT, are associated with higher rates of mobility loss at two-year follow-up among people with PAD (15). Among 370 PAD participants in our WALCS II cohort, those in the lowest tertile for calf muscle area at baseline and those in the highest (worst) tertile for calf muscle percent fat at baseline had the highest rates of mobility loss (Hazard Ratio (HR) = 3.29, 95% Confidence Interval (CI)-1.40-7.73) and HR =5.55, CI=1.82-16.7), adjusting for confounders at two-year follow-up (15). In summary, people with PAD have adverse calf skeletal muscle characteristics, characterized by loss of muscle fibers and impaired mitochondrial function. These skeletal muscle impairments are associated with walking impairment and mobility loss in people with PAD.

2.2 Relevant Preliminary Data.

The TELEX Trial builds on our prior work. Prior study has established that patients with PAD have significant functional impairment and faster functional decline and mobility loss than people without PAD (1-6). We have successfully completed large randomized trials of exercise in PAD patients (43,60). Our preliminary evidence supports our hypotheses and shows that PAD participants taking an ACE inhibitor or an ARB have more favorable mitochondrial function and respond more favorably to an exercise intervention than those not taking these medications.

2.3 Scientific background and significance of research based on existing literature.

A. Telmisartan improves oxygen consumption and running endurance in mice by up-regulating peroxisome proliferator activated receptor delta (PPARδ) and increasing skeletal muscle levels of adenosine monophosphate-activated protein kinase (AMPK) (16,18). In cell culture and animal studies, telmisartan up-regulates PPARδ and AMPK, suggesting a mechanism underlying beneficial effects of telmisartan on muscle contractile properties and energy production (16,18,36,37). PPARδ, expressed in high concentrations in skeletal muscle, regulates the metabolic and contractile properties of myofibers (36,37). Mice that overexpress PPARδ have greater oxidative Type I muscle fibers, improved oxygen consumption, enhanced whole-body insulin sensitivity, and greater walking endurance (36,37). Type I muscle fibers are rich in mitochondria that provide a steady supply of ATP and are fatigue resistant. AMPK is a major regulator of energy metabolism in skeletal muscle that directly up-regulates PGC-1α, increases mitochondrial biogenesis, and enhances mitochondrial function (37).

Two studies from the Zhu laboratory showed that telmisartan fed mice had increased quantities of Type I muscle fibers, increased oxygen consumption, and improved running endurance compared to control mice (16,18). In *in vitro* analyses of cultured myotubes, telmisartan increased PPAR-δ mRNA and protein expression by 105% and 102%, respectively, and increased AMPK expression by more than two-fold (16). The resulting increased PPAR-δ quantity in gastrocnemius muscle was associated with increased AMPK phosphorylation, increased Type I muscle fiber quantity, improved insulin mediated glucose uptake, increased oxygen consumption, and improved running endurance (16,18). None of these favorable effects of telmisartan occurred in mutant mice lacking PPARδ skeletal muscle receptors (16,18). In summary, in normal mice, telmisartan improves oxygen consumption and increases running endurance and these favorable effects are mediated by higher levels of PPARδ and AMPK that act to increase abundance of Type I muscle fibers and improve mitochondrial function. We hypothesize that telmisartan will improve walking performance in patients with PAD by increasing the abundance of Type I muscle fibers and by improving mitochondrial function. We further hypothesize that these changes will be mediated by increased expression of PPARδ and AMPK in calf skeletal muscle.

B. Angiotensin receptor blockers (ARBs) increase skeletal muscle perfusion (38). Angiotensin Type 1 (AR1) and Type 2 (AR2) receptors exist throughout the skeletal muscle microcirculatory system (39). AR1

activation promotes vasoconstriction and smooth muscle proliferation. AR2 activation promotes vasodilation in small vessels. Chai and colleagues studied the effect of losartan, an ARB, on skeletal muscle blood flow in mice (38). Losartan increased muscle blood volume by more than three-fold and increased muscle interstitial oxygenation by two-fold. These favorable effects of losartan were independent of femoral artery blood flow and were due to blocking the vasoconstrictive properties of AR1 and allowing the vasodilatory properties of AR2 to predominate (38). The net result was an increase in skeletal muscle perfusion and oxygen delivery. Telmisartan has more than a 3000-fold greater affinity for AR1 blockade, compared to AR2 and has a much stronger affinity for AR1, compared to alternative ARBs (40). To our knowledge, telmisartan is the only pharmacologic agent with properties that both increase skeletal muscle perfusion and intrinsically improves skeletal muscle quality. Together, these properties make telmisartan an extremely promising therapy for PAD.

C. A pilot study suggests that telmisartan improves treadmill walking performance and endothelial function in people with PAD. Zankl and colleagues randomized 36 individuals with PAD to telmisartan vs. placebo for 12 months (19). Participants randomized to telmisartan achieved greater gains in maximal treadmill walking distance compared to participants randomized to placebo (from 132 to 191 meters in the telmisartan group vs. from 100 to 103 meters in the placebo group, $P<0.001$) and greater increases in brachial artery flow-mediated dilation compared to placebo (from 0.06 to 0.08 mm in the telmisartan group vs. from 0.05 to 0.04 mm in the placebo group, $P<0.001$). This pilot study supports our hypothesis that telmisartan improves treadmill walking performance as compared to placebo. However, the sample size was small. To our knowledge no other trials have studied telmisartan in PAD patients.

D. Telmisartan may enhance benefits of supervised treadmill exercise in people with PAD. Supervised treadmill exercise significantly improves treadmill walking and six-minute walk performance in people with PAD (42-44). The mechanism by which supervised treadmill exercise improves functional performance in people with PAD is unclear (45). However, several studies that obtained gastrocnemius muscle biopsies before and after a supervised exercise intervention in PAD patients have begun to delineate biologic pathways of improved walking performance in response to supervised exercise (46-49). Collectively, these studies indicate that supervised treadmill exercise increases capillary density, but does not improve myofiber or mitochondrial function in PAD (46-49). For example, Duscha and colleagues randomized 35 patients with PAD to supervised treadmill exercise vs. a less intensive home-based walking program for 12 weeks (46). PAD patients randomized to supervised exercise increased their calf muscle capillary density (from 216 capillaries/mm^2 $\pm$ 66 to 286 capillaries/mm^2 $\pm$ 78, $P<0.01$), but participants randomized to the less

intensive home-based exercise had no change in capillary density (from 238 capillaries/mm^2 ± 78 to 235 capillaries/mm^2 ± 91). Neither group had a meaningful change in quantity of calf skeletal muscle Type I fibers or levels of citrate synthase, a measure of mitochondrial function. These data and others demonstrate that supervised treadmill exercise, conducted at the intensity recommended by clinical practice guidelines, increases calf muscle capillary density but does not improve calf muscle metabolism (46-49). We propose that by combining telmisartan (an intervention that increases Type I muscle fibers and mitochondrial function) with supervised treadmill exercise (an intervention that increases calf muscle capillary density), the combination of telmisartan + supervised treadmill exercise will achieve greater benefit than either therapy alone (Figure 1).

E. Additional evidence to support combined therapy with telmisartan and supervised exercise. Consistent with our hypothesis, a study of sedentary mice and a separate study of a muscular dystrophy mouse model each demonstrated that PPARδ agonist drugs act synergistically with exercise to improve running capacity (37,41). In both studies, the synergistic effect of the PPARδ agonist drugs was mediated by PPARδ receptors and AMPK. As described in section 2.3C, telmisartan is a PPARδ agonist drug that increases quantities of PPARδ and AMPK in skeletal muscle of normal mice. Narkar and colleagues treated normal mice with the PPARδ agonist GW1516. When administered alone, the PPARδ agonist GW1516 did not improve running endurance in mice. However, when administered in conjunction with exercise, the PPARδ agonist GW1516 significantly increased oxidative myofiber quantity and improved running endurance more than exercise alone. This combined beneficial effect appeared to be due to an interaction of the PPARδ agonist GW1516 with exercise-induced increases in AMPK, which together favorably altered gene transcription to achieve increased oxidative myofibers and improved running endurance (37). Consistent with this observation, a similar synergy was observed when the PPARδ agonist GW1516 was combined with AICAR, an oral agent that increases AMPK levels (37). Because telmisartan is also a PPARδ agonist, this evidence supports our hypothesis that telmisartan combined with supervised exercise will achieve greater gains in walking endurance compared to telmisartan alone or supervised exercise alone, respectively.

F. Telmisartan may promote skeletal muscle regeneration by increasing muscle satellite cells. Prolonged or repeated skeletal muscle injury is associated with skeletal muscle fibrosis and impaired myofiber regeneration (21,50). PAD patients experience mitochondrial and myofiber injury from ischemia/reperfusion-induced oxidative stress in calf muscle during walking activity (8,12). Skeletal muscle injury is normally repaired through the activity of resident muscle stem cells, known as satellite cells (51). Satellite cells reside beneath the basement membrane, closely

associated with the muscle fiber. In response to muscle injury, they are activated, proliferate and fuse to either form new muscle fibers *de novo* or fuse with existing fibers to repair and replace lost fiber nuclei. In addition to promoting muscle fiber regeneration, satellite cell activity facilitates endothelial cell function in a mouse model of ischemic injury (52). Satellite cells increase in response to resistance training, likely in response to associated muscle damage induced by training, contributing to the hypertrophic response (53-55). Satellite cells also increase in response to aerobic exercise (56), potentially contributing to both muscle fiber growth (57) and to muscle adaptation and remodeling, independent of myofiber hypertrophy in humans (58). The angiotensin receptor blocker (ARB) losartan increases muscle regeneration in damaged muscle (59). We hypothesize that satellite cells are an important but unexplored target for improving muscle function in PAD patients and that similar to the ARB losartan, telmisartan, will increase satellite cells in damaged muscle. This hypothesis will be evaluated in our Exploratory Aim.

Theoretical Framework. The underlying pathophysiology of PAD-related functional impairment consists of ischemia-reperfusion damage of calf skeletal muscle that reduces the quantity of calf muscle myofibers, impairs mitochondrial function, reduces walking endurance, and leads to mobility loss (Figure 1a). Telmisartan targets these PAD-related skeletal muscle deficiencies with therapeutic actions that increase abundance of Type I calf muscle fibers, improve mitochondrial function, increase calf muscle perfusion, and promote calf muscle regeneration after injury (Figure 1b). Supervised exercise targets PAD-related skeletal muscle deficiencies by increasing calf muscle capillary density, increasing satellite cells, and promoting skeletal muscle regeneration (Figure 1b). Based on this evidence, we hypothesize that telmisartan will improve the six-minute walk as compared to placebo and that the combination of telmisartan with supervised exercise will improve six-minute walk more than either therapy alone.

Figure 1. Theoretical Model for the TELEX Trial

Figure 1a. Underlying Pathophysiology of Peripheral Artery Disease

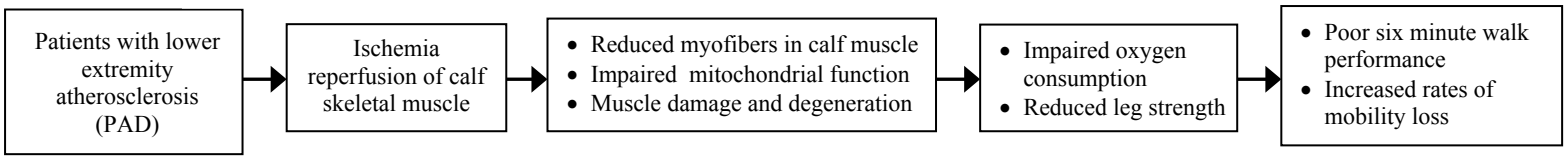
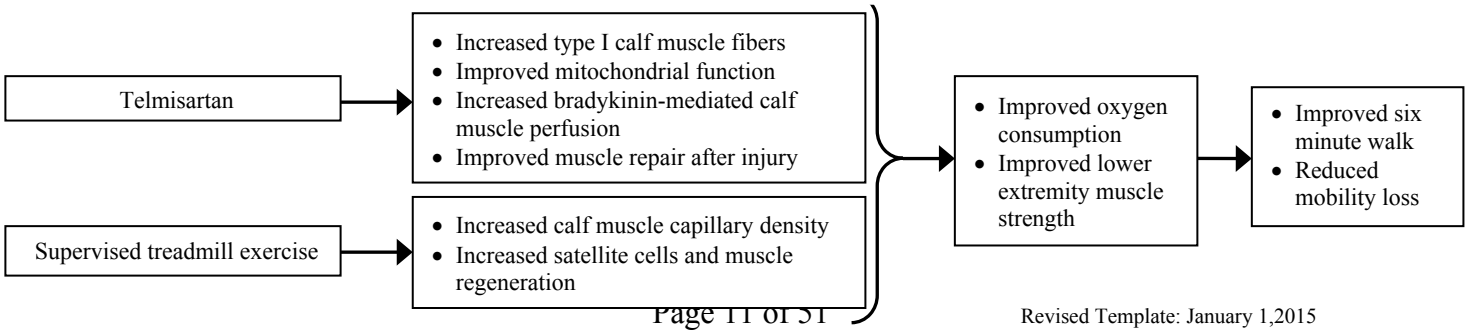


Figure 1b. Therapeutic Potential of Telmisartan combined with exercise



Innovation of the Research.

A. To our knowledge no prior studies have assessed whether the <u>combination</u> of telmisartan and supervised treadmill exercise improves walking performance more than either individual therapy (i.e. more than telmisartan alone or more than supervised exercise alone) in <u>any</u> population. We hypothesize that by combining telmisartan therapy, which increases calf skeletal muscle Type I fibers and improves mitochondrial function in mice, with supervised exercise, which increases calf muscle capillary density and skeletal muscle regeneration in humans, the combination will be better than either individual therapy (16,18,46-49). Telmisartan is a PPARδ agonist (16,18). In healthy mice, and in mice models of muscular dystrophy, other PPAR-δ agonists that are not clinically available act synergistically with exercise induced-increases in AMPK to increase oxidative myofiber quantity, improve mitochondrial function, and increase running endurance (37,41). Together, these findings support our hypothesis that the combination of telmisartan plus supervised exercise will have substantially greater benefit than either individual therapy. Yet no randomized trials in any human population have ever tested whether the combination of any ARB with exercise improves walking performance more than either treatment alone.

B. The TELEX Trial will measure changes in gastrocnemius muscle biopsy measures of satellite cell number, Type 1 muscle fiber composition, and quantity and activity of PPARδ, PGC-1α, AMPK, and relative gene expression of PPARδ, PGC-1α, AMPK, FOXO3A, and SIRT-1 in response to study interventions. Changes in these muscle outcomes in response to telmisartan, with or without exercise, have not been measured in any human population. This component of the TELEX Trial enables us to delineate biologic pathways by which the interventions may improve functioning in patients with PAD. Identifying biologic mechanisms of these therapies will help identify new therapies, with similar biologic actions, that improve walking performance in people with PAD. This is a highly innovative feature of our proposal.

C. Summary of distinctive features of this trial, compared to prior work. Only one previous study, a small pilot study, demonstrated that telmisartan increased treadmill walking performance and endothelial function in patients with PAD (19). Our proposal has multiple unique features as compared to this small pilot study (19). First, the primary outcome in the pilot study was treadmill walking performance (19). In contrast, our primary outcome is the six-minute walk, a well-validated

outcome in people with PAD that better reflects mobility in the community than treadmill walking performance. Second, the TELEX Trial will test whether the combination of telmisartan plus supervised treadmill exercise is superior to telmisartan alone and supervised treadmill exercise alone, respectively, for improving functional performance in PAD. As described above, preliminary evidence supports our hypothesis that telmisartan may be more efficacious when delivered with supervised treadmill exercise, but this question has never been addressed in any human study to our knowledge. Third, our proposed muscle biopsies will delineate myocellular pathways of improved walking performance in people with PAD.

3.0 Inclusion and Exclusion Criteria

3.1 Screening for eligibility

Initial eligibility criteria will be assessed by telephone. Potential participants who remain eligible after the telephone screening will be scheduled for a baseline visit, where they will undergo additional testing to determine their eligibility for randomization.

3.2 Inclusion and Exclusion Criteria.

Inclusion Criteria. All participants will have PAD. PAD will be defined as follows. First, an ABI $\leq$ 0.90 at the baseline study visit is an inclusion criterion for PAD. ABI $\leq$ 0.90 is a well-accepted standard for defining PAD (61-64). Second, potential participants who have an ABI > 0.90 but $\leq$ 1.00 and experience a 20% or higher drop in ABI after heel-rise exercise will be eligible. Third, potential participants with an ABI > 0.90 who have vascular lab evidence of PAD or angiographic evidence of PAD will be eligible. Finally, potential participants with a history of lower extremity revascularization who do not meet the criterion above and have an ABI > 0.90 with a 20% or higher drop in ABI after heel-rise exercise will be eligible.

Exclusion Criteria.

1. Above or below knee amputation, critical limb ischemia, wheelchair confinement, inability to walk without a walker, or current foot ulcer. These are exclusion criteria because they prevent full participation in the intervention or imply an underlying impairment that is too severe to be improved with trial interventions.

2. Walking is limited by a condition other than PAD. This is an exclusion because the intervention is designed to improve PAD-related walking impairment.

3. > Class II NYHA heart failure or angina, increase in angina, angina at rest, or abnormal baseline treadmill stress test. This is an

exclusion because exercise may not be safe for these individuals. Potential participants may become eligible following an abnormal baseline treadmill stress test if they have evidence of an absence of coronary ischemia based on testing with their own physician.

4. Currently taking an angiotensin receptor blocker or an ACE inhibitor or use of these medications in the past three months. This is an exclusion because these individuals are already receiving a major component of the trial intervention.

5. Currently taking aliskiren (Tekturna). This is an exclusion because telmisartan may not be safe to take concurrently with akiskiren.

6. Blood pressure < 100/50 at baseline or potassium > 5.0 meq/L at baseline.

7. Blood pressure < 100/50 after run-in or potassium ≥ 5.5 meq/L at the end of run-in.

8. Severe hepatic impairment defined by two or more liver function enzyme values greater than 2.5 the upper limit of normal.

9. Acute decline in renal function on telmisartan, defined as a 30% or greater decline in eGFR following the two-week run-in as compared to baseline. If the participant had a baseline eGFR performed by his/her physician within two months of the baseline eGFR for the TELEX trial, the participant's physician's eGFR may be considered the baseline measure, at the study principal investigator's discretion.

10. Allergy to ARBs.

11. Congestive heart failure with an ejection fraction <40.

12. Failure to successfully complete the 2-week study run-in, defined as failing to attend the health education and treadmill exercise run-in sessions and/or failing to take the study medication daily for 10 or more days in the two-week period (i.e. one pill per day for ≥ 10 days out of the 14 day run-in period).

13. Surgery including lower extremity revascularization, coronary revascularization with stenting, or orthopedic surgery during the past 3 months or anticipated in the next 6 months or myocardial infarction or stroke in the past 3 months.

14. Major medical illness including renal disease requiring dialysis, lung disease requiring oxygen, Parkinson's disease, a life-threatening illness with life expectancy less than six months, or cancer requiring treatment in the previous two years. [NOTE: potential participants may still qualify if they have had treatment for an early stage cancer in the past two years and the prognosis is excellent. Patients who only use oxygen at night may still qualify.] This is an exclusion

because these conditions may interfere with the ability to fully participate in and complete the study.

15. MMSE score < 23 (65) or dementia. This is an exclusion because it may interfere with the ability to fully participate in the study. However, investigator discretion may be used to allow some people below this threshold to participate, if the investigator determines there is another reason for their lower score, including lack of sufficient familiarity with the English language or lack of sufficient education to achieve a score of 23 or higher. Note that the MMSE includes some spelling and English writing proficiency.

16. Currently walking regularly for exercise at a level similar to the study intervention. This is an exclusion because these individuals are already engaged in a significant component of the intervention.

17. Participation in another clinical trial or cardiac rehabilitation or completion of a clinical trial or cardiac rehabilitation in the previous three months. [NOTE: after completing a stem cell or gene therapy intervention, participants will become eligible after the final study follow-up visit of the stem cell or gene therapy study so long as at least six months have passed since the final intervention administration. After completing an exercise intervention or a supplement or drug therapy (other than stem cell or gene therapy), participants will be eligible after the final study follow-up visit as long as at least three months have passed since the final intervention of the trial.] This is an exclusion because interference with ability to determine whether study interventions are responsible for improved outcomes.

18. Non-English speaking, a visual impairment that limits walking ability, or a hearing impairment that interferes with study participation. This is an exclusion criterion because these potential participants may not be able to participate fully in the intervention.

19. In addition to the above criteria, investigator discretion will be used to determine if the trial is unsafe or not a good fit for the potential participant.

3.3 Special Populations.

Vulnerable populations (fetuses, pregnant women, children, prisoners, and institutionalized persons) and adults unable to consent will not be included in this study.

4.0 Study-Wide Number of Subjects

NA

5.0 Study-Wide Recruitment Methods

NA

6.0 Multi-Site Research

To accommodate the recruitment rate for this study, we will use additional sites, Ochsner Medical Center and Tulane University. Dr. Lydia Bazzano will serve as the site investigator for TELEX at Ochsner and Tulane. Participants will complete all study measures at Ochsner or Tulane's site. However, muscle biopsies and long-term storage of blood may not be offered at Oschner or Tulane. The Tulane IRB acknowledges Ochsner's IRB decision based on a reliance agreement between each site's IRB to facilitate single IRB review of multi-site research.

7.0 Study Timelines

Each participant's part in this study will last approximately six months. We plan to enroll participants within five years of the study start date. The estimated date to complete primary analyses is between five and six years from the study start date.

8.0 Study Endpoints

The primary study endpoint is the six-month change in the six minute walk data.

Secondary study endpoints include a) six-month change in treadmill walking performance; b)six-month change in Walking Impairment Questionnaire; c) six-month change in health-related quality of life, measured with the Short-Form-36 Physical Functioning Score.

Exploratory study endpoints are change in calf muscle biopsy measures, consisting of calf muscle biopsy-obtained satellite cell number, Type I muscle fiber composition, PPARδ, PGC-1α, AMPK quantity and activity, and relative gene expression of PPARδ, PGC-1α, AMPK, FOXO3A, and SIRT-1.

Additional exploratory outcomes are a) six-month change in usual-paced four-meter walking velocity; b) six-month change in fast-paced four meter walking velocity; c) six-month change in the short physical performance battery (SPPB) score.

All data will be collected at baseline and at the 6-month follow-up visit.

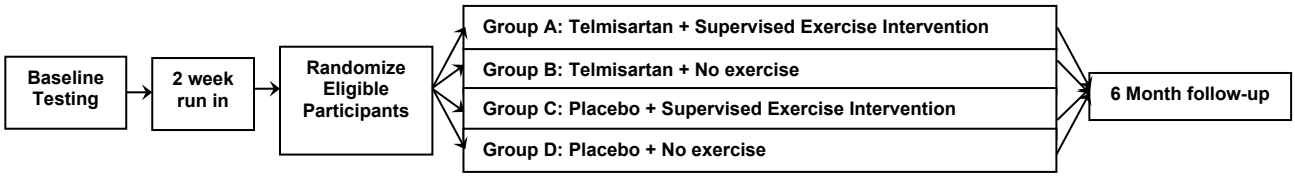
9.0 Procedures Involved

9.1 Study design.

STUDY OVERVIEW. We will randomize a minimum of 112 and up to 240 participants with PAD to one of four parallel study arms: Group A: telmisartan + supervised exercise; Group B: telmisartan + a "no exercise"

control group; Group C: placebo + supervised exercise; and Group D: placebo + a "no exercise" control group. Participants will undergo baseline testing, a two-week study run-in period, six months of their assigned study group, and six-month follow-up testing (Figure 2).

Figure 2. Overview of the Telmisartan Trial Design.



Telephone screening.
Initial eligibility criteria will be assessed by telephone via a telephone call script. The study will be described to the potential participant and the participant will be asked a series of eligibility questions to determine whether they qualify for a baseline study visit. If they qualify for a baseline visit, we will collect their name, address, telephone number(s), email address, date of birth, gender, race, and ethnicity.

Baseline testing.
Participants will be asked to come to Northwestern Memorial Hospital at baseline for the purposes of providing informed consent. In addition, at the baseline study visits, we will obtain the ankle brachial index (ABI) measurement, to ensure they are eligible for the study. If the participant meets initial eligibility requirements, we may mail a letter to the participant's physician to notify him or her of their patient's involvement with the study, unless the participant does not have a physician or requests that we do not notify their physician. We will administer study questionnaires, such as the Walking Impairment Questionnaire and the Short-Form-36 Physical Functioning Score, to obtain information about their medical history. We will perform baseline physical functioning tests including the six-minute walk test, chair stands, balance testing, and the treadmill walking performance test. We will take a blood sample, measure participants' height and weight, and measure the blood pressure in their arm. In addition, participants will be asked to undergo a calf muscle biopsy at baseline. Participation in the calf muscle biopsy is optional. Participants will be asked to have a physical examination prior to randomization. Baseline study visits will be performed over multiple days.

Details of baseline visit procedures are described in section 9.2.

Run-in period.
Prior to randomization, all potential participants will be required to successfully complete a two week run-in period, during which they will take

20 mgs daily of telmisartan. Participants will also be required to attend one exercise session and one attention control session prior to randomization. Participants will return for a blood pressure check and measurement of potassium and renal function at the end of the run-in period. Participants unable to tolerate telmisartan due to hypotension (i.e. blood pressure $\leq$ 100/50 on telmisartan) or hyperkalemia (potassium level $\geq$ 5.5) or a 30% or greater decline in renal function compared to baseline, measured by eGFR, will be excluded for safety reasons. Participants who fail to take the study medication for 10 or more days in the two-week period (i.e. one pill per day for $\geq$ 10 days out of the 14 day run-in period) will be excluded. Participants who report significant new or increased symptoms of lightheadedness or dizziness during run-in will also be excluded if the symptoms are thought to be related to the study medication. If a participant's blood pressure is less than or equal to 100/50 at the end of the telmisartan run-in period, the blood pressure may be rechecked after 3 to 10 additional days of telmisartan at the discretion of the principal investigator. For instance, if the participant had another medical condition that was thought to be contributing to the low blood pressure after run-in- OR if the blood pressure reading is very discordant from prior readings. If a participant's baseline eGFR substantially differs from their prior recent eGFR values, and the discrepancy in the baseline value, compared to prior recent values, may contribute to a 30% or greater decline in eGFR after run-in, then at the investigator's discretion, the baseline eGFR and run-in may be repeated. This protocol change was approved by the study's Data Safety Monitoring Board during the week of September 14, 2020.

Randomization. Participants will be randomized to one of four arms using a SAS computer program. Block randomization will be implemented to ensure balance between the four groups throughout recruitment. Block sizes will be randomly selected from eight and twelve. Randomization will be stratified according to whether or not the participant will have a muscle biopsy at baseline. Randomization was stratified by site (added on 1/27/2021 to reflect that when a new site was added, randomization was stratified by site).

Participants who are in the supervised exercise group will attend sessions three times weekly for six months, and participants that are in the "no exercise" group will attend one hour educational sessions once a week for six months. Participants randomized to telmisartan (Group A and Group B) will take 40 to 80 mgs of telmisartan per day. Participants randomized to placebo (Groups C and D) will take placebo daily.

Telmisartan/placebo and assessments. Participants randomized to receive telmisartan will begin at a dose of 20 mgs or 40 mgs daily based on the results of post-run-in assessments. The dose will be increased as tolerated to 80 mgs daily based on results of dose-increase visits and monthly

assessments post-randomization. Using results of these assessments, the pharmacy will receive a drug order specifying whether the dose should be changed in order to maintain blinding. The telmisartan dose may be reduced or discontinued and/or replaced with placebo pills. Participants randomized to receive placebo will also return for dose-increase visits and monthly assessments to maintain blinding. All participants will have their blood pressure checked at least monthly and their potassium levels checked at 2- and 5-month follow-up. Patients with a baseline eGFR < 30 will have their potassium level checked at the one-month follow-up visit as well. Participants will have blood pressure, potassium, and eGFR measurements approximately two weeks after telmisartan dose increases. All participants who are eligible for a dose increase based on their assessments will return for follow-up blood pressure and/or blood work whether they are on telmisartan or placebo in order to maintain blinding. Participants may be asked to return for additional measurements as needed for safety purposes. If a participant returns two weeks after a dose increase for a blood pressure and potassium measurement, and these blood pressure and potassium measurements are also within 30 days of an upcoming scheduled 2- or 5-month follow-up visit, the 2- or 5-month visit is not also required (e.g. if a participant is eligible for a dose increase at the 1-month follow-up visit and returns at 1.5 months for a measurement of blood pressure, potassium, and eGFR, their blood pressure and potassium will not necessarily need to be checked again at the 2-month mark). In these instances, investigator discretion will be used to determine whether the additional 2- or 5-month follow-up visit measures are also needed.

Medication will be administered in a double-blinded fashion. Northwestern Memorial Hospital's (NMH) Investigational Pharmacy will receive randomization assignments from the study's data management team and prepare identical appearing 30 day supplies of medication (telmisartan vs. placebo) for participants. Participants will receive a new 30 day supply of medication each month.

Six-month follow-up testing. After six months of participation in the study, participants will be asked to return for follow-up testing. All measures and tests that were conducted at baseline will be repeated.

In the event that a participant is unable to return after six months of participation and follow-up testing is delayed, the participant may be given additional study pills to ensure that they are still on the study pills at the time of follow-up testing. In this instance, the participant may take study pills for more than six months. Study pills will not be provided for more than an additional three months. Investigator discretion will be used to determine if additional monthly assessments of blood pressure and/or blood tests are necessary prior to the completion of the study follow-up visits.

Some or all study measures may be repeated at baseline or follow-up for data quality (for example if a treadmill test must be stopped due to extremely high blood pressure before the patient completed the test- this is just one potential example). In some cases, it may be necessary to take an additional, unscheduled blood pressure measurement. For instance, if a participant has high blood pressure during the ABI and investigators would like to double check their arm pressure measurement before performing the six-minute walk either at the same visit or at a subsequent visit. Determinations about blood pressure checks will be made on a case-by-case basis in consultation with Dr. McDermott, Dr. Lloyd-Jones, or other qualified personnel.

Supervised treadmill exercise program. Based on recommendations from clinical practice guidelines and evidence from clinical trial data, our supervised treadmill exercise intervention is a high-intensity exercise regimen (43,44,70). Supervised exercise will be delivered three times weekly for six months. In week one, participants will be asked to exercise on the treadmill for 15 minutes per session (excluding rest periods). Exercise duration will be increased by five minutes per session each week until 50 minutes of exercise per session is achieved (42,43,70). At this point, exercise intensity will be increased by alternately increasing treadmill speed and treadmill grade. Exercise intensity will be selected to ensure that participants experience ischemic leg symptoms within five minutes after onset of exercise. Participants will be asked to continue walking until they achieve leg symptom severity of "4 or 5" on a visual analog pain scale ranging from 1 to 5 (43,70). In the subset of participants without leg symptoms (i.e. those with asymptomatic PAD), participants will be asked to exercise to achieve a Borg Rating of Perceived Exertion (RPE) score of 12-14 (71-75). Participants may be asked to participate in up to three focus groups to discuss their experience in the study. We will ask consecutive patients who finished with the TELEX study if they would be willing to participate in a focus group, starting with the most recent finishers and working backwards. Participants would be asked to sign a separate focus group consent prior to participating. The purpose of the focus groups is to learn more about their experience with the study. The investigative team is specifically interested in barriers to participation in supervised treadmill exercise for people with PAD, because the investigative team is developing an exercise program for people with PAD that maximizes efficacy and is also acceptable and accessible for people with PAD.

Attention Control Group. Participants who are randomized to the non-exercising group will attend weekly one-hour educational sessions at Northwestern University for six months. These educational sessions are on topics of interest to the typical PAD patient and are led by physicians and other health care workers. Topics include pneumonia, nutritional supplements, and hypertension. Sessions do not include information about

exercise. We have substantial experience with these weekly educational lectures in our previously conducted randomized trials (43,60,75). The attention control group may include participants who are taking part in other studies of PAD participants conducted by Dr. McDermott, including participants at other recruitment sites who may videoconference into the lecture (for instance, participants enrolled in one of Dr. McDermott's PAD studies at Tulane University or University of Chicago or University of Minnesota may participate in the lecture via videoconference).

COVID-19 Questionnaire. Currently enrolled and past participants may be called to see if they are willing to complete a questionnaire related to the COVID-19 pandemic. The questionnaire will be completed over the telephone and will help investigators determine how the pandemic is affecting older adults with PAD and how physical activity levels are affected during this time.

9.2 Research procedures.

Data collection overview. Table 3 shows the outcome measures planned at baseline and follow-up.

Table 3. Data Collection Plan

Outcomes (prioritized)	Study Measure	Baseline	6-month follow-up
Primary outcome	Change in six minute walk	X	X
Secondary outcomes	Change in treadmill walking performance	X	X
	Change in Walking Impairment Questionnaire	X	X
	Change in health-related quality of life[1]	X	X
Exploratory outcome	Change in calf muscle biopsy measures[2]	X	X

[1]Health related quality of life will be measured with the Short-Form-36 Physical Functioning Score. [2]Calf muscle biopsy measures consist of calf muscle biopsy-obtained satellite cell number, Type I muscle fiber composition, PPARδ, PGC-1α, AMPK quantity and activity, and relative gene expression of PPARδ, PGC-1α, AMPK, FOXO3A, and SIRT-1.

Ankle Brachial Index (ABI). We have extensive experience measuring the ABI (4-9,50-52). After the participant rests supine for five minutes, the right brachial, dorsalis pedis (DP), posterior tibial (PT) and left DP, PT, and brachial artery pressures are measured using a hand-held Doppler probe. Pressures are measured twice. The ABI is calculated for each leg by dividing the average of the DP and PT pressures by the average brachial pressure. If a participant qualifies for a heel-rise ABI based on their initial ABI, they will be asked to perform 50 heel-rises at a rate of one per second followed by additional measurements of the right and left brachial, DP, and PT pressures.

Questionnaire Administration. Participants will be administered study questionnaires by a trained and certified health interviewer. Health Related Quality of Life will be assessed with the SF-36 Physical Functioning score (80). Patient perceived walking ability will be assessed with the Walking Impairment Questionnaire (WIQ) (78,81,82). Both are well-validated measures that improve in response to effective interventions (43,60,78,80-82).

At either baseline or the six-month follow-up visit, the Supervised Exercise Questionnaire will be administered either verbally by a coordinator or the participant will fill out a written version of the questionnaire. Typically the questionnaire will be administered by a coordinator; however, in some instances (e.g. if a participant is waiting for a research room to become available for testing) it may be self-administered.

Six-minute walk. Participants will be asked to walk back and forth along a 100-foot hallway for six minutes. They will be instructed that the purpose of the six-minute walk test is to measure the distance they can walk in six-minutes. A script will be read to describe the study procedure. Participants will be asked whether they feel the test is safe to try and whether they have any questions.

Treadmill testing. The Gardner graded treadmill exercise test is the standard, accepted treadmill protocol for measuring change in maximal treadmill walking time in response to interventions among PAD participants (70,76-78). In the Gardner exercise protocol, speed is maintained at 2.0 miles per hour (mph) and treadmill grade increases by 2.0% every two minutes (76,77). If patients cannot walk at 2.0 mph, treadmill speed is started at 0.50 mph and increased by 0.50 mph every 2 minutes until the participant reaches 2.0 mph, after which the treadmill grade is increased every two minutes.

Blood collection and long-term storage. At baseline and six-month follow-up study visits, participants will have up to approximately 45 mls of blood drawn for processing and long-term storage at -70 degrees Celsius. Approximately 10% of participants selected by chance will have an additional set of blood drawn for quality assurance, for a total of 90 mL at each visit. Blood obtained will be collected in serum, plasma EDTA, and plasma citrate tubes. A subset of participants will be invited to have an additional 9 ml tube of blood collected for measurement of the P16 marker, a measure of cell senescence. For participants who agree to the optional element, blood will be obtained in blood tubes supplied by Sapere Bio, labeled with study ID number, and sent to Sapere Bio (400 Park Offices Dr, Research Triangle Park, NC 27709) for measurement of senescent cells. Sapere Bio will either destroy or return to Northwestern the remaining blood

after measuring senescent cells. Stored blood will await later analyses for inflammatory biomarkers and other emerging blood markers that may change in response to the intervention. Genetic testing may also be performed on stored blood samples.

Participants will have additional blood drawn (approximately 5 mls) at baseline, the end of the two-week run-in, and after randomization for safety measurements as detailed above. Participants with potassium levels greater than 5.0 at baseline may return for an additional blood draw to see if their potassium level meets the eligibility criterion at a later date. Additional blood samples may be ordered at the discretion of the principal investigator or safety officer.

Calf muscle biopsies. Muscle biopsies will be performed by co-investigator Robert Sufit MD, a board-certified neurologist with > 30 years of experience performing muscle biopsies. Dr. Sufit completed all biopsies for our pilot study. The muscle biopsy will be obtained in the medial head of the gastrocnemius muscle in the leg with lowest ankle brachial index, at the point that is 67% of the distance between the medial malleolus and the medial aspect of the proximal tibia. This site represents greatest calf muscle diameter in >95% of individuals (83). Anesthesia is achieved with subcutaneous lidocaine. Subcutaneous and adipose tissue are dissected until muscle is identified. Approximately 250 mgs of muscle tissue is removed and immediately prepared for freezing at -70 degrees Celsius. Approximately 100 to 150 mgs of fat may be removed from the subcutaneous fat may be removed from below the fascial line during the muscle biopsy. In patients with more fat tissue, up to approximately 250 mgs of fat will be removed from the subcutaneous fat and from below the fascial line, respectively, at the discretion of the physician performing the muscle biopsy. The fascia and wound are closed with absorbable and subcuticular sutures, respectively. Participants are asked to return for a wound check approximately one week later. At 6-month follow-up, we will repeat the biopsy using identical techniques.

In addition, in a subset of participants, we will obtain a muscle biopsy on both the left and right legs, respectively. These bilateral biopsies could be obtained at baseline, 6-month follow-up, or at both baseline and follow-up. The first biopsy will be performed using our current procedures. The second biopsy will be performed on the opposite leg approximately seven to thirty days later.

The incision at follow-up is made adjacent to the baseline incision. In the open biopsy, muscle tissue is directly visualized, ensuring an optimal muscle sample and providing substantial advantages over blind needle biopsy. Specimens will be stored and analyzed at Northwestern, the University of Florida, and/or the University of Kentucky. Other measures

related to skeletal muscle quality and function may also be performed at Northwestern or at laboratories outside of Northwestern.

Measures of muscle protein and gene expression will be performed by Dr. Leeuwenburgh's laboratory at University of Florida. Dr. Leeuwenburgh's laboratory performed measures of PGC-1α, citrate synthase, and cox enzyme in our pilot muscle biopsy study. Methods are well standardized and validated with excellent test re-test reliability in the University of Florida laboratory (84). We will determine protein and gene expression of select markers of metabolism and mitochondrial biogenesis. Protein expression of PPARδ, PGC-1α, and AMPK (phosphorylated and total) in whole tissue homogenate will be performed using Western Blot techniques as described previously (85). Gene expression of PPARδ, PGC-1α, AMPK, FOXO3, and SIRT-1 will be analyzed using quantitative real time PCR (qRT-PCR) as described previously (86,87). These measures of gene expression will allow us to more fully delineate biologic pathways of improved functioning in PAD. FOXO3 and SIRT-1 for example are downstream targets of AMPK. Other measures related to skeletal muscle quality and function may also be performed.

Measures of muscle fiber type and satellite cells with be performed by Dr. Peterson's laboratory at University of Kentucky. Muscle morphology will be characterized on 7-μm thick fresh frozen serial muscle sections. Sections will be stained with hematoxylin & eosin to examine muscle morphology and determine if overt muscle degeneration/regeneration or cellular infiltration is observed. Fibrosis will be quantified by picrosirious red staining of collagen and lectin binding to proteoglycans in the extracellular matrix using rodamine-conjugated wheat germ agglutinin (96). Fiber typing will be performed with monoclonal antibodies against myosin heavy chain (MyHC) isoforms. Digital images are captured of the entire cross-section on a ZeissAxioImager MI microscope equipped with excitation/emission and dichroic filter sets for detection of DAPI/Hoechst, Coumarin, TRITC (Rhodamine), FITC (Fluorescein), Cy3.5 (Texas Red) and Cy5. Fiber type distribution and cross-sectional area are quantified using automated software recently developed in the Peterson lab (89,90). Quantification of satellite cells using immunohistochemistry with the Pax7 mouse monoclonal antibody (88), together with DAPI staining, will measure changes in response to the interventions.

Other measures related to skeletal muscle quality and function and related to fat measures of inflammation and senescence may also be performed at Northwestern, the University of Florida, and/or the University of Kentucky, Mayo Clinic or at other institutions as designated by the Principal Investigator.

Medications. Participants and their physicians will be asked not to change their medications during the study if possible. Participants will be asked to bring all of their medications to baseline and follow-up visits and to monthly blood pressure check visits. We will systematically record names and doses of medications and inquire about medication changes at each of these visits. If we find differences in the use of specific medications between study groups (such as statins or cilostazol), we will adjust for these differences.

Other measures. Body mass index (BMI) will be assessed at baseline and follow-up by objectively measuring height and weight. Patient report will be used to document comorbidities. A four-meter walk test will be administered at usual and fastest pace at the baseline and follow-up visits. Participants will be asked to perform the usual paced four-meter walk at usual pace and the "fast paced" four meter walk at their fastest pace. Each of these short walks will be performed twice. Participants will be asked to complete a series of standing balance exercises and chair stands. Participants will undergo a physical exam by a physician and will have the blood pressure in their arm checked. Participants may be asked to return for a second blood pressure measurement at the discretion of the investigator (e.g. if the sitting blood pressure is not consistent with their typical blood pressure or if changes in medical condition or treatment may have spuriously altered the blood pressure value).

9.3 Overview of protection against risks.

Adequacy of protection against risks and methods to minimize potential risks. Dr. McDermott and the study safety officers are responsible for overseeing results of monthly blood pressure checks and regularly scheduled potassium levels and measures of renal function and will follow up with the participant and/or their physician as necessary.

All research staff members have completed human subjects training required by Northwestern's institutional review board (IRB). This training includes education about the importance of maintaining confidentiality of personal health information. The study principal investigator or a co-investigator is available to answer questions that arise during the informed consent process as needed.

Participants are asked to sign a study consent form at baseline. The research coordinator reviews study procedures including risks and benefits associated with study participation. The research coordinator answers participants' questions. Dr. McDermott and other study investigators are available to answer participants' questions. Both the participant and the individual administering the consent form will sign the consent form. Dr. McDermott's pager, direct telephone line, and cellular telephone number are provided to participants.

Minimizing risks related to exercise. According to current clinical practice guidelines (70), all participants will undergo baseline exercise stress testing prior to randomization. Potential participants with an abnormal baseline exercise stress test will be excluded. A safety manual will be developed prior to beginning the exercise intervention and will be reviewed and approved by the Data Safety Monitoring Board (DSMB) before implementation. In addition, participants will be monitored during supervised exercise for development of chest discomfort, new dyspnea, or new fatigue during exertion. Dr. McDermott or Dr. Lloyd-Jones will be promptly notified when this occurs (by pager). Our exercise physiologists have significant experience working with populations of participants with PAD and have been trained in CPR, ACLS, and use of the automatic external defibrillator.

Minimizing risk related to telmisartan. Telmisartan is an FDA approved medication. Side effects include sinus discomfort and congestion, back pain, and diarrhea. Other side effects include hypotension, kidney problems, and hyperkalemia. The study drug is in a class of drugs known to lower red blood cell count, potentially causing anemia which may potentially lead to worsening of leg pain, fatigue, and shortness of breath. The drug labeling indicates that a greater than 2 g/dL decrease in hemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. However, no patients have needed to stop telmisartan because of anemia. Rarely, serious allergic reactions may happen. Side effects of telmisartan will be carefully monitored. To maximize safety, we will measure blood pressure, liver enzymes, eGFR and potassium level at baseline. Individuals with a baseline blood pressure < 100/50, those with baseline hepatic function abnormalities defined as two or more liver function enzyme values greater than 2.5 times the normal value, and those with a baseline potassium > 5.0 will be excluded. Remaining potential participants who successfully complete baseline testing (except the muscle biopsy, which will be performed after successful completion of the run-in) will be asked to complete a two-week run-in, during which they will be asked to take telmisartan 20 mgs daily. Participants will return at the end of the two-week run-in for a repeat blood pressure check and measurement of potassium and eGFR. Individuals with a blood pressure < 100/50 or a potassium level ≥ 5.5 at the end of the two-week run-in will be excluded. Individuals with a 30% or greater decline in eGFR following two-week run-in as compared to baseline will also be excluded. If the participant had a baseline eGFR performed by his/her physician within two months of the baseline eGFR for the TELEX trial, the participant's physician's eGFR may be considered the baseline measure, at the study principal investigator's discretion. Finally, after randomization, all participants will be assessed monthly for pill counts, blood pressure monitoring, and administration of an adverse event form and will have their study medication adjusted appropriately. In addition, potassium levels will be measured at month two and at month five of the

study. Participants with a baseline GFR of < 30 will also have their potassium level measured at the one-month follow-up visit. Study medications will be appropriately adjusted depending on potassium level. Participants who have a potassium level of 5.0 or greater at any time in the study will receive a handout on how to avoid potassium-rich foods. Participants will return for blood pressure, potassium, and eGFR measurements following increases in dose. If a participant returns two weeks after a dose increase for a blood pressure and potassium measurement, and these blood pressure and potassium measurements are also within 30 days of an upcoming scheduled 2- or 5-month follow-up visit, the 2- or 5-month visit is not also required. In addition, participants will be provided with a list of side effects of telmisartan and will be provided with Dr. McDermott's home and cellular telephone numbers, in case the participant develops side effects or has questions. It is important to point out that in prior randomized trials of telmisartan therapy for prevention of cardiovascular events, telmisartan was well tolerated (19,66-68). For example, in the pilot trial of telmisartan in 36 PAD participants, there were no adverse events (19).

Minimizing risks related to muscle biopsy. The muscle biopsy procedure will be performed by Dr. Robert Sufit who has more than 30 years of experience performing these muscle biopsies, primarily as part of his clinical practice as a Board-Certified Neurologist. As in our muscle biopsy pilot study, completed in preparation for this proposal, the muscle biopsy procedures will be performed under sterile conditions using sterile technique. Local anesthesia will be obtained using subcutaneous lidocaine. All participants will be provided with written and verbal instructions about wound care and will be advised to contact Dr. McDermott immediately if any signs of wound infection occur.

Many PAD participants take anti-platelet therapy to prevent cardiac and cerebrovascular events. If potential participants are taking anti-platelet therapy, they may be asked to hold their anti-platelet therapy during the seven days leading up to each muscle biopsy procedure. Participants who undergo bilateral biopsies may be asked to hold their anti-platelet therapy for approximately 14 days. At follow-up, if the participant has had a coronary revascularization with stenting in the previous three months, the participant will not be asked to hold their anti-platelet therapy. Permission from the participant's physician will be obtained before asking the participant to hold their anti-platelet therapy. If the participant's physician does not provide permission for the patient to stop the anti-platelet therapy, then the participant will either be excluded from the muscle biopsy portion of the study or the biopsy will be performed while the participant is taking anti-platelet therapy. Participants who are taking warfarin or other anti-coagulant therapy will be excluded from the muscle biopsy portion of the study.

Minimizing risk related to baseline and follow-up testing. All study coordinators undergo baseline training and are certified by Dr. McDermott before beginning data collection. Training and certification involves ensuring that coordinators are trained in methods to help minimize falls. Dr. McDermott or a senior study coordinator re-certifies coordinators approximately every six months to ensure continued adherence to study protocol. Those who are not adhering to protocol undergo additional training followed by re-certification.

Minimizing risk related to loss of confidentiality. The following methods will be employed to maintain confidentiality of participants. First, study recruitment letters will be mailed, using IRB-approved methods, only after notifying the participant's physician. The personal physician of each study participant will have the option of not allowing investigators to contact the potential participant. Lists of potentially eligible participants will be obtained by individuals who normally have access to these lists as part of their daily work requirements. Recruitment letters for potential participants identified from hospital and outpatient lists are prepared by research staff members whose job is to assist study investigators with recruitment. These research staff members have completed training in the ethical conduct of human subject research, including maintaining participant confidentiality. Recruitment letters to potential participants identified from medical center lists are mailed in sealed envelopes and addressed to the potential participant. All potential participants who receive mailed information about the study will have the opportunity to call a voicemail system to ask NOT to be further contacted about this study. Secondly, only study investigators and key research staff will have access to the study database. Third, participants will be assigned a unique study identifier. Individual names will ultimately be removed from the study database and only the unique study identifier will be used to distinguish participants in the database. Fourth, collected data will be maintained in locked computer files and file cabinets to which only study investigators have access. Collected data will be used only for research purposes. Any published data will not contain individual identifiers.

10.0 Data and Specimen Banking

10.1 Storage of specimens.

Muscle specimens and blood specimens for long-term storage will be stored in a freezer belonging to Dr. McDermott's research program at Northwestern University, in the freezer farm in the basement of Olson Pavilion. Specimens will be stored for up to 70 years, after which they will be destroyed.

10.2 Data to be stored or associated with each specimen.

Specimens will be coded; meaning that a key will exist that can link the codes back to the direct subject identifiers. Each participant will be assigned a unique study ID number that can be traced back to the study participant. The muscle specimens and the blood samples that are stored will be labeled with this unique identifier and the date and time of the blood collection.

10.3 Procedures to release data or specimens.

Only Dr. McDermott has control over release of study data or specimens. Any investigators seeking to analyze blood or muscle specimens must contact Dr. McDermott for permission. Each request, if it occurs, will be considered on a case-by-case basis. Dr. McDermott will obtain IRB approval prior to releasing any blood or muscle specimens for analysis, other than those tests specifically named in this application.

11.0 Data and Specimen Management

11.1 Data management.

We will use REDCAP for data entry, via NUCATS.

*11.2 Power Estimates/Calculations***.**

On October 31, 2019 investigators along with the DSMB and the study sponsor, NHLBI, agreed to change the primary aim to a single comparison of telmisartan (with and without supervised exercise) vs. placebo (with and without supervised exercise) due to difficulty recruiting participants for the trial who were not already taking an ACE inhibitor or an angiotensin receptor blocker. Although the investigators will still aim to recruit as many participants as possible (up to the originally proposed sample size), this change in primary aim provides statistical power for a sample size of 112 participants. Power calculations still take into account an anticipated 10% drop-out rate at 6-month follow-up, i.e., we expect to have approximately 25 participants per group (i.e. 100 overall) completing the 6-month follow-up.

PAD participants will be randomized to one of four study groups:
Group A: telmisartan + supervised exercise therapy;
Group B: telmisartan + a “no exercise” control group;
Group C: placebo + supervised exercise therapy; and
Group D: placebo + a “no exercise” control group.
For our revised Primary Aim, we will determine whether Group A+B improves six-minute walk performance at 6-month follow-up, compared to Group C+D, stratified by the exercise status. 50 PAD participants in each group provides 80% power to detect a minimum difference of 0.566 standard deviations (SD) between Groups A+B and C+D in changes of six-minute walk performance, using a two-sided two-sample t-test with a significance level of 0.05. As a sensitivity analysis, the following table summarizes the power for testing the primary aim with different total numbers of enrolled participants.

#total patients	112	116	120	128
Power for detecting 0.566 SD	80%	82%	83%	85%

In our SILC and GOALS trials (43,60), the observed differences in change of six-minute walk performance at 6-month follow-up between the intervention and control groups were 0.70 SD and 0.78 SD, respectively. In our SILC and GOALS trials, these observed differences represented a difference in six-minute walk change of 40 meters between the intervention and control groups (43,60), a clinically meaningful difference (79). Thus, we have adequate power for detecting similar or slightly smaller difference in the Primary Aim.

For Secondary Aim 1, we will determine whether Group A achieves greater improvement in six-minute walk at 6-month follow-up, compared to Group B and Group C, respectively. 25 participants in each group provides 70% power to detect a minimum difference of 0.72 SD between Groups A and B and between Groups A and C, respectively, in change of six-minute walk performance, using a two-sided two-sample t-test with a significance level of 0.05. For our Secondary Aim 2, we will determine whether Group B improves maximal treadmill walking, the WIQ, and the SF-36 PF score at 6-month follow-up, compared to Group D. The 25 PAD participants in each group also provide 70% power to detect a minimum difference of 0.72 SD.

For our Secondary Aim 3, we will determine whether Groups A+B combined improves maximal treadmill walking distance, the WIQ, and the SF-36 functioning score, compared to Group C+D combined, stratified by exercise status. 50 PAD participants in each group provides 80% power to detect a minimum difference of 0.566 SD between Groups A+B and C+D using a two-sided two-sample t-test with a significance level of 0.05. Thus, we have adequate power to detect effect sizes similar to the effect size in 6-minute walk distance in SILC and GOALS for all three Secondary Aims. For Tertiary Specific Aim 1, we will determine whether Group B achieves greater improvement in maximal treadmill walking distance, the WIQ, and the SF-36 functioning score, compared to Group D. For Tertiary Specific Aim 2, we will determine whether Group A achieves greater improvement in maximal treadmill walking distance, the WIQ, and the SF-36 functioning score, compared to Group B and Group C, respectively. 25 participants in each group provides 60% power to detect a minimum difference of 0.64 SD between Groups A and B and between Groups A and C, respectively, using a two-sided two-sample t-test with a significance level of 0.05.

In our SILC trial (43), the observed differences in change of maximal treadmill walking distance, WIQ distance score, and SF-36 functioning score were 0.60 SD, 0.59 SD, and 0.61 SD, respectively. Thus, we should

have reasonable power to detect similar effect sizes for outcomes in our Tertiary Aims.

Statistical Analyses. Analyses will be performed according to the intention to treat principle. Data will be analyzed according to each participant's originally assigned group, irrespective of whether the participant adheres to the assigned group. For the Primary Aim, we will use analysis of covariance (ANCOVA) to compare changes in six-minute walk performance at 6-month follow-up between Group A+B combined and Group C+D combined, adjusting for study site (Northwestern or Tulane) and randomization to exercise status. For our Secondary Aim 1 and our Secondary Aim 2, we will use two sample two-tailed t-tests to compare changes in six-minute walk at 6-month follow-up between Groups A and B, between Groups A and C, and between Groups B and D, all stratified by study site. For our Secondary Aim 3, we will use ANCOVA to compare changes in maximal treadmill walking distance, the WIQ, and the SF-36 physical functioning score between Groups A + B vs. Groups C + D, adjusting for study site and randomization to exercise. For our Tertiary Specific Aim 1, we will use t-tests to compare maximal treadmill walking distance, the WIQ, and the SF-36 functioning score, between Groups B and D stratified by study site. For our Tertiary Specific Aim 2, we will use t-tests to compare maximal treadmill walking distance, the WIQ, and the SF-36 physical functioning score, between Groups A and B, and between Groups A and C, respectively, also stratified by study site. For our Exploratory Aims, we will use ANCOVA to compare changes in gastrocnemius muscle biopsy measures of each muscle measure between Groups A+B vs. C+D adjusting for study site and randomization to exercise. We will also compare Groups A, B, and C, respectively vs. Group D using two sample t-test stratified by study site. When the distribution of changes in the primary, secondary, and exploratory outcomes of interest is "very non-Gaussian", we will either apply appropriate transformation before conducting t-tests or perform Wilcoxon rank-sum test for the comparisons. Prior to analyses, we will also check the potential imbalance of socio-demographic factors and prognostic factors (such as age, sex, race, baseline outcome measure, ABI, BMI, smoking status, comorbidities, and relevant medication use) between the two groups using t-tests for continuous factors and chi-square test for discrete factors. If there is any indication of major imbalance in these factors or baseline variables are associated with the change in outcome of interest, we will perform ANCOVA to further adjust for the relevant baseline factors as potential confounders, in addition to randomization to exercise status and site, for two-group comparison. Similar analysis will be performed for exploratory aims. In the analysis for the secondary, tertiary and exploratory aims, we will not adjust for multiple testing. However, we will report all the results regardless of their significance to present an overall picture of the treatment effect of

telmisartan. In additional exploratory analyses, adjustment for multiple comparisons may be performed.

Analyses regarding missing data: If missing data due to participant dropout is missing completely at random, then the aforementioned analyses based on available data provide valid statistical inferences. When missing data due to dropout is not missing completely at random, we will perform several sensitivity analyses. Specifically, we will employ the multiple imputation approach to account for missing data at 6-month follow-up under the assumption of missing at random (91). We will perform additional sensitivity analyses to guard against the possibility of missing not at random using extreme value imputation, selection models and shared-parameter models (92).

11.3 Steps to secure data to maintain confidentiality during storage, use, and transmission.

First, all research assistants must complete training in protection of subject privacy and prevention of disclosure of identifying information.

Second, all data collection forms are maintained in a secure office space.

Third, our study databases are maintained in locked computer files or on secure hard-drives that are password protected; to which only authorized staff have access. Dr. McDermott or a study manager must provide permission for programmers and research assistants to access study databases.

Fourth, a study identification number will be assigned to each participant. This identification number will be used to label blood specimens, for example. In addition, most pages of our data collection forms will have only the study identification number listed (and not the participant's name, for example).

11.4 Quality Control.

Health interviewers will be trained by a senior coordinator and certified by Dr. McDermott in each data collection element, using a detailed checklist. Health interviewers are rigorously evaluated for adherence to protocol, delineated in our manuals, prior to beginning data collection. They are re-certified approximately every six months by a project manager or Dr. McDermott. When deficiencies are identified, interviewers undergo additional training and re-assessment. Ten percent of participants are randomly identified for quality control. This subset has their ABI measured twice by

independent examiners and may have a split sample of muscle tissue (i.e. two samples from the same participant) sent for analyses. The second muscle sample is designated an arbitrary identification number to which the technician is blinded. Thus, quality control is monitored continuously. Dr. McDermott meets with the exercise physiologist(s) to review individual participant's progress.

Blinding for data collection. The health interviewer collecting outcome data will be blinded to the study group assignment. Participants are instructed not to reveal their group assignment. If a participant reveals their group assignment, data collection is immediately stopped and another certified health interviewer is paged or contacted by telephone to continue the visit.

Missing Data. Missing data may occur when some participants are lost to follow-up. First, we will make every effort to ensure that participants return for 6-month follow-up. We will use proxies to help us locate participants we are unable to reach and we will mail letters to participants who do not respond to our telephone contacts. We will encourage participants who do not adhere to their assigned groups to return for six-month follow-up. We will provide transportation and monetary incentives. Thus, we anticipate that most participants will complete six-month follow-up data collection. Second, we will record the reason for dropout for each participant. If dropout is completely at random, then the aforementioned analyses based on available data provide valid statistical inferences. When dropout is not completely at random, we will perform several sensitivity analyses. Specifically, we will employ the multiple imputation approach to account for missing data at 6-month follow-up under the assumption of missing at random (91). We will perform additional sensitivity analyses to guard against the possibility of missing not at random using extreme value imputation, selection models and shared-parameter models (92).

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

A Data Safety Monitoring Board (DSMB), approved by the National Heart Lung and Blood Institute, will monitor safety throughout the study. Please see separate Data Safety Monitoring Board (DSMB) charter. The DSMB charter will be a living document that can be modified during the study. The DSMB met to review the study protocol and data collection forms prior to the start of the study. The DSMB will receive notice of serious adverse events within seven days of the principal investigator learning of a serious adverse event. The DSMB will be notified of deaths within 24 hours of the principal investigator learning of deaths. The DSMB will meet in person or by telephone approximately every six months to review

safety data. However, additional meetings may be called by the DSMB at any time.

Safety data will be systematically collected at monthly study visits using data collection forms. In addition, serious adverse events that occur between monthly events and are communicated to the study team will be reported directly to the DSMB by Dr. McDermott using a case report form. In addition to notifying the DSMB, the study statisticians and the study safety officer will be notified of serious adverse events.

During their meetings every six months, the DSMB will review data on recruitment, adverse events, serious adverse events, and adherence rates (to study drug and to the exercise intervention and health education sessions).

The DSMB is comprised of two clinicians, including two vascular medicine experts, and a statistician. Any statistical analyses of data on harms (or efficacy) will be analyzed by the statistical DSMB member. The DSMB has the ability to stop the study at any time if there are concerns about safety.

13.0 Withdrawal of Subjects

13.1 Anticipated circumstances under which subjects will be withdrawn from the research without their consent, including stopping participation for safety reasons. We anticipate that subject withdrawal from the research without their consent will be infrequent. However, a potential example is if a participant develops new chest pain during the study and the Principal Investigator and/or the medical safety officer feel it is not safe for the participant to continue exercising until the chest pain is evaluated by the participant's physician. In this circumstance, the participant would be advised to follow-up with their physician for chest pain evaluation. If the participant refuses to follow-up with their physician, it may be necessary for them to be withdrawn without their consent.

13.2 Procedures when subjects withdraw from the research. Subjects may withdraw from the research at any time. If they decide to leave the research, they should contact the principal investigator, Dr. Mary McDermott. If they stop being in the research, already collected data may not be removed from the study database. They will be asked whether the investigator can collect data from their routine medical care. If the subject agrees, this data will be handled the same as research data.

14.0 Risks to Subjects

Risks associated with the exercise program. The exercise program might be associated with an increased risk of heart attack, arrhythmia, or death. In addition, patients may develop ischemic chest pains during exercise. If participants develop chest pain during supervised exercise, Dr. McDermott or the trial's medical safety officer will be notified immediately. Dr. McDermott or the medical safety officer will oversee arrangement of appropriate follow-up (including immediate transport to the emergency room if appropriate). The exercise physiologist is certified in Cardiopulmonary Resuscitation (CPR) and use of an Automatic External Defibrillator (AED). Safety manuals and protocols will be developed prior to beginning the intervention. Dr. McDermott's direct line, pager, and cellular telephone number will be provided to all participants.

Chest pain during exercise may result in additional cardiac work-up and may lead to procedures to improve coronary blood flow. Subjects will be screened for active heart problems with a baseline exercise treadmill test prior to enrollment, according to currently recommended standards of screening PAD patients for coronary artery disease prior to their beginning an exercise program (70). These exercise stress tests will be performed as part of our protocol and interpreted by board-certified cardiologist and co-investigator Dr. Lloyd-Jones. Participants must have a normal 12-lead exercise stress test to be eligible. Abnormal baseline exercise stress tests may also lead to additional cardiac work-up by the participant's physician that may lead to coronary angiography or coronary revascularization. If the baseline exercise stress test is equivocal or abnormal, the participant must demonstrate evidence of a recent (within the past six months) normal coronary perfusion test or coronary angiogram in order to be eligible for participation. The latter tests would be ordered by the participant's physician at their discretion.

Exercise may sbe associated with muscle fatigue or soreness. These symptoms typically resolve with rest. Exercise may increase the risk of falling. However, the exercise physiologist who will supervise exercise has been trained to prevent falling. The risk of falling is less than 1 in 200. Falling during these tests may be associated with fracture. The risk of a fracture secondary to a fall during the walking tests is less than 1 in 5,000.

Risks associated with Telmisartan. Telmisartan is FDA approved for treating hypertension. Side effects are infrequent and rarely require discontinuation of telmisartan (67-69). Side effects include sinus discomfort and congestion, back pain, and diarrhea. Other side effects include hypotension, kidney problems, and hyperkalemia. The study drug is in a class of drugs known to lower red blood cell count, potentially causing anemia which may potentially lead to worsening of leg pain, fatigue, and shortness of breath. The drug labeling indicates that a greater than 2 g/dL

decrease in hemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. However, no patients have needed to stop telmisartan because of anemia. Rarely, serious allergic reactions may happen. Side effects of telmisartan will be carefully monitored using monthly questionnaires administered to all participants. Potassium level and blood pressure will be measured after the two-week run-in period in which participants will receive telmisartan. Those with a potassium level $\geq$ 5.5 and those with a blood pressure < 100/50 after run-in will be excluded from the study. After randomization, blood pressure will be measured monthly in all participants. Potassium levels will be monitored at 2- and 5-month visits during the study. Potassium level will be monitored at the 1-month visit for participants with a baseline eGRF < 30. Participants will be provided with a list of telmisartan side effects and will be provided with Dr. McDermott's home and cellular telephone, in case the participant develops side effects or has questions. Telmisartan may be discontinued at any time during the study based on investigator discretion.

Risks associated with the muscle biopsy. Risks associated with the muscle biopsy include discomfort during the muscle biopsy procedure, scarring from the muscle biopsy skin incision, bleeding (including a hematoma), and infection. Potential participants who are asked to hold their anti-platelet therapy during the week leading up to the muscle biopsy procedure may experience a cardiovascular event related to the temporary reduction or discontinuation of the anti-platelet therapy.

To minimize risk, all participants undergoing muscle biopsy will receive a written hand-out regarding signs to watch for of wound infection after the muscle biopsy. They will also receive verbal instructions. The participant will be instructed to call Dr. McDermott immediately if any signs of infection occur. In addition, permission from the participant's primary care physician will be required before asking participants to hold their anti-platelet medication for the seven days prior to the procedure. If the potential participant's primary care physician does not provide permission for holding anti-platelet therapy, the potential participant will either not be eligible for muscle biopsy portion of the study or the biopsy will be performed while the participant is taking anti-platelet therapy.

Six-minute walk test, four-meter walks, balance, and chair stands. The physical functioning tests may be associated with muscle fatigue or soreness. These symptoms typically resolve with rest. These tests may be associated with falling or coronary ischemia or dyspnea due to heart failure or lung disease. Rarely, falling may result in a fracture. However, the research assistant who will collect these data has been trained to prevent falling. The risk of a fracture secondary to a fall during physical functioning tests is less than 1 in 5,000.

Risks associated with ABI measurement. The ankle brachial index measurement consists of measuring systolic blood pressure in each extremity using a hand-held Doppler. The ABI is non-invasive, safe and does not have any known lasting side effects. During the ankle brachial index test, participants may experience discomfort from the inflated blood pressure cuff. However, this discomfort resolves immediately when the cuff is released.

Risks associated with questionnaire administration. Participation includes a risk of loss of confidentiality regarding personal health information. However, all research staff have undergone formal human subjects training. They are trained to protect the privacy of research subject participants.

Risks associated with drawing blood. The potential risks of drawing blood include a bruise at the site of vein puncture, inflammation of the vein, and infection. Participants undergoing a blood draw may experience lightheadedness, dizziness, or fainting.

15.0 Potential Benefits to Subjects

If our hypotheses are correct, millions of people with PAD will benefit from telmisartan therapy, thereby improving functioning and preventing mobility loss. This is important because PAD is associated with significant disability (1-7), yet few effective therapeutic options are available to improve mobility or prevent disability in people with PAD. Furthermore, our exploratory aim will delineate biologic pathways by which these interventions may improve functioning in patients with PAD. Identifying biologic mechanisms of these therapies will help identify new therapies, with similar biologic actions, that improve walking performance in people with PAD.

Participants who are randomized to supervised treadmill exercise will receive an intervention at no cost to them that has been shown to improve walking performance in people with PAD. Other participants will receive no direct benefits.

16.0 Vulnerable Populations

NA

17.0 Community-Based Participatory Research

NA

18.0 Sharing of Results with Subjects

Participants will receive results of their ankle brachial index (ABI) test results immediately after this testing is completed. They will be provided with a "result letter" at the end of their baseline visit. They will be asked whether they would like ABI and stress test results mailed to their physician. They will not be provided with other study results routinely,

However participants will be notified of abnormal stress test results, abnormal blood pressure results, and about dangerously elevated levels of potassium and significant declines in kidney function at the two-week follow-up visit.

19.0 Setting

Baseline and follow-up data collection will take place at Northwestern Memorial Hospital in the Galter Pavilion (675 N. St. Clair) on floors 11 or 18 or at 680 N. Lake Shore Drive on the 14th floor. Attention control sessions will take place at 750 N. Lake Shore Drive. Supervised treadmill exercise sessions will take place at LA Fitness (355 E. Grand or 55 E. Randolph).

20.0 Resources Available

Collaborating sites. Dr. Christiaan Leeuwenburgh (University of Florida) is an internationally recognized expert in skeletal muscle biology and mitochondrial function. Dr. Leeuwenburgh's laboratory will measure protein expression of PPARδ, PGC-1α, and AMPK (phosphorylated and total) using standard Western Blot techniques. Gene expression of PPARδ, PGC-1α, AMPK, FOXO3, and SIRT-1 will be analyzed using quantitative real time PCR (qRT-PCR) following standard protocols.

In addition, Dr. Charlotte Peterson (University of Kentucky) is internationally recognized for her work focusing on elucidation of cellular and molecular mechanisms controlling skeletal muscle structure and function. Dr. Peterson's laboratory will measure changes in calf skeletal muscle Type I fiber composition and satellite cell number in response to the study interventions in frozen human muscle biopsies shipped to the University of Kentucky from Northwestern University.

Drs. Michael H. Criqui (University of California at San Diego), Jack M. Guralnik (University of Maryland), and Luigi Ferrucci (National Institute on Aging) have worked with Dr. McDermott on PAD studies of functional impairment for over eleven years and bring expertise in functional assessment, PAD, and clinical trials to the study team.

21.0 Prior Approvals

NA

22.0 Recruitment Methods

22.1 When, where, and how potential subjects will be recruited.

PAD participants will be identified from among individuals with PAD who have participated previously in research conducted by Dr. McDermott

and/or who have expressed an interest in participating in future studies conducted by Dr. McDermott.

In addition, some PAD participants may be identified from among consecutive patients diagnosed with PAD in the non-invasive vascular laboratory at Northwestern Medical Group (NMG). Dr. Mark Eskandari is medical director of the non-invasive vascular laboratory at NMG and will assist with identifying potential participants from the non-invasive vascular laboratory. As director of the vascular laboratory at NMG, Dr. Eskandari formally reads many of the non-invasive vascular laboratory tests. He maintains all non-invasive vascular test results in his vascular laboratory. As director of the vascular laboratory, Dr. Eskandari could conceivably contact the patients whose test results are maintained in his laboratory. However, Dr. Eskandari prefers that the contact of potential participants in studies come from the physicians referring him for testing. Lists of patients who have undergone lower extremity arterial testing in the non-invasive vascular laboratory are generated monthly and e-mailed by Dr. David Leibovitz from NMG to Dr. McDermott using an encrypted file. Dr. Leibovitz is the Director of Clinical Information Systems at Northwestern Medicine. A research assistant, working on behalf of Dr. Eskandari, will contact referring physicians of potential participants identified from the vascular laboratory via fax, phone, page, or electronic message (EPIC or e-mail), to ask for permission to contact their patient about the study. If a reply is not received within three weeks, up to five letters are mailed from Dr. McDermott about the research study. We have substantial experience with our recruitment methods, which are IRB approved for our previous or ongoing studies.

We also propose to obtain lists of consecutive patients with a diagnosis of lower extremity peripheral arterial disease and individuals at high risk for peripheral artery disease from Northwestern's Enterprise Data Warehouse (EDW). EDW lists will be obtained by an individual who is employed by the Division of General Internal Medicine who has received training and permission to obtain the lists from the EDW.

Similar methods will be used as those described above, in which the patient's physician will be contacted via fax, telephone, page, or electronic message (EPIC or email) to ask for permission to contact their patient about the study. If a reply is not received within three weeks, up to five letters are mailed from Dr. McDermott about the research study.

We may also contact by telephone (after three weeks) those who do not respond to the first mailing within three weeks.

In the recruitment letters, recipients are asked to call us if they are interested in participation or if they do not want to be contacted further. Potential participants who do not call us within three weeks of the first mailed

recruitment letter may be telephoned by study staff and invited to participate.

In addition, we will use newspaper advertising and radio advertising to identify potential participants for this study. We will also use brochures, flyers, or posters that we will post in relevant office practices and public areas. We will also advertise on public transportation vehicles or trains.

We will obtain a list of patients who may be in an eligible age range for the study and live in the Chicago area from a mass mailing company. Using this, we will send postcards to those individuals on the list. The postcards will instruct people to call a study number if they are interested.

Participants who have participated in previous studies and indicated interest in future studies will be contacted. Participants who we screen for ongoing studies who may have PAD but are ineligible for that study and interested participating in a study may be screened for this study.

We will also use the PCOR-NET for recruitment. PCOR-NET is a PCORI-funded network of institutions in the Chicago area. The purpose of the PCOR-NET is to assist investigators with recruitment for clinical trials. PCOR-NET has its own IRB (University of Illinois at Chicago). PCOR-NET uses ICD-9 codes and the electronic health record to identify potential participants who have PAD. These patients with PAD receive a recruitment letter that describes the TELEX trial and invites the PAD patients to participate.

We will mail letters to Jesse Brown VA Medical Center patients with known PAD. A research coordinator with WOC status at JBVAMC will send letters to JBVAMC patients with PAD and make follow-up calls from JBVAMC. Participants recruited through these methods will sign a VA consent document and will undergo some study testing on-site at the VA. Study tests include questionnaires and functional performance measures.

We will use the University of Chicago for recruitment. The University of Chicago will obtain IRB approval at their site to identify potential participants who have PAD. Those patients will PAD will be mailed recruitment letters that describes the trial and invites the patient to participate. A University of Chicago coordinator will screen potential participants over the telephone and schedule participants for baseline visits at Northwestern.

22.2 Payment

Participants will receive up to $225 for taking part in this research study.

Participants will receive $25 for completing six-month follow-up testing and $100 per muscle biopsy.

Participants will be given assistance and/or reimbursement for expenses related to travel such as parking, bus/train fare, taxi fare, and mileage, if requested. A receipt will be required for taxi fare reimbursement. Participants will be provided up to $90 per visit for travel reimbursement. If they require the use of our taxi service, we will estimate the fare on www.taxifarefinder.com. A one-way fare estimate must be less than or equal to $45.00 (i.e. round trip of $90) in order for the study to provide taxi service.

23.0 Local Number of Subjects

We will identify and randomize 112 eligible PAD participants.

24.0 Confidentiality

NA

25.0 Provisions to Protect the Privacy Interests of Subjects

All research staff undergo training (human subjects training) in the protection of participant confidentiality and privacy. Research staff have access to medical records only for the purpose of conducting research that is approved by the IRB.

Questionnaires and all research procedures will be conducted in an enclosed space by a trained and certified research assistant. Dr. McDermott personally certifies research assistants in data collection to help ensure that participants are treated with the highest level of professionalism.

26.0 Compensation for Research-Related Injury

If the subject needs medical care because of taking part in this research study, they should contact the investigator and medical care will be made available. This care will be billed to the subject, their insurance, or other third party. *Northwestern University* has no program to pay for medical care for research-related injury.

27.0 Economic Burden to Subjects

NA

28.0 Consent Process

The "SOP: Informed Consent Process for Research (HRP-090)" will be followed. Participants will be consented by a research assistant who has been trained and certified by Dr. McDermott in obtaining informed consent. A research assistant will explain the study to

potential participants by telephone prior to their first study visit. When a potential participant arrives to the medical center for study participation, the research assistant will explain the full details of the research study, including risks and benefits. The informed consent process will take place at the initial baseline study visit in a private area on Northwestern's medical campus.

Potential participants will be provided plenty of time to read the consent form. The research assistant will answer questions and Dr. McDermott or another study investigator at Northwestern is also available to answer any questions that participants may have about the research. If the participant would like more time to discuss the research study with their physician or family member before signing the consent document, they will be allowed to do so and the study visit will be rescheduled for a later date.

Potential participants who do not speak English, subjects who are not yet adults, cognitively impaired adults, and adults unable to provide written consent will not be eligible for study participation.

29.0 Process to Document Consent in Writing

The "SOP: Written Documentation of Consent (HRP-091)" will be followed.

30.0 Drugs or Devices

Northwestern Memorial Hospital (NMH) Pharmacy will receive randomization assignments from the study's data management team and prepare identical appearing 30 day supplies of medication (telmisartan vs. placebo) for participants. Participants will receive each 30 day supply at their monthly visits.

The Food and Drug Administration concluded that the TELEX trial meets all of the requirements for exemption from IND regulations. A copy of this exemption letter has been uploaded to the eIRB.

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