Protocol

1. Project Title:

Resveratrol and Exercise to Treat Functional Limitations in Late Life (RESTORES)

2. Investigators:

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3. Abstract:

With persons aged ≥ 65 years representing the fastest growing segment of the U.S. population, the prevention of age-related functional decline and disability is an important public health priority. The loss of functional abilities in advanced age is associated with not only the onset of disability and the loss of independence but also with increased rates of morbidity and mortality. To date, physical exercise is the only intervention consistently demonstrated to improve physical function among older adults and is increasingly being considered the standard of cared for treating functional limitations. However, significant variability exists in responsiveness to exercise. As such, many individuals do not achieve clinically-significant improvements in function despite good adherence. Accordingly, there is a need to identify adjuvant therapies capable of improving the efficacy of exercise in treating older adults with functional impairments. This project is a pilot study to investigate the potential of resveratrol, a commercially-available nutritional product, to enhance the efficacy of physical exercise in improving physical function among older adults with functional limitations. The overarching objective of this project is to evaluate the safety and efficacy of an intervention combining resveratrol supplementation and physical exercise among sedentary persons aged 65 years objectively-measured functional limitations. A total of 60 participants will be recruited to participate in this three month intervention study. All participants will engage in a center-based exercise program 2/days per week and will be randomly assigned to consume 1) placebo, 2) 500 mg/day resveratrol, or 3) 1000 mg/day resveratrol. This study will provide critical information regarding the influence of the combination of resveratrol and exercise (REX) on objectively-measured and self-assessed indices of physical function. The study will also provide biologic information regarding the relative effects of REX on skeletal muscle mitochondrial function.

4. Background:

The maintenance of one's physical capabilities during older age is an essential part of healthy aging. Declines in physical abilities are associated with not only the onset of disability and the loss of independence but also with increased rates of morbidity and mortality.[1-3] To date, physical exercise is the only intervention with consistent evidence supporting its use in treating age-related functional limitations. However, despite strong adherence to training, clinically-significant improvements in physical function are not obtained by many individuals.[4,5] Thus exercise appears to be essential, but insufficient, for maintaining function among many seniors.[6] Alternative strategies are therefore needed to improve the therapeutic efficacy of exercise in physically-limited older adults. Therefore, our long-term goal is to develop interventions that optimize the efficacy of exercise as a strategy to prevent disablement among this high-risk population.

As our group has shown previously, skeletal muscle mitochondrial function declines with age and is a key factor in the maintenance of physical function among older adults.[7,8] Moreover, several studies have demonstrated that mitochondrial adaptations to both acute and chronic exercise are attenuated in late life.[9-12] Thus adjuvant therapies which stimulate mitochondrial function may hold promise for enhancing functional responses to exercise. Resveratrol, a polyphenol compound commonly found in the skin of red grapes, was previously suggested as a potential adjuvant to exercise due to its ability to stimulate mitochondrial biogenesis through peroxisome proliferator-activated receptor gamma co-activator 1 alpha (PGC-1α) activity.[13] In a recently completed pilot study, we observed that 12 weeks of resveratrol supplementation was well tolerated by overweight older adults and induced a dose-dependent (300 vs. 1000 mg/day) increase in resting muscle oxidative metabolism. Additionally, 30 days of resveratrol supplementation (150 mg/day) was recently reported to increase skeletal muscle mitochondrial function and PGC-1α content in obese, middle-aged men.[14]

Subsequent studies using animal models of aging have reported that improvements in physical performance are greater in response to the combination of exercise and resveratrol than from either treatment alone.[15-18] These studies overwhelmingly suggest that improvements in performance likely manifest as a result of enhanced skeletal muscle mitochondrial function. Thus, resveratrol appears to specifically target a key physiologic mechanism through which exercise improves physical function among older adults. We hypothesize that enhancing mitochondrial function may enhance physiologic adaptations to exercise such as aerobic fitness and skeletal muscle endurance. However, despite the promising findings from pre-clinical models, experimental data are sparse regarding the effects of this combined approach in humans. Consequently, well-controlled studies are needed to determine if the benefits of combining resveratrol with exercise demonstrated in pre-clinical studies can be translated to humans. *Therefore, the purpose here, as the next step in pursuit of our long-term goal, is to evaluate the relative efficacy of combining physical exercise with oral resveratrol supplementation for improving the physical function of older adults at risk for disability.*

5. Specific Aims:

The objective of this study is to conduct a pilot study to refine and finalize elements critical to conducting a future, definitive randomized, controlled trial (RCT). We propose to recruit 60 persons aged ≥ 65 years with functional limitations and follow them for 12 weeks. Participants will be randomly assigned to receive either (1) placebo plus 2 days/week of supervised, center-based, multi-modal exercise (EX), or (2) the same exercise program combined with either 500 or 1000 mg/day of resveratrol (REX). We will also collect skeletal muscle biopsies at baseline and 12 weeks from willing participants (i.e. optional for study participation) to evaluate skeletal muscle mitochondrial adaptations to the interventions. This study will enable us to address the following aims, all of which are of critical importance for designing a full-scale trial.

1. To obtain critical data necessary to project the sample size needed for a full-scale trial using the change in 4m usual gait speed, a key predictor of health and survival in older adults,[2,19,20] as the primary outcome.
2. To determine the variance of secondary outcomes and short-term effects of the intervention on these outcomes, including: (1) exercise capacity, evaluated by distance walked during the 6-minute walk test, (2) lower-extremity function, assessed by the Short Physical Performance Battery (SPPB), (3) skeletal muscle strength and endurance, assessed by isokinetic muscle testing, and 4) self-assessed functional limitations, evaluated by the Late-Life Disability Questionnaire.
3. To (a) assess the effects of resveratrol on exercise-induced changes in key indices of skeletal muscle mitochondrial function and quantity, and (b) determine the extent of association between changes in these mitochondrial outcomes and changes in measures of physical function.

6. Research Plan:

We propose to conduct a randomized, controlled pilot trial to test that resveratrol improves functional responses of physically-limited older adults to chronic exercise training. Following study entry, participants (N = 60) will be randomly assigned to either EX or one of two REX groups for 12 weeks. Each condition will consist of two center-based resistance training sessions per week.

6.1 Participants: Eligible participants will be males or females ≥ 65 years of age with a sedentary lifestyle and objectively-measured functional limitations.

Table 6.1. Inclusion and exclusion criteria

Inclusion Criteria

- Age 65 years
- > 290 seconds needed to complete long-distance corridor walk test, as an indicator of functional limitation and moderate to low aerobic fitness[3]
- Sedentary lifestyle, defined as <150 min/wk of moderate physical activity as assessed by CHAMPS questionnaire[21]
- Willingness to be randomized to either treatment group
- Willingness to participate in all study procedures

Exclusion criteria

- Failure to provide informed consent;
- Regular consumption of a resveratrol supplement
- Current involvement in supervised rehabilitation program
- Absolute contraindication(s) to exercise training according to American College of Sports Medicine guidelines[22]
- Pain classification > Grade 3 on Graded Chronic Pain Scale[23]
- Peripheral vascular disease; peripheral neuropathy; retinopathy
- Severe cardiac disease, including NYHA Class III or IV congestive heart failure, clinically significant aortic stenosis, history of cardiac arrest, use of a cardiac defibrillator, or uncontrolled angina;
- Myocardial infarction or stroke within past year
- Significant cognitive impairment, including known dementia diagnosis or a Mini-Mental State Examination exam score < 24
- Progressive, degenerative neurologic disease, e.g., Parkinson's Disease, multiple sclerosis, ALS;
- Severe rheumatologic or orthopedic diseases, e.g., awaiting joint replacement, active inflammatory disease;
- Severe pulmonary disease, requiring either steroid pills or injections or the use of supplemental oxygen;
- Hip fracture, hip or knee replacement, or spinal surgery within past 4 mos.;
- Other significant co-morbid conditions that would impair ability to participate in the exercise-based intervention
- Simultaneous participation in another intervention trial

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- Use of prescription anti-platelet medications (not including aspirin)
- Prescription anti-coagulant use (e.g. warfarin)
- Conditions which reduce wound healing, e.g. peripheral vascular disease, venous stasis
- Known allergy to lidocaine

6.2 Recruitment: Participant recruitment will be coordinated in conjunction with the *OAIC Clinical Research Core*, led by co-investigator Dr. Stephen Anton. We will develop a targeted recruitment approach based on previous experiences utilizing methods of recruitment that include direct mailings, newspaper classified and print ads, community luncheons and health fairs, as well as clinic referrals. We have extremely successful in implementing this approach in past studies

6.3 Screening and Study Entry: Interested individuals will initially complete a pre-screening interview by phone. Participants deemed eligible based on the pre-screening invited to an in-person screening visit. During this visit, potential participants will first be asked to give their informed consent and then will be screened for study entry criteria. Initial screening procedures will include a review of their medical history, physical activity habits, medication use, cognitive function (assessed by the Mini Mental State Exam), and a physical exam performed by a study physician. The study physician will review collected information relevant to potential participant's health and make recommendation on this individual's participation in this trial.
Participants will then be asked to complete the long-distance corridor walk test to evaluate functional status and aerobic fitness. If all study entry criteria are met, participants will be scheduled to return to the clinic for baseline assessments. In addition, the study participants will be asked to sign Medical Records Release Authorization. This Authorization will be used exclusively to obtain medical records to acquire facts, details, and outcomes of Serious Adverse Events that occurred during the study and have to be reported to the sponsor and/or IRB.

6.4 Baseline Assessment and Randomization: If all study entry criteria are met, participants will be scheduled to return to the clinic for baseline assessments prior to randomization. During this visit, participants will be asked to complete validated study questionnaires, including the Late-Life Disability Instrument[24] and provide a fasting blood sample for evaluation of clinical safety lab values. Participants will also complete the Short Physical Performance Battery (SPPB), a 6-minute walk test, and assessments of muscle strength. Finally, the study coordinator will provide participants with an armband physical activity monitor and dietary intake form to take home to objectively evaluate baseline physical activity and dietary habits. Staff members will then discuss randomization procedures with participants. Participants who agree to participate in the muscle biopsy procedure will be scheduled for a separate visit prior to initiation of study interventions.

6.5 Exercise Intervention: After random assignment to either the EX or the REX groups, participants will engage in a two days a week, center based resistance exercise intervention for 12 weeks. Following a brief warm-up, participants will be instructed to walk for 30 minutes at a 5-6 on the CR10 scale with encouragement for 10 minutes to be vigorous (7-8 on CR10 scale). Sessions will also include 30 minutes of strength exercises for both lower- and upper-body followed by flexibility exercises and balance training to promote cool-down. Participants will be introduced to exercises in such a way that they begin with lighter intensity and gradually increase. The progressive nature of the intervention is designed to minimize discomfort and prevent injury. During the first week of the intervention, resistance exercises will be performed using lighter resistance where the focus will be on learning proper technique. Resistance training will be performed using standard isotonic resistance training equipment.

Participants in the REX groups will be randomly assigned to receive, in a double-blind fashion, either 500 or 1000 mg/day of encapsulated resveratrol or placebo. The company Reserveage Organics (Gainesville, FL) provided the resveratrol and placebo capsules for our previous study and will provide both the resveratrol and placebo capsules for the proposed study. Placebo capsules will be identical to those including resveratrol. Our 12-week resveratrol pilot study demonstrated that resveratrol supplementation at a dose of 1000 mg/day was safe and improved markers of metabolic function (i.e., blood glucose) in overweight, older adults. This dosage is also in line with

another recent pilot study by Crandall et al. (2012) which demonstrated safety and improvements in glucose metabolism and insulin sensitivity in older adults (mean age = 72 years) following 1000 mg/day of resveratrol.[25] The low dose has been previously shown to be sufficient for improving mitochondrial function[3] and will allow for comparison with findings from the only human study of REX to our knowledge published to date.[26,27]

Data from the exercise interventions will be collected and stored in the study database. Following each session, participants will be asked to provide a rating of perceived exertion (RPE) for the session according to the Borg CR10 scale. Additional data collected includes session attendance, 1 repetition maximum, and repetitions completed for each exercise per session.

6.6 Adherence to interventions. To enhance adherence to the study interventions (compliance), we will utilize empirically-supported techniques which we have successfully utilized in prior studies. Our first step will to fully inform participants of study requirements before randomization and enroll only those persons who are willing to complete all study procedures. Undoubtedly, however, issues arise after randomization with the potential to limit compliance. Common causes of poor compliance include vacations, spouse care, fatigue, and fluctuations in motivation, perceived lack of benefit, physical discomfort, and adverse health experiences. First, we have designed the trial, including the inclusion/exclusion criteria and physician monitoring, to limit the likelihood of experiencing adverse health events in response to the interventions. In addition, care will be taken by the interventionists to promote the safe engagement in the exercise intervention. For other issues of non-compliance, we will approach this potential problem using a social problem solving model ("toolbox") approach in dealing with individual adherence problems.[28] This approach assumes that the process of changing behavior is a collaborative effort between the participant and the interventionists, and that behavior change can be readily undertaken during the regular weekly contacts that intervention staff will initiate throughout the course of the intervention, as well as during face-to-face visits. Our team has successfully applied this type of problem-solving approach in promoting adherence to behavioral interventions in prior studies.

6.7 Follow-up and Close-out visits. In addition to baseline and screening visits, assessment visits will be conducted at 6 weeks (follow-up) and 12 weeks post-randomization. During the 6-week assessment visit, the research team will evaluate participant vital signs, collect blood samples, inquire about any adverse experiences since the last visit, and perform tests of physical performance evaluated performed at baseline. During the close-out (12 week) visit, the team will perform the same evaluations as during the 6-week visit, as well as administer study questionnaires, perform the SPPB, and collect home-based physical activity and dietary information from participants. Skeletal muscle biopsies will also be collected at 12 weeks from willing participants.

6.8. Primary and Secondary Outcome Measures.

Walking speed	We will assess walking speed by asking the participants to walk at their usual pace over a 4 m course. Participants will be instructed to stand with both feet touching the starting line and to start walking after a specific verbal command. Timing will begin when the command is given, and the time needed to complete the entire distance will be recorded. The faster of two walks will be used. The reliability of the 4 m walk test is excellent – with an intraclass correlation coefficient (ICC) > 0.9.[29]
Lower-extremity function (SPPB)	The SPPB is based on the 4m walk (above), repeated chair stands and a balance test. This test is reliable[30] and valid for predicting institutionalization, hospital admission, mortality and disability.[31,32-34] Each task is scored from 0 to 4, with 4 indicating best level of performance and 0 the inability to complete the test. A summary score (0-12) is then calculated.

Skeletal muscle function	Isokinetic strength and endurance of the knee flexors and extensors of the dominant limb will be assessed by a standard dynamometer as published previously.[35,36]
Exercise capacity	We will assess exercise capacity of participants using the six-minute (6-min) walk test, a safe and reliable test of aerobic endurance in older persons and those with cardiovascular conditions.[37,38] This test has strong reproducibility, with intra-subject coefficients of variation averaging < 10%, and has a modest correlation with peak VO_2.[39] Participants will be asked to walk as far and fast as possible for 6-min on a 60 m track.
Self-assessed physical function	We will document self-assessed functional status using the Late Life Function and Disability Instrument.[40,41] The instrument includes 16 tasks representing a broad range of disability indicators that assesses both frequency of doing a task and perceived limitation. The instrument uses a scale from 0 to 100, with higher scores indicating higher levels of function. The scale has strong concurrent and predictive validity with physical performance.[24]

6.9 Mitochondrial Outcome Measures.
Measurement of skeletal muscle (1) *in situ* mitochondrial respiration, (2) proliferative activated receptor-γ coactivator 1α (PGC-1α), (3) mitochondrial DNA, (4) citrate synthase (CS) activity, and (5) cytochrome C oxidase (COX) activity will be completed the *OAIC Metabolism and Translational Science Core*, led by co-investigator Dr. Christiaan Leeuwenburgh. Mitochondrial respiration will be determined immediately on freshly saponin-permeabilized muscle fibers as published previously[8] using the high-resolution Oxygraph-2k (Oroboros, Innsbruck, Austria). Skeletal muscle PGC-1α, mitochondrial DNA content, as well as CS and COX activities will be determined using well-standardized, validated methods with excellent test re-test reliability in the Core laboratory.[42]

6.10 Sample size justification. This study will help generate precise estimates of effect variance in the population in which a subsequent larger-scale study will be conducted. Published recommendations for the design of pilot studies indicate that a sample of 15-20 participants per randomized arm is typically sufficient to estimate a parameter for a future trial.[43-45] The enrollment sample of 60 participants is intended to provide preliminary data necessary to indicate feasibility of a larger trial and to provide descriptive estimates of effects. It will also provide for nominal estimation (using a 95% CI) of mean changes in dependent variables within each arm. While it is possible that statistically significant differences between arms may be observed, this pilot trial is not intended to be powered to observe such differences with high probability. For aims 1 and 2, assuming $\alpha = 0.05$, we will have 80% power to detect an effect size of 0.74 for outcomes with three assessments (walking speed, muscle function, exercise capacity) and 0.79 for outcomes with two assessments (SPPB, self-assessed function, mitochondrial measurements), assuming a repeated measures correlation of 0.5. For the primary outcome of walking speed, we expect this detectable difference to be 0.12 m/sec based on a SD of 0.16 m/sec observed in the LIFE studies. For secondary aims, the following detectable effects sizes are expected based on our prior experience in LIFE and LIFE-P: SPPB, 1.3 points; 6-minute walk distance, 22.2 m; isokinetic peak torque, 27.8 Nm; and Late Life Disability Instrument Score; 3.8 points.

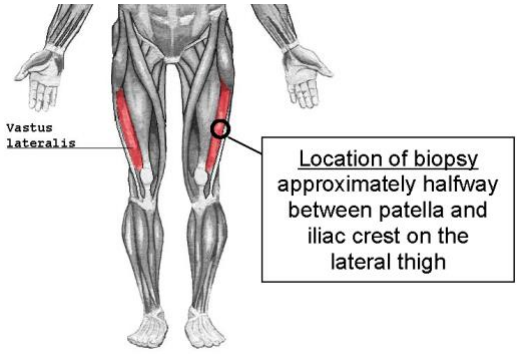
6.11 Safety monitoring plan. To ensure participant safety in the proposed study, we will adapt procedures that we have implemented successfully in other studies including LIFE,[46,47] Weight Loss + Exercise,[48] and Task Specific Exercise.[49] As he has for a number of our prior studies, Dr. Bhanuprasad Sandesara will serve as the Study Physician who is responsible for assessment, monitoring and interventions for health events. To maximize participant safety we will follow a standardized screening protocol. Accordingly, all

potential participants will undergo screening for cardiovascular and other major diseases by means of a health questionnaire, medication inventory, and physical exam. Those with conditions that meet the exclusion criteria described in section 6.1 as determined by Dr. Sandesara will be excluded. Dr. Sandesara will also review clinically significant abnormal laboratory values and indicate the need for study withdrawal if he deems it necessary. Each participant will be instructed to report the occurrence of an adverse event at scheduled data collection times (scheduled clinical exams or phone interviews). Participants also have access to study clinic personnel at other times to report serious adverse events or concerns about the safety of participating in the study. If necessary, Release of Medical Records Authorizations signed by the study participants will be used to obtain medical records to collect details and outcomes of SAEs for safety and reporting purposes.

Venipuncture will be performed by a trained and experienced phlebotomist using standard techniques. Participants will always have venipuncture performed while seated upright with both feet on the floor. Muscle biopsies will be performed by a licensed physician trained in the technique. A detailed description of the procedure is provided below.

Muscle Biopsy Procedure – Vastus Lateralis

- Participant should lie comfortably in a reclined position with both legs outstretched. Support can be added for calves/feet with pillows to maintain relaxed position
- The participant is asked if they are allergic to latex, and if so, alternative material gloves must be used.
- The muscle biopsy will be obtained approximately midway between the patella and iliac crest on the lateral thigh. See figure below. This distance was chosen so each participant will receive the biopsy at the same relative length of their lower extremity.



- If necessary, an area of skin can be shaved to prevent hair from entering the incision and to improve adhesion of the sterile bandage
- The skin is cleaned with an alcohol-based solution such as ChloraPrep® Swab, starting from the anticipated biopsy site in a circular motion extending to a diameter of approximately 4-5 inches.
- 1 to 2 ml of 2% lidocaine is injected intradermally and subcutaneously. A brief period (i.e. 30-60 seconds) allows for the skin to numb before injecting the remaining volume more deeply. The needle is inserted to just below the fascia, a small amount of lidocaine is injected starting below the fascia and injection is continued while the needle is drawn straight up through the subcutaneous tissue. This step is repeated in a star pattern.
- 8 to 10 minutes are allowed to pass after injection of the lidocaine before proceeding, to ensure maximal participant comfort.
- Scalpel skin test: Using a blade scalpel, gently touch the scalpel to the anticipated site and ask the patient if they can feel anything where touched. It may help to have the patient close their

eyes. If they can feel the scalpel, allow more time and retest in 5 minutes. If the participant can still feel the blade touch, consider switching to carbocaine.

- When the participant's area of the leg is properly numbed, approximately 5 mm incision is made in the skin down through the muscle fascia. The biopsy needle trocar is inserted through the incision, and through the fascia, advancing it into the muscle belly to obtain the muscle sample. If the yield is insufficient with study participant's consent the trocar may re-inserted up to three times through the same hole in the fascia but at slightly different angles in the numbed area, as long as the participant is comfortable.
- After completing the procedure, the study physician holds firm direct pressure over incision site for at least 5 minutes or longer until external bleeding has ceased. He/she then closes the incision with a sterile liquid bonding agent (such as Dermabond) or butterfly bandage. This will help prevent bleeding and scarring. Finally, the physician will apply a small amount of antibiotic and a sterile gauze pad over the incision and cover with a waterproof transparent dressing.

The study participant will be provided with detailed instructions (discussion and a leaflet) on how to take care of the incision site. Study staff will make follow-up phone calls in the days following the procedure to monitor healing and any potential adverse events.

Center-based assessments and interventions will be conducted and supervised by trained staff who will monitor potential adverse experiences and symptoms. All assessors and interventionists receive CPR training and training on management of acute events including syncope, chest pain, acute dyspnea, focal neurological symptoms and abnormal vital signs. Portable defibrillators are available at each intervention and assessment site and all study staff have on-call access to the study physician and contact numbers for emergency services are. Institutional and community EMS services will be activated if needed. As indicated previously, participants will be taught the importance and proper method of warming-up prior to and cooling-down following structured activity sessions. If at any point during an exercise session, participants develop chest pain, shortness of breath, or dizziness, they will be instructed to rest and to contact the center and their physicians if these symptoms persist or recur with further exercise.
Blood pressure and heart rate will be measured before and after the resistance training at each center based session in participants who had experienced any of the following during a previous exercise session: decrease in diastolic blood pressure $\geq$20 mm Hg during the activity, increase in systolic blood pressure to $\geq$250 mm Hg or in diastolic blood pressure $\geq$115 mm Hg during the activity, increase in heart rate $\geq$90% of age predicted maximum, unusual or severe shortness of breath, chest pain or discomfort, palpitations, light headedness, dizziness or feeling about to faint, a session had to be discontinued because of other symptoms, excluding musculoskeletal symptoms (e.g., knees, ankles, hips), reported by the participant.

Procedures to minimize discomfort include warm-up and cool-down activities that include cycling and flexibility exercises. The participants will also be introduced to the intervention exercises in a structured way, such that they begin with lighter resistance and gradually increase over the course of the first 2-3 wks. During the intervention visits, participants will be supervised at all times and instructed on correct exercise techniques. Participants will also be instructed to move slowly when rising from a seated or lying position to reduce the risk of experiencing orthostatic hypotension. Study staff will be instructed to stand in a supportive position when participants are rising to prevent a fall in case of syncope. Participants will be instructed to talk with the interventionists about any muscle soreness. Exercise will be stopped if the participant reports pain, tightness or pressure in the chest, significant shortness of breath, feeling faint, lightheaded or dizzy, or significant other medical problems.

Any significant adverse events will be reported promptly to the IRB and to the OAIC Data Safety Monitoring Board (DSMB). Otherwise, annual reports will be prepared for both. The OAIC DSMB consists of an established board which has reviewed all studies conducted within the University of Florida's Pepper center during bi-annual conference calls for the past seven years. This board consists

of the following individuals: (1) Stephen Kritchevsky, Ph.D., Chair, an epidemiologist who has been involved in research for many years, (2) Jing Cheng, Ph.D., a biostatistician who has been involved with a number of clinical trials, and (3) John Meuleman, M.D., a physician who has been involved in the conduct of clinical research for many years.

Again, written informed consent will be obtained after explanation to subjects of all procedures and time commitments. The study interviewers will explain to prospective participants the purpose, methods and extent of the study. Potential participants will be asked to read the informed consent form and to ask questions. The form will be written in simple, easy-to-understand language. Staff members will also review all key aspects of the study verbally.

Confidentiality of data will be maintained by using research identification numbers that uniquely identify each individual. Data will be used only in aggregate and no identifying characteristics of individuals will be published or presented. Safeguards will be established to ensure the security and privacy of participants' study records. The information collected from participants in this study has a low potential for abuse, since the data do not address sensitive issues. Nevertheless, appropriate measures will be taken to prevent unauthorized use of study information. The research records will be kept in a locked room at the Institute on Aging. The files matching participants' names and demographic information with research ID numbers will be kept in a separate room and will be stored in a locked file that uses a different key from that of all other files. Only study personnel will have access to these files, and they will be asked to sign a document that they agree to maintain the confidentiality of the information.

After the study is completed, local data will be stored with other completed research studies in a secured storage vault. In compliance with the Health Insurance Portability and Accountability Act (HIPAA) and the Standards for Privacy of Individually Identifiable Health Information of the Department of Health and Human Services, we will access personal health information and medical records only after receiving signed informed consent, as described above.

Finally, the study protocol will be registered at www.ClinicalTrials.gov before study enrollment begins.

7. Possible Discomforts and Risks:

Potential risks are those associated with health information privacy, venipuncture, muscle biopsies, and participation in exercise training and testing.

Venipuncture can be associated with pain, bruising, hematoma formation, superficial phlebitis, and rarely cellulitis or fainting. The potential risks of the muscle biopsy procedure include infection, mild muscle soreness, scarring from the incision, mild nerve damage, swelling, and bleeding. The primary risk associated with moderate-intensity exercise training is skeletal muscle soreness. There are also other risks that relate to soft tissue injury, falls and fractures, exacerbation of arthritis and other joint conditions, post-exercise hypotension, and cardiovascular events. There is a risk that a participant may trip, stumble, or fall during the physical performance tests and experience shortness of breath, dizziness, palpitations, chest pain or discomfort, heartburn, light headedness, or feeling about to faint. Strength training may involve a minimal risk of increasing intraocular and systemic pressures associated with use of the Valsalva maneuver to levels that may cause injury.

8. Possible Benefits:

Importantly, the proposed project should have tangible benefits for participants. These benefits include information about their health and assessments of their functional status. All study participants will be encouraged to communicate the results from the study to their primary care providers. Moreover, all participants – regardless of randomized group– will receive supervised exercise training and instruction about how to maintain exercise habits at home. We expect that these benefits will improve quality of life for all participants.

9. Conflict of Interest:

Dr. Anton, a Sub-Investigator, is a paid adviser to Reserveage Organics that makes the resveratrol product that will be used in the study.

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