

Lifestyle Intervention plus Metformin to Treat Frailty
in Older Veterans with Obesity

NCT04221750

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Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

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Section Aa: Title & PI

A1. Main Title

LIFESTYLE INTERVENTION PLUS METFORMIN TO TREAT FRAILTY IN OLDER VETERANS WITH OBESITY

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A3a. Financial Conflict of Interest

Does any member of study personnel (Investigator (including investigator's spouse and/or dependent children)) that are involved in the design, conduct, or reporting of the research have a Significant Financial Interest (SFI) that would reasonably appear to be affected by the research for which funding is sought and/or associated with an entity/business that would reasonably appear to be affected by the research?

No

Section Ab: General Information

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A5. Funding Source:

Organization: VA CSR&D

[A5a. ESP2 proposal\(s\) linked to this protocol:](#)**A6a. Institution(s) where work will be performed:**

BCM: Baylor College of Medicine
Michael E. DeBakey Veterans Affairs Medical Center

A6b. Research conducted outside of the United States:**A7. Research Category:****A8. Therapeutic Intent**

Does this trial have therapeutic intent?

No

A9. ClinicalTrials.gov Registration

Does this protocol/trial require registration on ClinicalTrials.gov due to it: meeting the definition of an Applicable Clinical Trial, being required under the terms and conditions of an award, or being proposed to be published in ICMJE journals?

Yes

Who will be responsible for registering and maintaining the registration of this Applicable Clinical Trial?

The BCM PI will register the trial because either:

- the trial is BCM PI-initiated,

- BCM is the lead site of this multicenter trial, or,
- the industry sponsor has instructed the BCM PI to register the trial, or,
- registration of this trial is required as a term and condition of the reward by the funding agency.

ClinicalTrials.gov Identifier:
NCT04221750

Section B: Exempt Request

B. Exempt From IRB Review

Not Applicable

Section C: Background Information

The growing prevalence of obesity in older adults, which includes many older veterans, has become a major concern in our already strained health care system in general and the VA in particular. In older adults, obesity exacerbates the age-related decline in physical function resulting in frailty, decrease in quality of life, loss of independence, and increase in nursing home admissions. We previously reported that frailty is common in the understudied population of sarcopenic obese older adults. However, we also demonstrated that weight loss from lifestyle therapy improves physical function and ameliorates frailty. Nevertheless, this improvement in physical function is modest at best and most obese older adults remain frail. More importantly, there are concerns that the weight loss-induced loss of muscle and bone mass could worsen the underlying age-associated sarcopenia and osteopenia in the subset of frail obese elderly. Because weight loss may have potential harmful effects in the older population, the appropriate clinical approach to obesity in the elderly remains controversial.

Metformin, a biguanide, is a widely available drug used as first line treatment of type 2 diabetes. Animal studies suggest that metformin improves health span and increases lifespan,⁹ hence, may represent a novel intervention for frailty. Because metformin reduces cellular senescence and SASP, it is believed to retard accelerated aging most especially in obese older adults. Observational studies show that metformin reduces frailty and mortality, associated with lesser decline in muscle mass. A randomized controlled trial (RCT) showed that metformin significantly improved gait speed in pre-frail elderly. Indeed, secondary analyses of multiple data from our prior RCTs revealed that metformin users had higher scores in the Physical Performance Test (PPT) and that use of metformin predicted larger improvements in PPT scores in response to our lifestyle interventions. Although our findings suggest that metformin may enhance the effects of exercise on physical function, to our knowledge there are no direct head-to-head comparisons of the efficacy of lifestyle therapy or metformin, or both, in improving physical function and reversing frailty in older adults with obesity.

Section D: Purpose and Objectives

Our primary goal is to conduct a head-to-head, comparative efficacy, placebo-controlled RCT to test the novel hypothesis that lifestyle therapy + metformin will be more effective than lifestyle therapy or metformin alone in improving physical function and preventing the weight loss-induced reduction in muscle and bone mass in frail, obese older veterans. The following specific aims will be evaluated:

Primary Aim: Determine the effects of lifestyle therapy (diet-induced weight loss and exercise training) + metformin compared to lifestyle therapy or metformin alone on physical function in older veterans with obesity.

Secondary Aim 1: Determine the effects of lifestyle therapy + metformin compared to lifestyle therapy or metformin alone on a) lean body mass and muscle quality and b) bone mineral density (BMD) and bone quality in older veterans with obesity.

Secondary Aim 2: Determine the effects of lifestyle therapy + metformin compared to lifestyle therapy or metformin alone on markers of cellular senescence and accelerated aging that underlie the improvements in physical function in response to the interventions in older veterans with obesity.

Section E: Protocol Risks/Subjects

E1. Risk Category

Category 2: Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects.

E2. Subjects

Gender:

Both

Age:

Geriatric (65+ yrs)

Ethnicity:

All Ethnicities

Primary Language:

English

Groups to be recruited will include:

Patients

Which if any of the following vulnerable populations will be recruited as subjects?

Vulnerable populations require special protections. How will you obtain informed consent, protect subject confidentiality, and prevent undue coercion?

E3. Pregnant woman/fetus

Will pregnant women and/or fetuses (as described in 45 CFR 46 Subpart B) be enrolled in the research?

No

E4. Neonates

Will neonates of uncertain viability or nonviable neonates (as described in 45 CFR 46 Subpart B) be enrolled in the research?

No

E5. Children

Will children be enrolled in the research?

No

Section F: Design/Procedure

F1. Design

Select one category that most adequately describes your research:

z.r) Randomized, Efficacy Study -- Surgical Techniques/Interventions

Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.

This will be a randomized controlled trial of the effects of lifestyle therapy (diet and exercise training) and metformin on the changes in 1) physical function, 2) lean body mass and muscle quality, and BMD and bone quality, and 3) markers of cellular senescence and accelerated aging in frail, obese older adults in response to six months of lifestyle therapy, metformin, or both. Participants will be randomized to one of 3 study groups: 1) lifestyle therapy + metformin, 2) lifestyle therapy + placebo, and 3) metformin. Assignment to metformin (1500 mg/day or placebo) will be double-blinded for the lifestyle therapy groups and single-blinded (participant blinded) for the metformin only group. As in our prior intervention studies in this population, the lifestyle intervention will consist of behavioral/diet therapy for weight loss and supervised exercise training at our facility.

Only veterans will be enrolled.

Inclusion Criteria:

- Age 65 - 85 years - BMI > or equal to 30 kg/m² - Mild to moderately frail (score of 18 to 31 in the modified Physical Performance Test) - Stable body weight (± 2 kg) during the past 6 months - Sedentary (regular exercise <1 h/wk or <2 x/wk for the last 6 months) - Willing to provide informed consent

Exclusion Criteria:

Any major chronic diseases, or any condition that would interfere with exercise or dietary restriction, or use of metformin, in which exercise, dietary restrictions, or metformin are contraindicated, or that would interfere with interpretation of results - Cardiopulmonary disease (e.g. recent MI, unstable angina, stroke) or unstable disease (e.g., NYHA Class III or IV congestive heart failure, severe pulmonary disease requiring steroid pills or the use of supplemental oxygen) that would contraindicate exercise or dietary restriction - Severe orthopedic (e.g. awaiting joint replacement) and/or neuromuscular (e.g. multiple sclerosis, ALS, active rheumatoid arthritis) disease or impairments that would contraindicate participation in exercise - Renal impairment as defined by an estimated glomerular filtration rate (eGFR of less than 30 mL/min/1.73 m²) in which metformin is contraindicated - Other significant co-morbid disease that would impair ability to participate in the exercise based intervention (e.g. severe psychiatric disorder [e.g. bipolar, schizophrenia], excess alcohol use [more than 14 drinks per week]) - Severe visual or hearing impairments that would interfere with following directions - Significant cognitive impairment, defined as a known diagnosis of dementia or positive screening test for dementia using the Mini-Mental State Exam (i.e. MMSE score less than 24) - Uncontrolled hypertension (BP more than 160/90 mm Hg) - Malignancy that is active and/or undergoing treatment - Current use of bone acting drugs (e.g. use of estrogen, or androgen containing compound, raloxifene, calcitonin, parathyroid hormone during the past year or bisphosphonates during the last two years) - Osteoporosis (T-score -2.5 and below on hip scan) or history of fragility fractures - Known history of diabetes mellitus or any of the following: fasting blood glucose of more than or equal to 126 mg/dL, or HbA1c more than or equal to 6.5%. - Terminal illness with life expectancy less than 12 months, as determined by a physician - Use of any drugs or natural products designed to induce weight loss within past three months. - History of excessive alcohol consumption (e.g. 8 or more drinks a week for women and 15 or more drinks a week for men) - Positive exercise stress test for ischemia or any indication for early termination of exercise stress testing (see specific guidelines based on screening tests below under 2. Adequacy of protection against risks b. Protection against risk) - Lives outside of the study site or is planning to move out of the area in the next 2 years - Volunteers with history of previous use of metformin will be required to have a washout period of at least 3 months prior to consideration for study participation.

F2. Procedure

A. Screening tests- to determine eligibility volunteers will undergo a medical history, physical examination, blood tests, physical function tests, DXA (bone scan), electrocardiogram (EKG), and graded exercise test. B. Baseline and follow-up tests- if they are eligible to participate and choose to do so, they will undergo a series of tests and procedures: a. Body Composition: Dual energy x-ray absorptiometry (DXA). The amount of fat, muscle, and bone in the body will be measured by DXA and Magnetic Resonance Imaging (MRI). Fat and muscle in the thighs will be measured by MRI. High resolution quantitative computed tomography (HR-pQCT) to assess the 3-dimensional bone microarchitecture and volumetric bone mineral density of the leg and forearm. Coupled with computer-based finite element analysis (FEA) modeling, it will provide a newfound approach to assess bone strength. Waist circumference will be measured. MRI and HR-pQCT scan will be done at baseline and 6 mos. DXA scan will be done at baseline, 3 and 6 mos. b. Blood, stool, and urine tests: Blood will be drawn for routine chemistries (blood count and electrolytes), blood sugar, cholesterol, hormones, and markers of bone function/inflammation. Urine tests for biomarkers of aging and stools samples for microbiota analyses to be done at baseline, 3 and 6 mos. c. Physical function tests: The Physical Performance Test will evaluate ability to do activities such as walking, climbing steps, and picking up small objects such as a coin. Muscle strength will be tested by having them use their arms or legs to push and pull as hard as possible against a special machine. Endurance will be measured by how quickly and how far they can walk within a specific amount of time. These tests will be done at baseline, 3 and 6 mos. d. Questionnaires: The SF-36 will ask how they feel about their quality of life. The Functional Status Questionnaire will ask about things that they all need to do as a part of our daily lives. The Impact of Weight on Quality of Life Questionnaire-Lite will evaluate the effect of excess weight on their quality of life. The psychometric tests and

mood scale will assess cognition and mood. The St. George's Respiratory Questionnaire will evaluate the respiratory specific quality of life. These will be done at baseline and 6 mos. e. They will be asked to wear accelerometers (a small piece of equipment that measures level of physical activity) for 7 days at baseline and 6 mos. f. Measurement of aerobic capacity: They will be asked to walk on a treadmill while breathing through a mouthpiece, and the amount of oxygen they consume will be measured. This test evaluates the ability of their heart to provide muscles with oxygen. This will be done at baseline and 6 mos. g. Measurement of lung function. They will be asked to take a deep breath in and blow out as hard and fast as they can into a machine for at least 6 seconds. The machine measures the amount of air you can blow out and how fast you can blow it out. This will be done 3 or more times so we can get an accurate measure of lung function. This will be done at baseline and 6 mos. h. Diet evaluation: They will meet with a dietitian for about ½ hour. The dietitian will ask them to measure and write down everything that they eat and drink for 3 days. At the end of the 3 days, they will meet with the dietitian again to review their food diary. This will be done at baseline, 3 and 6 mos.

Muscle and fat studies: These tests are optional and are not required in order to take part in the overall study. These tests will be done at baseline and after 6 mos.

We will obtain biopsy samples of muscle tissue from the thigh. This involves numbing their skin with local anesthesia (by injecting 2% xylocaine), making a small (approx. the size of the dotted line -----; ½ cm) incision on the thigh for the muscle biopsy, removing a small (approx. 1/15th of an ounce) piece of muscle tissue. During the muscle biopsy, adipose tissue within and around the muscle may also be obtained. The incision is then closed with a piece of sterile tape. We will also obtain biopsy samples of fat tissue underneath the skin of the abdominal wall near the navel. This will also involve numbing the skin with local anesthesia (by injecting 2% xylocaine), making a small (approx. the size of the dotted line ----; ½ cm) incision on the abdomen, removing a small (approx. 1/15th of an ounce) of fat tissue using a liposuction needle under sterile conditions. The incision is then closed with a piece of sterile paper. Participants will be given instructions on how to take of the biopsy sites to prevent any complications. C. Interventions After the medical screening and baseline assessments are complete, they will be randomly assigned into 3 groups using computer-generated block random permutation stratified for BMI (<35 vs. ≥35). The 3 groups are: 1) lifestyle therapy+metformin, 2) lifestyle therapy+placebo, and 3) healthy lifestyle+metformin. The ICF states 2 groups purposefully to maintain blinding. a. Lifestyle therapy Behavioral diet therapy. The lifestyle modification will be achieved by group behavior therapy sessions designed to have older adults acquire positive weight-control skills/attitudes, and practice weight- maintenance skills. We have successfully used this approach in previous studies. Participants will attend weekly group sessions, which will last ~75-90 minutes. Group treatment will be provided by group therapists and dieticians experienced with lifestyle management. Participants will be instructed in behavioral strategies for modifying eating habits: goal setting and self-monitoring, stimulus control, problem solving skills, identification of high-risk situations, and relapse prevention. A balanced diet will be prescribed to provide a deficit of 500-750 kcal/day from daily energy requirement. The diet will contain ~1 g of high-quality protein/kg/day. We will provide all participants with a daily multivitamin/mineral supplement to protect against deficiencies. Exercise training. We will use the same supervised exercise program that was very successful in our previous studies in this population. Details regarding our exercise protocol are available online with the full text of the New Engl J Med article. Briefly, the exercise sessions are of ~90 min duration (~15 min warmup of flexibility exercise, followed by ~30 min of aerobic exercise, and after a brief rest period, ~30 min of resistance training, and ~15 min balance exercise) conducted three times weekly. Aerobic exercises consist of treadmill, stationary bike, and stair climbing. An initial goal of 65% of VO2peak will be achieved, followed by an increase in intensity to 70-85% of VO2 peak. Heart rate will be monitored during each session and used to adjust exercise intensity relative to the VO2 peak. The resistance training program includes nine upper extremity and lower- extremity exercises with the use of weight-lifting machines. Initially, the participants perform 1 or 2 sets at a resistance of ~65% of their 1-repetition maximum (1-RM), with 8 to 12 repetitions of each exercise; they gradually increase the intensity to 2 to 3 sets at a resistance of ~80% of their 1-RM, with 6 to 8 repetitions of each exercise. Compliance to this exercise program in our frail older adults was 83 - 98%. Due to unexpected changes in circumstances, interruption of regular exercise and/or participation in diet classes may occur. Such subjects may be reintegrated into the exercise program. The exercise physiologist will reassess their maximal strength and aerobic capacity to establish a new exercise prescription. b. Healthy lifestyle. Participants in the healthy lifestyle+metformin group will receive group educational sessions that focus on diet, exercise, and social support once a month throughout the study. The sessions will provide an opportunity to discuss issues related to living with obesity and aging. c. Metformin or placebo. Metformin will be initiated at a dose of 500 mg (one tablet) taken orally once a day with meals, with placebo tablets also given once a day. After a week, the dose of metformin or placebo will be increased to 1000 mg 2 tablets daily. After another week, the dose of metformin or placebo will be increased to 1500 mg (3 tablets) daily. If gastrointestinal symptoms appear as the dose is advanced, the unblinded physician- investigator will decrease the dose to the previous lower dose, and the dose will be advanced at a later time (four weeks). To maintain blinding, a participant in the placebo group will be treated similarly. Adherence to the medication will be assessed monthly based on pill counts. Dispensing of metformin under blinded conditions. The research coordinator will inform the MEDVAMC pharmacy when a subject is ready for randomization. The metformin and placebo will be provided in identical form and dispensed by the pharmacy. The pharmacy will complete a group assignment form, copies of which will be provided to the study biostatistician. A list of participants with treatment assignment will be kept by the pharmacy. The pharmacy will dispense metformin and placebo directly to the participants monthly and maintain a record of dispensed dosage. Blinding. Participants in all groups will be blinded to study drug. During the informed consent process, participants will see in writing and be told that they will receive metformin or placebo. The study team (except Dr. Reina Villareal) will be blinded to study drug in the exercise groups. The study team will by default know that non- exercisers will be receiving metformin. However, the non-exercisers will have little opportunity to interact with other participants. Additionally, exercise logs will be stored separately from the main study folders.

Muscle and fat biopsies are needed to address secondary aim 2. Determine the effects of lifestyle therapy+metformin compared to lifestyle therapy or metformin alone on markers of cellular senescence and accelerated aging that underlie the improvements in physical function in response to the interventions. We will compare changes in p16, p21, and other markers of cellular senescence, SASP, and telomere length from either muscle, fat, or PBMCs by immunohistochemistry (IHC), RT-PCR, or

western blot. a. Markers of cell cycle arrest. The presence of p16 and p21 expression and other markers of cell cycle arrest will be evaluated by IHC from vastus lateralis muscles and adipose tissue. We will also perform IHC for CD34 and CD68. We will also stain for satellite cells and fiber type and measure fiber cross-sectional area to assess the effect of removal of senescent cells on fiber type-specific cell response and muscle-fiber size as exploratory outcomes. Laminin staining will demarcate cell borders. b. SASP. We will measure the expression of TNF- α , IL-6, TLR4, and other markers of inflammation, anabolism, and catabolism from either muscle, fat, or serum using RT-PCR, western blotting, or ELISAs. c. Telomere length. Isolation of DNA from either PBMCs, skeletal muscles, or fat will be performed. We will measure telomere length using Q-PCR method.

During the COVID pandemic, participants may also receive their behavioral diet therapy through phone calls or telehealth at home, while they will be instructed on performing their exercises at home. Skype will be used to conduct conference calls with research participants. Skype meeting automatically generates 1-800 numbers that will be distributed to the subject.

1. At the end of the study, we will remind the subjects that the study pill could be either metformin or placebo and therefore there are 3 groups not 2 groups. 2. We will also remind that the purpose of blinding this information (metformin or placebo) is to make sure that the decision to enroll a subject is NOT biased by the knowledge of treatment the subject will receive.

Section G: Sample Size/Data Analysis

G1. Sample Size

How many subjects (or specimens, or charts) will be used in this study?

Local: 500 Worldwide: 500

Please indicate why you chose the sample size proposed:

Based on our power calculations below, 114 subjects randomized are needed to have strong power to detect significant differences in our primary outcomes. Because of the extensive screening process that are needed to determine eligibility, we anticipate that up to 500 subjects will need to be consented to come up with 114 eligible subjects to be randomized for the study. Power calculations. The data used in the sample size calculations came from our preliminary studies and those reported in the literature. Because all analyses will be intention-to-treat, dropouts will be included in all analyses and will be encouraged to provide follow-up data. Our computations are conservative because 1) we used the largest SD as the basis for our projected values, 2) we assumed that outcome values in all dropouts will not change. Many dropouts will be active participants prior to their dropping out and may therefore respond partly to the interventions, and 3) we based our power calculations on t-test that compare pre to post intervention changes between any two groups. Because longitudinal analyses of data will further reduce variability by including intermediate time points, we expect more power than is described below. Our primary aim is to determine the effects of lifestyle therapy + metformin compared to lifestyle therapy alone or metformin alone on physical function while our secondary aims are to determine the effects of lifestyle therapy + metformin compared to lifestyle therapy alone or metformin alone on lean body mass, muscle quality, BMD and bone quality, and markers of cellular senescence. Therefore, our primary outcome is change in PPT score while secondary outcomes include changes in lean body mass, VO₂peak, knee strength/thigh muscle (muscle quality), hip BMD, buckling ratio, and μ FEA (bone quality), and p16, TNF- α , TLR4, and telomere length (cellular senescence).

Accordingly, sample power calculations are as follows: *Change in PPT score (%): Expected difference in means (6.7), expected SD (8.2), alpha level (0.025), desired power (0.80), Sample size/group (30) Change in lean body mass (%): Expected difference in means (2.1), expected SD (2.7), alpha level (0.05), desired power (0.80), Sample size/group (27) Change in muscle quality (%): Expected difference in means (23.2), expected SD (25.6), alpha level (0.05), desired power (0.80), Sample size/group (20) Change in hip BMD (%): Expected difference in means (1.5), expected SD (2.0), alpha level (0.05), desired power (0.80), Sample size/group (29) Change in FEA (%): Expected difference in means (7.0), expected SD (9.3), alpha level (0.05), desired power (0.80), Sample size/group (30) Change in muscle P16 (no. per micromm): Expected difference in means (14), expected SD (13), alpha level (0.05), desired power (0.80), Sample size/group (15) Change in muscle TNF (fold change): Expected difference in means (0.50), expected SD (0.42), alpha level (0.05), desired power (0.80), Sample size/group (12) Change in TLR4 (fold change): Expected difference in means (0.15), expected SD (0.17), alpha level (0.05), desired power (0.80), Sample size/group (21) Change in Telomere length (T/S): Expected difference in means (0.05), expected SD (0.05), alpha level (0.05), desired power (0.80), Sample size/group (17) *Primary outcome with Bonferroni correction ($p < 0.025$) for lifestyle + metformin vs either lifestyle + placebo or metformin.

Based on the above, we will enroll 38 subjects/group with the intent of having ~30 finishers/group to account for a maximum of 20% dropouts. (We only had ~14% dropout at 6 mos. in prior lifestyle intervention studies)

G2. Data Analysis

Provide a description of your plan for data analysis. State the types of comparisons you plan (e.g. comparison of means, comparison of proportions, regressions, analysis of variance). Which is the PRIMARY comparison/analysis? How will the analyses proposed relate to the primary purposes of your study?

Intention-to-treat analyses will be performed by analyzing data from all participants originally randomized using SAS software version 9.3 (Cary, NC). Baseline characteristics between groups will be compared using ANOVA with Fisher's post hoc t-test. Longitudinal changes between groups will be tested using mixed model repeated-measures ANCOVA adjusting for baseline values, thus reducing variability and providing greater power for statistical tests. The primary focus of the analyses will be the significance of the interaction between group and time point. Within the framework of the mixed model, when the P value for an interaction is $< .05$, we will use the specific contrasts to test the null hypothesis that changes between 2 specific time points in 1 group are equal to corresponding changes in the other group. Bonferroni correction will be used to prove statistical significance for the primary outcome (PPT). Within-group changes will be tested using mixed model repeated-measures ANOVA. Conditions required for a statistical method will be checked by diagnostic tests, using analysis of residuals for bias, non-homogeneous variances, and non-normality. Stepwise multiple linear regression analyses (forward elimination method, validated by backward elimination and standardized betas) will assess which among the body composition and bone factors or mechanistic cellular senescence factors are the most important independent predictors for the observed changes in our primary outcome (PPT).

Sensitivity analyses to validate the above statistical results will include multiple imputation for missing fitness data. We will use SAS Procedure Multiple Imputation (MI) to impute missing values and verify our results. This procedure computes a complete database, say, 50 times; by filling in the missing values randomly based on the mean and covariance structure estimated from the original database. PROC MIANALYZE will combine the results from the 50 imputations (now 50 complete databases) to obtain unbiased estimates and P-values. Results will be further verified using 200 imputations.

Section H: Potential Risks/Discomforts

H1. Potential Risks/Discomforts

Describe and assess any potential risks/discomforts; (physical, psychological, social, legal, or other) and assess the likelihood and seriousness of such risks:

We anticipate no psychological, social or legal risks beyond those of participation in health-related research in general. The potential risks of this study are small. The program of weight loss treatment presents few risks to subjects. The potential risks of the study are primarily associated with the testing measures, exercise testing and training, and metformin therapy. Risks of testing procedures The general data collection procedures involve patient interviews and questionnaires that are time-consuming (60-90 minutes) and may result in fatigue or aggravation. Some questions may touch on emotionally sensitive issues that could cause anxiety. There is a small risk of a hematoma, and infection associated with insertion of needles for blood withdrawal. An experienced technician, using aseptic technique will minimize these risks. The muscle strength testing are brief and simulate those performed in a standard neuromuscular exam. The risk of these evaluations is minimal. However, an occasional patient might experience muscle fatigue or soreness after testing. The gait and balance measures could result in a fall. The DXA and HR-pQCT will involve exposure to radiation. The amount averaged over the entire human body is 6.5 mrem (0.065 mSv). This is $< 1\%$ of the allowable annual dose to radiation workers and $< 3\%$ of the amount of natural background radiation exposure of people in the Houston, TX area receive annually. It is of little consequence when compared to other everyday exposure risks. With the MRI exam, some patients experience tingling or tapping sensations in the arms or legs. This occurs in 2-4% of patients and does not cause any damage to tissue. The muscle and fat biopsies may result in some mild discomfort or infection. To minimize the discomfort a small amount (2-3 ml) of local anesthetic (2% lidocaine) is injected at the incision site just prior to the biopsy. Bleeding at the incision is minimized by applying direct pressure to the incision. The muscle sample is removed from a superficial portion of the vastus lateralis muscle where the risk of cutting a large artery or nerve is minimal. Our group has obtained over 1050 muscle biopsies in participants ranging in age from 24 to 92 yr, the majority of whom have been elderly (e.g. Villareal et al Obesity 2011, PMID: 20489691). The only complications have been one mild hematoma and some soreness in the thigh for several days following a biopsy. Our group also has considerable experience with fat biopsies (e.g. Colleluori et al Nutrients 2018, PMID 30181488). The risks of the biopsy procedures include discomfort, bleeding, or infection at the site of insertion. Spirometry is a routine, non-invasive outpatient diagnostic procedure that is widely employed for the diagnosis and surveillance of respiratory disease. Participants may experience transient lightheadedness, headache, flushing, and in very rare ($< 1\%$) of circumstances, neurocardiogenic syncope. The risks are greatest during the forced exhalation portion of the procedure, which involves bearing down. Exercise testing, using an appropriate protocol in carefully selected patients is associated with serious complications in fewer than 1 in 5,000 patients. In a review of complications of 170,000 exercise tests conducted in 73 medical centers in the USA, Rochmis and Blackburn (JAMA 271:1060, 1971) reported a mortality rate of one per 10,000 patients tests; these were patients who were known to have or suspected of having ischemic heart disease. Repeated exercise testing, when properly monitored under the supervision of an experienced physician, does not appreciably increase the risk to the patient. During the 11 years of the Program Project "Physiological Adaptations to Exercise" and during our 5-year Claude Pepper Older Americans Independence Center project, repeated maximal exercise tests have been performed on more than 650 people age 60-96 years enrolled in research projects without any significant problems. Complications can include severe angina, acute myocardial infarction, serious arrhythmias, and death. Less serious problems include fatigue, dyspnea, and lightheadedness. Risks associated with fecal collection: emotional stress related to working with feces. Mishandling can lead to infections; personal protection equipment will be provided, and safe hand washing will be taught to reduce the risk.

Risks of exercise training The potential risks of exercise training include development of ventricular arrhythmia, myocardial infarction, cardiac arrest, and death. Haskell (Circulation 57:220, 1978) has reviewed the experience of 30 cardiac rehabilitation programs in North America and reported information on 13,750 participants, who accumulated 1,629,634 patient hours of supervised exercise. A total of 50 cardiac arrests were observed during exercise, 42 of which were successfully resuscitated, while 8 were fatal. Available information from randomized trials of exercise training in the secondary prevention of ISCHD suggests that the mortality rate is lower in ISCHD patients who exercise than in comparable patients who remain sedentary when mortality from these studies are combined, the average total percent mortality for the exercising groups is 8.9%, versus 12.4% for the controls ($p < 0.05$). The above information regarding complications of exercise testing and training in CAD patients is reviewed because no statistical information is available regarding the complication rates during exercise in healthy people without evidence of ISCHD. It seems reasonable to assume that people without evidence of clinical ISCHD will have a lower incidence of cardiovascular complication during medically supervised exercise testing and training than patients with ISCHD. In our OAIC studies of exercise in frail older adults we have not encountered any significant problems with the exercise testing or training ($n=150$). The exercise training could cause problems due to injury of tendons, ligaments, joints, or muscles. There is risk of a fall during exercise training, with related injury. In our current study we have not had any significant injuries related to the exercises, or any injurious falls. The exercise facility is equipped with a defibrillator and all appropriate emergency medications. Subjects with known or suspected serious heart disease will not be accepted into the study. Apart from non-participation there is no specific alternative to this study. Subjects may choose to participate in other clinical research at our Center.

Risks of metformin. The most common side effects of metformin are gastrointestinal. Nausea and/or vomiting may occur in around seven to twenty-six percent of patients while diarrhea is usually experienced by fifty-three percent of patients. These gastrointestinal side effects are usually temporary and lessen over a few weeks time, eventually going away on their own. Metformin may possibly reduce the absorption of vitamin B12. An estimated seven percent of individuals who are undergoing treatment with Metformin experience reduced levels of vitamin B 12. A physician can easily monitor vitamin levels, keeping a close eye on your B12 levels. Headaches are experienced as a side effect by six percent while dizziness and/or lightheadedness are experienced by five percent. Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use but could occur when caloric intake is deficient when strenuous exercise is not compensated by caloric supplementation, or during concomitant use of other glucose-lowering agents (such as sulfonylureas and insulin). Lactic acidosis is a very rare side-effect of metformin which usually occurs when there are possible risk factors such as renal impairment, use of radiologic studies with contrast, hypoxic states (e.g. CHF, CV collapse, sepsis), hepatic impairment, excess alcohol intake.

Protection against risk. To protect against or minimize potential risks subjects will be carefully evaluated and closely supervised. Before being enrolled in the study, volunteers will undergo a medical history, a physical examination, a resting ECG, and exercise stress test, and assessment of blood and urine chemistries. Volunteers will be excluded if they have any of the medical problems listed in item above. We will monitor the participants for development of abnormal signs and symptoms and health problems. Subjects will receive blood tests at frequent intervals, including CBC, CMP, and eGFR and the results will be monitored by Dr. Villareal to ensure patient safety during weight loss. During the visits, they will be questioned regarding health-related signs and symptoms. Both patients and their primary care physicians will be made aware of any abnormal findings. The participants will be given the phone numbers of the members of the research team and told to phone one of us immediately if they develop any unusual signs or symptoms. Volunteers will be excluded from participation if their eGFR is less than 30. Study drug will be stopped, at the time of, or prior to, an iodinated contrast imaging procedure in those with eGFR between 30 and 60 mL/min/1.73 m², or in any volunteer who will be administered intra-arterial contrast during the period of study. Study drug also will be temporarily discontinued while participants have restricted food and fluid intake (e.g. during surgery and other procedures that may increase the risk of volume depletion, hypotension and renal impairment). Phlebotomy procedures will be performed by trained personnel using aseptic technique. To avoid/minimize symptoms of fatigue, agitation, or emotional distress due to testing, subjects will be instructed to notify the interviewer or examiner of any discomfort they experience. They will also be questioned about their tolerance for the tests/interviews every 15-20 min. Testing will be terminated if the subject develops fatigue, agitation, or emotional distress. During spirometry, participants will be in a seated position to prevent injury should syncope occur. The procedure will be interrupted to allow time for the resolution of symptoms if any occur. An emergency response system will be activated if a clinical emergency is perceived. Exercise testing will be conducted only after the subject is examined by a physician and after a resting ECG is obtained and evaluated. During exercise testing, the patient's ECG is monitored constantly, and BP is measured frequently. An experienced physician supervises the tests. The paramedical personnel who assist in the test are trained in arrhythmia recognition and cardiac resuscitation. A DC defibrillator is kept on hand during the exercise stress test. The exercise stress test will be performed at the Exercise Center at Bldg. 110, room 264 of the MEDVAMC. Any subject who develops a positive stress test or any other indication for early termination of exercise stress testing will be excluded from participation. The subject will be continuously monitored before, during, and after the exercise stress test by an experienced physician and paramedical personnel trained in arrhythmia recognition and cardiac resuscitation. The MEDVAMC emergency telephone number (extension 2222) will be dialed for any medical emergency. The subject will be stabilized and adequately treated before being considered for discharge. The exercise training will be closely geared to the subject's exercise capacity so as to keep the exercise intensity well within their ability. The exercise sessions will be closely supervised by exercise technicians to keep the subjects from over-exerting or straining. A physician will be in attendance or in close proximity. The exercise technicians involved in supervising the exercise are trained in exercise physiology, arrhythmia recognition, and cardiac resuscitation. A DC defibrillator and emergency medications will be kept on hand during the exercise sessions.

H2. Data and safety monitoring plan

Do the study activities impart greater than minimal risk to subjects?

Yes

NOTE: The answer to the questions in H2 requires the completion of the form: 'Section H – Data and Safety Monitoring Plan' as an attachment in Section S.

H3. Coordination of information among sites for multi-site research

Is the BCM Principal Investigator acting as the SPONSOR-INVESTIGATOR for this multi-site research?

No or Not Applicable

Is BCM the COORDINATING CENTER for this multi-site research?

No or Not Applicable

Section I: Potential Benefits

Describe potential benefit(s) to be gained by the individual subject as a result of participating in the planned work.

The benefits to the subjects studied in this research protocol, and to society at large, far surpass the risks. In previous studies of frail elderly men and women, we have found that exercise training has numerous beneficial effects. We have found improvements in many measures of health and function in response to exercise, including aerobic exercise capacity, cardiovascular function, muscle strength, body composition, bone mineral density, blood pressure, glucose tolerance, and blood lipid profile. Thus, the benefits of exercise training in this population far outweigh the risks. Importantly, the benefits of exercise training will be made available to all the participants in the study. Moreover, weight loss may improve physical function and quality of life in frail obese elderly subjects. In addition to the known benefits of exercise and possible benefits of weight loss in this age group, subjects in the proposed research will receive several immediate benefits. There is also evidence that metformin has life extension properties and improves lifespan. Therefore, metformin can have added benefits to weight loss and exercise training in obese older adults including helping to preserve muscle and bone mass during dieting. The most important of these is repeated assessment and monitoring of several health factors including blood chemistries, body composition and bone density. The results of these assessments will be made available to the participants and their health care providers.

Describe potential benefit(s) to society of the planned work.

Obesity in older adults, including many aging veterans, is a major public health problem. In fact, the public health success that has occurred in recent years could be in danger if lifestyles of older adults are neglected. The novel health outcomes and mechanistic-based data generated from this proposed RCT will have important ramifications for the standard of care for this rapidly increasing segment of the aging veteran population. The results could be incorporated in the MOVE (Managing Overweight/Obese Veterans) program, which currently does not have any guidelines for eligible veterans if they are 70 years or older.

Do anticipated benefits outweigh potential risks? Discuss the risk-to-benefit ratio.

The prevalence of obesity in the elderly has increased dramatically because of an increase in the elderly population and percentage of elderly persons who are obese. Not only does obesity causes serious medical complications, decreases physical function, and impairs quality of life, but in elderly persons, obesity can lead to frailty and loss of independence because of decreased strength, balance and immobility associated with aging and physical inactivity. However, there is little evidence-based data to guide treatment of obesity in older adults and appropriate treatment remains controversial. In fact, the MOVE program does not have any guidelines for eligible veterans if they are 70 or older. Health care providers are reluctant to prescribe weight loss in this older population because of the uncertainty as to whether the benefits outweigh the risks. Although weight loss can be beneficial in obese older adults by improving function and quality of life it may also be potentially harmful by causing a decrease in muscle mass and bone mass and thus further decrease the capacity of these tissues. We have found that exercise attenuates the weight-loss-induced reduction of muscle mass and bone mass although exercise is not adequate to completely prevent these losses of lean tissues induced by weight loss. Metformin is widely available drug, has an affordable price and is fairly safe with low risk for hypoglycemia. Metformin may represent a novel intervention for frailty by reducing cellular senescence and SAP, especially in older adults with accelerated aging. If we can show that metformin when added to lifestyle therapy (weight loss and exercise) preserves muscle and BMD and reverses frailty in obese older adults, these novel data will have important ramifications for the standard of care for this rapidly increasing obese older population that includes many aging veterans. Therefore, the risks of the intervention are reasonable in relation to the immense importance of the knowledge that is expected to result from the proposed research.

Section J: Consent Procedures

J1. Waiver of Consent

Will any portion of this research require a waiver of consent and authorization?

Yes

Please describe the portion of the research for which a waiver is required. (Example: chart review to determine subject eligibility)

A waiver of consent and HIPAA authorization is requested for access to Corporate Data Warehouse (CDW) and CPRS/VISTA to determine subject eligibility

A waiver of consent and HIPAA authorization is requested to transmit the following limited Protected Health Information (PHI) elements at the time of biospecimen submission to the VA SHIELD (Science and Health Initiative to Combat Infectious and Emerging Life-Threatening Diseases): 1. First name; 2. Last name; 3. Date of birth and 4. Last 4 of Social Security Number (SSN). This waiver applies only to the transfer of limited PHI to VA SHIELD repository management. It does not permit any PHI to be used for research without additional IRB review.

Explain why the research and the use or disclosure of protected health information involves no more than minimal risk (including privacy risks) to the individuals.

This waiver is needed to identify patients that may be eligible.

We will review the patients charts in the electronic medical record system in the VA known as Computerized Patient Record System (CPRS) in the same way as we review records of our clinical patients, the access to which is password protected. All members of the research team will be issued an individual password. We will also access CDW data and vital status files through the Data Access Request Tracker (DART) to include real SSNs in order to identify potential subjects for recruitment purposes.

We plan to protect identifiers from improper use or disclosure.

For the CPRS records that are queried will be stored in folders on VA computer space to which access is restricted to personnel authorized by the VA Research and Development Committee (L drive), specifically the PI and study coordinator. Data will not be shared on hard drives of any workstation, or transmitted to any other facility. All printing will be directed to a printer in a private office, not to common work areas. All data used will be kept until a schedule of destruction is approved.

For the CDW data and vital status files accessed through DART, the data will be transferred electronically to the local server (behind the VA firewall). Data access will be stored in a secure folder on the secure folder on Drive: L of the local VA server (behind the VA firewall). Data access will be restricted to the PI, programmer, and the project staff. Data will be used only to identify patients for study recruitment as outlined above. No data will be removed from this folder.

For the waiver for the transfer of limited PHI to VA SHIELD for repository management, the PHI is used only for repository linkage purposes, not in analysis. VA SHIELD operates under the VA Central IRB approval and follows VA privacy and data security standards, including encryption, role based access, and separation of research and PHI systems. No PHI will be returned to, accessed by, or retained by the study team.

Explain why the waiver will not adversely affect the privacy rights and the welfare of the research subjects.

Data will be used only to identify patients for study recruitment. Any information that is collected as part of the research including PHI will not be used or disclosed to a third party except as required by law or permitted by a HIPAA authorization.

Participants consented to the use of their coded biospecimens for future research, including submission to VA repositories. The PHI will not be accessed or used for any identifiable research activities.

Explain why the research could not practicably be conducted without the waiver and could not practicably be conducted without access to and use of the protected health information.

There are a large number of patients in the database and it is not possible to identify whether they might meet basic eligibility criteria without first accessing PHI and we would not be able to obtain HIPAA authorization from all of these patients prior.

The study is completed and participants are no longer under active follow up. Re-consenting participants is not feasible and would undermine the ability to submit specimens to VA SHIELD. The PHI required by VA SHIELD for proper specimen coding, deduplication, and secure storage. The infrastructure of VA SHIELD relies on limited identifiers to maintain accuracy across national VA systems and to support potential future IRB-approved linkages.

Describe how the research could not practicably be carried out without using the collected identifiable biospecimens in an identifiable format.

Access to the CPRS at the MEDVAMC is limited to individuals who are involved in patient care or human research and is password protected. Paper documents will be placed in double locked doors with only members of research team are allowed access. In addition, no names will be used in any communication or publication resulting

from the study.

As also noted above, access to the CDW data and vital status files through DART, will be restricted to the PI, programmer, and the project staff. The data will be stored in a secure folder on Drive: S of the local VA server (behind the VA firewall). No data will be removed from this folder.

The PHI required by VA SHIELD is for proper specimen coding, deduplication, and secure storage. The infrastructure of VA SHIELD relies on the limited identifiers to maintain accuracy across national VA systems and to support potential future IRB-approved linkages.

Describe how an adequate plan exists in order to protect identifiers from improper use and disclosure.

Any files that contain identifiers for the specific purpose of screening and determining eligibility (as part of this waiver of consent) will be destroyed at the earliest opportunity (i.e. when no longer used to determine eligibility and recruit for the study) according to VA guidelines.

Describe how an adequate plan exists in order to destroy identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.

Any files that contain identifiers for the specific purpose of screening and determining eligibility (as part of this waiver of consent) will be kept for 6 years after study closure, according to VA guidelines.

Describe how adequate written assurances exist in order to ensure that the PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

Names will not be used in any communication or published reports about this study. In the event that samples had to be shared with other laboratories, coded samples will be transferred without identifiers.

The PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule

Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.

Yes

Specific information concerning alcohol abuse:

Yes

Specific information concerning drug abuse:

No

Specific information concerning sickle cell anemia:

No

Specific information concerning HIV:

No

Specific information concerning psychiatry notes:

No

Demographic information (name, D.O.B., age, gender, race, etc.):

Yes

Full Social Security #:

Yes

Partial Social Security # (Last four digits):

Yes

Billing or financial records:

No

Photographs, videotapes, and/or audiotapes of you:

No

Other:

No

Will additional pertinent information be provided to subjects after participation?

No

If No, explain why providing subjects additional pertinent information after participation is not appropriate.

The information we review from the database to screen potential subjects are not new information (e.g. age, demographics) and/or are already part of their medical record system in the VA, for which they are getting ongoing medical care through their VA primary care providers. We are only reviewing medical records to determine whether or not potential subjects meet eligibility criteria and are not obtaining new tests or results during the medical record reviews.

J1a. Waiver of requirement for written documentation of Consent

Will this research require a waiver of the requirement for written documentation of informed consent?

Yes

Explain how the research involves no more than minimal risk to the participants, and the specifics demonstrating that the research does not involve procedures for which written consent is normally required outside of the research context.

This waiver is needed to identify patients that may be eligible over the phone. For example those who call us over the phone in response to our advertisements, we can screen them over the phone and make a decision whether it is worth for the person to come over for more detailed discussion of what the study is involved or whether they are interested and can commit to the study, or if the person can be screened out over the phone (e.g. if cant come three times a week for exercise training to the facility, or clearly has contraindications to participate or is not eligible because of age or not overweight or obese).

We will go over the phone and screen the vet in or out of the study (please see brief screening phone form in attachment S) for example, for those who call us in response to our advertisements. If preliminary phone screening indicates they might be eligible or they express interest in the study, we will then invite them for an orientation and to get written informed consent.

Brief phone interview will save time and effort for the potential volunteer by quickly screening over the phone if they are eligible or interested or not. If they are ineligible based on screening criteria or they are not interested or cannot commit time to come to study (e.g. conflicts with their job) then we can decide over the phone that we do NOT need to proceed with the volunteer coming to our facility for orientation and obtain written informed consent.

If volunteers screened over the phone are determined to be ineligible or they are not interested after the brief interview, we will not collect any identifiers or information or discard them after we learn that that the volunteer is ineligible, is not interested and we decide not to proceed after the phone interview saving time and effort for the potential volunteer.

J2. Consent Procedures

Who will recruit subjects for this study?

PI

PI's staff

Describe how research population will be identified, recruitment procedures, any waiting period between informing the prospective participant and obtaining consent, steps taken to minimize the possibility of coercion or undue influence and consent procedures in detail.

To determine whether potential subjects meet eligibility criteria, a review of medical records will be done. There are large number of patients in the database and it is not possible to identify whether they might meet basic eligibility criteria without first accessing PHI. We will access the Corporate Data Warehouse (CDW) data and vital status files through the Data Access Request Tracker (DART) to include real SSNs in order to identify potential subjects for recruitment purposes. The CDW data are

part of VA Informatics and Computing Infrastructure, which is an initiative to improve researcher's access to VA data and to facilitate data analyses while ensuring Veteran's privacy and security. Guidelines that allow data to be released can be found in the DART user guide, which outlines a review process of Project Documents and Approvals and Data Request Forms that undergo a privacy review and additional reviews by the Office of Research and Development and security review of information provided in the Research Request Memo. The patients will be recruited only for this research project.

We will recruit patients attending the Geriatric, Endocrine, and Primary Care clinics. Advertisements through posters and flyers, presentations, and direct mailings of printed materials to potential subjects will be done. Subjects will be identified from direct referral by the health providers or by list generated from the Health Outcomes Section of patients under the Inclusion Criteria. The records will be reviewed for exclusion criteria. A letter will be sent to the patient describing the study and introducing the investigators. Interested patients will be asked to return a postcard. Other methods of recruitment will also be considered, including use of direct mails to potential participants in the community. We may utilize direct mailing list services (e.g. InfoUSA, GotPrint) to provide direct mailing lists based on industry-standard and widely used Postal Service and Experian data. These lists can be targeted based on demographic specifications (e.g. age, ethnicity, distance to research site), that characterize our study population, to ensure relevance of mailings and optimal response rates. Postcards containing the approved advertisement will be sent to the selected addresses. The postcard will contain the study contact phone number allowing for potential participants to express interest in the study.

Individuals who express an interest in participation will undergo a brief telephone interview. Individuals who express an interest and meet the inclusion criteria will be invited to discuss their participation in greater detail. Detailed information will be provided regarding the aims of the study, and all of the tests that they will undergo if they participate. Verbal and written information about the potential benefits and risks of the study will be provided; their questions will be answered and any concerns will be addressed. If the individual is interested in participating, a screening evaluation will be scheduled. Prior to randomization (after obtaining consent), the volunteers will undergo a detailed medical history and physical examination, and a clinical laboratory. They will have the nature and purpose of the study explained to them again, discuss their reasons and motivation for participation to determine whether they are realistic and discuss any potential problems, that might interfere with participation and have their questions answered. Data which include HIPAA identifiers such as names, date of birth or age, dates of tests and medical record numbers (first letter of last name plus 4 digits of social security number) will be collected.

Are foreign language consent forms required for this protocol?

No

J3. Privacy and Intrusiveness

Will the research involve observation or intrusion in situations where the subjects would normally have an expectation of privacy?

No

J4. Children

Will children be enrolled in the research?

No

J5. Neonates

Will non-viable neonates or neonates of uncertain viability be involved in research?

No

J6. Consent Capacity - Adults who lack capacity

Will Adult subjects who lack the capacity to give informed consent be enrolled in the research?

No

J7. Prisoners

Will Prisoners be enrolled in the research?

No

Section K: Research Related Health Information and Confidentiality

Will research data include identifiable subject information?

Yes

Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.

Yes

Specific information concerning alcohol abuse:

No

Specific information concerning drug abuse:

No

Specific information concerning sickle cell anemia:

No

Specific information concerning HIV:

No

Specific information concerning psychiatry notes:

No

Demographic information (name, D.O.B., age, gender, race, etc.):

Yes

Full Social Security #:

Yes

Partial Social Security # (Last four digits):

Yes

Billing or financial records:

No

Photographs, videotapes, and/or audiotapes of you:

No

Identifiable biospecimens

Yes

Will identifiable biospecimens be stored for future research?

Yes

If yes, is the storage of biospecimens optional for subjects?

Yes

Will identifiable private information be stored for future research?

Yes

If yes, is the storage of information optional for subjects?

Yes

Questionnaire, Survey, and/or subject diary

Yes

Other:

No

At what institution will the physical research data be kept?

Paper records will be kept at Michael E DeBakey VA Medical Center, Building 110, Room 258 and Room 262.

How will such physical research data be secured?

Paper records will be kept at MEDVAMC Building 110, Room 258 and Room 262 in locked cabinets at all times and closely monitored by the research coordinator. Rooms 258 and 262 will also be locked every day and whenever the research coordinator steps out of the room. Therefore, the physical data will be secured by two locks. In addition, the entrance to Building 110 and entrance to our research laboratory (where Rooms 258 and 262 are located), is secured through PIV card access to approved research personnel only.

At what institution will the electronic research data be kept?

Data to include PHI will be stored at the Michael E DeBakey VA Medical Center located at S\Research\Villareal,Dennis\H-46970.

Coded data (Study ID number) and PHI (limited to date of birth and date of visit, which are needed for specialized computer software to analyze the data) will also be entered, analyzed, and stored in specialized testing equipment (ParvoMed indirect calorimeter and Q-stress computer equipment in Room 254, Biodex dynamometer housed in Room 220 and 262, dual energy x-ray absorptiometer (DXA) in Room 226, Ipad containing NIH toolbox software for analyzing cognition) all located in the PI's secured research lab at the second floor in Building 110, MEDVAMC and HR-peripheral CT scan in Room 140 in Building 109. All data will be coded, password protected, room locked protected, and entry to research lab will be PIV card-access protected (i.e. entry access to the research lab are given only to co-investigators using their PIV cards). Coded HR-pQCT data will be kept in Building 109, Room 138 in a computer locked, password protected. In addition, the entrance to Building 109 is secured through PIV card access to approved research personnel only. Also, Room 138 will be locked every day and whenever the research operator steps out of the room.

There will be software to be used for the conduct of the study, namely, Nutritional Data System for Research (Minneapolis, Minn) for analyses of food diaries, SF-36 software and Impact of Weight on Quality of Life software for analyses of Quality of Life, accelerometer software for analyses of physical activity, Hologic DXA and Galgo for body comp analyses, Parvo for calorimetry, Biodex for strength, Finite element analysis (FEA) software for bone strength assessment with HR-pQCT, Cardiac science for cardiac stress test and End note for reference manager; the PI has a licenses for these software's funded by his grant and SPSS and SAS statistical software for statistical analyses; the PI and VA have licenses for SAS software. Web application will NOT be used.

Coded data will also be stored in PI's Baylor computer network drive for analyses using specialized soft wares described above in PI's Baylor computer located in Building 110. Coded data are transferred to the PI's Baylor computer network drive using VA issued flash drive. Link to code are stored only in VA computer S drive. The key to the code will not leave the MEDVAMC. CD or DVD will also be used to back up data from the above medical device equipment and used to transfer the data to S drive. The CD or DVD are stored in locked cabinet and locked room (Room 226).

Flash drive will be used issued by the VA to the PI, which has VA FIPS 140-2 approved encryption. Data stored on mobile storage devices do not contain the only copy of research information. VA research data stored on all mobile devices or outside VA protected environment will be backed up regularly and stored securely within VA's protected environment.

Such electronic research data will be secured via BCM IT Services- provided secured network storage of electronic research data (Non-Portable devices only):

Yes

Such electronic research data will be secured via Other:

Yes, (describe below):

VA IT Services - provided secured network (Non-portable devices only)

Will there be anyone besides the PI, the study staff, the IRB and the sponsor, who will have access to identifiable research data?

Yes, identify the classes of the persons:

Yes, identify the classes of the persons: Federal agencies such as the Department of Veterans Affairs Office of Research Oversight, Office of Inspector General, Office of Human Research Protection, and Government Accounting Office and Food and Drug Administration (FDA) and Data and Safety Monitoring Board will be permitted to

access patient records. Names will not be used in any published reports about the study. The research team may also share information with Hospital or University representatives, to complete Hospital or University responsibilities, primary care physician if a medical condition that needs urgent attention is discovered, and the Research Subjects Advocate at the VA. People who ensure the quality from the institutions where the research is being done, federal and other regulatory agencies will have access to all of the research data.

Please describe the methods of transmission of any research data (including PHI, sensitive, and non-sensitive data) to sponsors and/or collaborators.

We will only send non-sensitive de-identified data to co-investigator, Dr. Clifford Qualls (Biostatistician who has a WOC VA appointment) via secure/encrypted VA email at the Biomedical Research Institute of New Mexico nonprofit organization associated with the New Mexico VA Health Care System) for statistical analyses. The data will be reviewed and confirmed as de-identified by the privacy officer before the de-identified data are sent to Dr. Clifford Qualls via secure/encrypted VA email.

The limited PHI will be: 1. transferred securely to VA SHIELD per data handling protocols; 2. stored only in encrypted, access-controlled systems; 3. not visible to researchers; and 4. managed by the VA SHIELD honest broker, a separate and independent entity responsible for any future linkage under IRB approval. The limited PHI will be transmitted securely and stored only within the VA SHIELD's encrypted, access controlled Laboratory Information Management System (LIMS).

Will you obtain a Certificate of Confidentiality (COC) for this study?

No

Please further discuss any potential confidentiality issues related to this study.

Research records, including identifiers will be destroyed 6 years after cutoff (at the end of the fiscal year) after completion of the research project, but may be retained longer if required by other federal regulations or sponsor archive requirement. It is understood by the PI that data will not be used or shared with others outside the scope of the research study as documented in the protocol approved by the IRB and MEDVAMC R&D Committee. Removal of access to research study data will be accomplished for all study personnel when they are no longer part of the research team. An Accounting of Disclosure (AOD) will be created and maintained for any disclosure of individually identifiable information (III) outside the VA. The manual spreadsheet will include the date of the disclosure, nature or description of the III disclosed, purpose of each disclosure and the name and address of person or agency to which the disclosure was made.

Research records, including identifiers will be destroyed 6 years after cutoff (at the end of the fiscal year) after completion of the research project, but may be retained longer if required by other federal regulations or sponsor archive requirement

Section L: Cost/Payment

Delineate clinical procedures from research procedures. Will subject's insurance (or subject) be responsible for research related costs? If so state for which items subject's insurance (or subject) will be responsible (surgery, device, drugs, etc). If appropriate, discuss the availability of financial counseling.

Subjects will nor be responsible for any costs related to participation in the research. Any research-related costs will be borne by the research grant.

If subjects will be paid (money, gift certificates, coupons, etc.) to participate in this research project, please note the total dollar amount (or dollar value amount) and distribution plan (one payment, pro-rated payment, paid upon completion, etc) of the payment.

Dollar Amount:

400

Distribution Plan:

Participants will be compensated for their time and inconvenience: \$50.00 after completing all the baseline testings, \$50.00 after completing all midpoint testings (at 3 months) and \$50.00 after completing all the final testings (at 6 months). In addition, if they agree to the optional muscle and fat studies, they will be paid \$125.00 for both muscle and fat biopsies to be done at baseline and at the end of the study. This will take approximately (3-4) weeks after each completed visit to process. Per the VA accounting office, the participants will receive payment via direct deposit through their bank account within approximately 5 days of completion of baseline testing, final testing, or muscle studies as above.

Section M: Genetics

How would you classify your genetic study?

Discuss the potential for psychological, social, and/or physical harm subsequent to participation in this research. Please discuss, considering the following areas: risks to privacy, confidentiality, insurability, employability, immigration status, paternity status, educational opportunities, or social stigma.

Will subjects be offered any type of genetic education or counseling, and if so, who will provide the education or counseling and under what conditions will it be provided? If there is the possibility that a family's pedigree will be presented or published, please describe how you will protect family member's confidentiality?

Section N: Sample Collection

SAMPLE: Blood

What is the purpose of the sample collection?

Blood samples will be collected for 1) medical screening to determine eligibility for the tests (see inclusion/exclusion criteria) 2) to monitor blood levels of glucose, lipids, hormones, vitamins, markers of bone function and inflammation, and other blood parameters of response to the interventions 4) to determine whether hereditary characteristics are associated with obesity in older adults and whether they can predict the response to lifestyle therapy and metformin, and 5) to measure telomere length.

For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subjects entire participation time.

total of up to six tablespoons each at baseline, 3 months, and 6 months

Is there the possibility that cell lines will be developed with this sample? No

Sample will be obtained from:

Clinical Labs, Research Labs

Will the sample be stripped of identifiers?

No

If sample will be released outside the hospital:

Will sample be released to anyone not listed as an investigator on the protocol? Will the information be identifiable, coded or de-identified?

Wash U, Mayo Clinic, and other Core labs (coded) for specialized tests not available in PI's lab.

Will sample material be sold or transferred to any third parties? Will the information be de-identified?

No

If sample will be banked for future use:

Where will the sample be banked and for how long?

At the Michael DeBakey VA Medical Center and VA Science and Health Initiative to Combat Infectious and Emerging Life-Threatening Diseases (VA SHIELD) for ten years or until used up. Specimens will have coded numbers and dates of tests.

Does the banking institution have an approved policy for the distribution of samples?

Yes

If the entire sample will NOT be used during the course of this research study:

Will the remaining tissue be discarded? If not what will be done with the remaining sample after study completion and how long will the sample be kept?

We will keep the samples for 10 years after study completion after which they will be discarded.

Will samples be made available to the research subject (or his/her medical doctor) for other testing?

No

If a subject withdraws from the study:

Will subject have the option to get the remaining portion of their sample back?

No

Will samples be destroyed? If not, will they be kept anonymously? What will happen to the sample if the subject revokes authorization?

We will keep the samples for 10 years after study completion after which they will be discarded. We will request approval from IRB if we decide to reopen the study and reuse the samples for a new research protocol with related scope of interest.

Will data obtained from their sample be deleted? What will happen to the sample if the subject revokes authorization?

For those who withdraw from the study, we will use the data generated from the samples. However, for subjects who revoked authorization, their data will be deleted and samples destroyed or discarded.

Will study data or test results be recorded in the subject's medical records?

No

Will results of specific tests and/or results of the overall study be revealed to the research subject and or his/her doctor?

In answer to above, standard test results that are done at VA lab and have clinical use are reported in CPRS, computerized Patient Record System, and thus they are automatically included in the subjects medical records (i.e. in CPRS, which is accessible to the vets primary provider). Any abnormal findings will be shared with the subject's primary care physicians for further evaluation and appropriate treatment. Record System (CPRS) which are shared with their VA primary care physicians.

Please identify all third parties, including the subject's physician, to receive the test results.

Subject's treating physician

SAMPLE: Feces/Stool

What is the purpose of the sample collection?

To determine whether lifestyle intervention (weight loss and exercise training) plus metformin (study pill) alters the type of bacteria that are normally present in the large intestine and mediate the improvement in the health status (slowing of aging) of research participants.

For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subjects entire participation time.

About 1/2 teaspoon

Is there the possibility that cell lines will be developed with this sample?No

Sample will be obtained from:

Clinical Labs, Research Labs

Will the sample be stripped of identifiers?

No

If sample will be released outside the hospital:

Will sample be released to anyone not listed as an investigator on the protocol? Will the information be identifiable, coded or de-identified?

No

Will sample material be sold or transferred to any third parties? Will the information be de-identified?

No

If sample will be banked for future use:

Where will the sample be banked and for how long?

Michael De Bakey VA Medical Center and VA Science and Health Initiative to Combat Infectious and Emerging Life-Threatening Diseases (VA SHIELD) for up to 10 years after study completion.

Does the banking institution have an approved policy for the distribution of samples?

Yes

If the entire sample will NOT be used during the course of this research study:

Will the remaining tissue be discarded? If not what will be done with the remaining sample after study completion and how long will the sample be kept?

The remaining samples will be stored for up to 10 years after study completion

Will samples be made available to the research subject (or his/her medical doctor) for other testing?

No

If a subject withdraws from the study:

Will subject have the option to get the remaining portion of their sample back?

No

Will samples be destroyed? If not, will they be kept anonymously? What will happen to the sample if the subject revokes authorization?

For patients who withdraw from the study, the samples will not be destroyed but will be stored anonymously. For those who revoke authorization, samples will be destroyed or discarded.

Will data obtained from their sample be deleted? What will happen to the sample if the subject revokes authorization?

No

Will study data or test results be recorded in the subject's medical records?

No

Will results of specific tests and/or results of the overall study be revealed to the research subject and or his/her doctor?

No

Please identify all third parties, including the subject's physician, to receive the test results.

None

SAMPLE: Other 1: Adipose tissue

What is the purpose of the sample collection?

In addition to muscle tissue samples, we will also collect adipose tissue to address secondary aim 2: Determine the effects of lifestyle therapy + metformin compared to lifestyle therapy or metformin alone on markers of cellular senescence and accelerated aging that underlie the improvements in physical function in response to the interventions in older veterans with obesity.

For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subjects entire participation time.

About 200 mg of fat tissue at baseline and at the end of 6 months.

Is there the possibility that cell lines will be developed with this sample?No

Sample will be obtained from:

Clinical Labs, Research Labs

Will the sample be stripped of identifiers?

No

If sample will be released outside the hospital:

Will sample be released to anyone not listed as an investigator on the protocol? Will the information be identifiable, coded or de-identified?

No

Will sample material be sold or transferred to any third parties? Will the information be de-identified?

No

If sample will be banked for future use:

Where will the sample be banked and for how long?

Michael De Bakey VA Medical Center and VA Science and Health Initiative to Combat Infectious and Emerging Life-Threatening Diseases (VA SHIELD) for up to 10 years after study completion.

Does the banking institution have an approved policy for the distribution of samples?

Yes

If the entire sample will NOT be used during the course of this research study:

Will the remaining tissue be discarded? If not what will be done with the remaining sample after study completion and how long will the sample be kept?

The remaining samples will be stored for up to 10 years after study completion.

Will samples be made available to the research subject (or his/her medical doctor) for other testing?

No

If a subject withdraws from the study:

Will subject have the option to get the remaining portion of their sample back?

No

Will samples be destroyed? If not, will they be kept anonymously? What will happen to the sample if the subject revokes authorization?

For patients who withdraw from the study, the samples will not be destroyed but will be stored anonymously. For those who revoke authorization, samples will be destroyed or discarded.

Will data obtained from their sample be deleted? What will happen to the sample if the subject revokes authorization?

For those who withdraw from the study, we will use the data generated from the samples. However, for patients who revoked authorization, their data will be deleted.

Will study data or test results be recorded in the subject's medical records?

No

Will results of specific tests and/or results of the overall study be revealed to the research subject and or his/her doctor?

No

Please identify all third parties, including the subject's physician, to receive the test results.

None

SAMPLE: Tissue

What is the purpose of the sample collection?

We will collect muscle samples to address secondary aim 2 Determine the effects of lifestyle therapy + metformin compared to lifestyle therapy or metformin alone on markers of cellular senescence and accelerated aging that underlie the improvements in physical function in response to the interventions in older veterans with obesity.

For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subjects entire participation time.

About 200 mg of muscle tissue at baseline and at end of study at 6 months

Is there the possibility that cell lines will be developed with this sample?No

Sample will be obtained from:

Clinical Labs, Research Labs

Will the sample be stripped of identifiers?

No

If sample will be released outside the hospital:

Will sample be released to anyone not listed as an investigator on the protocol? Will the information be identifiable, coded or de-identified?

No

Will sample material be sold or transferred to any third parties? Will the information be de-identified?

No

If sample will be banked for future use:

Where will the sample be banked and for how long?

Michael DeBakey VA Medical Center and VA Science and Health Initiative to Combat Infectious and Emerging Life-Threatening Diseases (VA SHIELD) for up to 10 years after study completion.

Does the banking institution have an approved policy for the distribution of samples?

Yes

If the entire sample will NOT be used during the course of this research study:

Will the remaining tissue be discarded? If not what will be done with the remaining sample after study completion and how long will the sample be kept?

The remaining samples will be stored for up to 10 years after study completion.

Will samples be made available to the research subject (or his/her medical doctor) for other testing?

No

If a subject withdraws from the study:

Will subject have the option to get the remaining portion of their sample back?

No

Will samples be destroyed? If not, will they be kept anonymously? What will happen to the sample if the subject revokes authorization?

For patients who withdraw from the study, the samples will not be destroyed but will be stored anonymously. For those who revoke authorization, samples will be destroyed or discarded.

Will data obtained from their sample be deleted? What will happen to the sample if the subject revokes authorization?

For those who withdraw from the study, we will use the data generated from the samples. However, for patients who revoked authorization, their data will be deleted.

Will study data or test results be recorded in the subject's medical records?

No

Will results of specific tests and/or results of the overall study be revealed to the research subject and or his/her doctor?

No

Please identify all third parties, including the subject's physician, to receive the test results.

None

SAMPLE: Urine

What is the purpose of the sample collection?

Urine sample will be collected to measure different biomarkers of aging. The tests will be done at baseline, 3 months and 6 months.

For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subjects entire participation time.

N/A

Is there the possibility that cell lines will be developed with this sample?No

Sample will be obtained from:

Clinical Labs, Research Labs

Will the sample be stripped of identifiers?

No

If sample will be released outside the hospital:

Will sample be released to anyone not listed as an investigator on the protocol? Will the information be identifiable, coded or de-identified?

Wash U, Mayo Clinic, and other Core labs (coded) for specialized tests not available in PI's lab.

Will sample material be sold or transferred to any third parties? Will the information be de-identified?

No

If sample will be banked for future use:

Where will the sample be banked and for how long?

At the Michael DeBakey VA Medical Center and VA Science and Health Initiative to Combat Infectious and Emerging Life-Threatening Diseases (VA SHIELD) for ten years or until used up. Specimens will have coded numbers and dates of tests.

Does the banking institution have an approved policy for the distribution of samples?

Yes

If the entire sample will NOT be used during the course of this research study:

Will the remaining tissue be discarded? If not what will be done with the remaining sample after study completion and how long will the sample be kept?

We will keep the samples for 10 years after study completion after which they will be discarded.

Will samples be made available to the research subject (or his/her medical doctor) for other testing?

No

If a subject withdraws from the study:

Will subject have the option to get the remaining portion of their sample back?

No

Will samples be destroyed? If not, will they be kept anonymously? What will happen to the sample if the subject revokes authorization?

We will keep the samples for 10 years after study completion after which they will be discarded. We will request approval from IRB if we decide to reopen the study and reuse the samples for a new research protocol with related scope of interest.

Will data obtained from their sample be deleted? What will happen to the sample if the subject revokes authorization?

For those who withdraw from the study, we will use the data generated from the samples. However, for patients who revoked authorization, their data will be deleted.

Will study data or test results be recorded in the subject's medical records?

No

Will results of specific tests and/or results of the overall study be revealed to the research subject and or his/her doctor?

In answer to above, standard test results that are done at VA lab and have clinical use are reported in CPRS, computerized Patient Record System, and thus they are automatically included in the subjects medical records (i.e. in CPRS, which is accessible to the vets primary provider). Any abnormal findings will be shared with the subject's primary care physicians for further evaluation and appropriate treatment. Record System (CPRS) which are shared with their VA primary care physicians.

Please identify all third parties, including the subject's physician, to receive the test results.

Subject's treating physician.

Section O: Drug Studies

Does the research involve the use of ANY drug* or biologic? (*A drug is defined as any substance(other than food) that is used to elicit a pharmacologic or physiologic response whether it is for treatment or diagnostic purposes)

Yes

Does the research involve the use of ANY gene transfer agent for human gene transfer research?

No

O1. Current Drugs

[Drug 1: Metformin \(Extended Release\)](#)

Is this study placebo-controlled?

Yes

If yes, be sure that you justify the use of the placebo for this research in the space below.

All participants are obese and all will get the benefits of weight loss and exercise therapy (lifestyle therapy) to improve overall health and physical function. However, it is not known whether adding metformin to lifestyle therapy in obese older patients will further improve overall health and physical function and importantly preserve muscle and bone mass while undergoing weight loss. The use of the placebo is necessary in order to conduct a randomized, comparative-efficacy, placebo controlled (for

metformin) trial of the effects of lifestyle therapy + metformin vs lifestyle therapy alone or metformin alone and will provide evidence to support the hypothesis that a multifactorial intervention by means of lifestyle therapy + metformin will be the most effective approach for reversing sarcopenic obesity and frailty in obese older veterans.

Will the research involve a radioactive drug?

No

Section P: Device Studies

Does this research study involve the use of ANY device?

No

Section Q. Consent Form(s)

None

Section R: Advertisements

Mode of Advertising: Billboard

Exact language of Advertisement:

OLDER VETERANS NEEDED

To participate in a study looking into the effect of weight loss, exercise training, and meformin on physical function, body fat, muscle, bone, memory and thinking, and mood..

Duration: Participation in the study will be ~ 8 months.

Tests/Procedures include medical examination, assessment of physical function, cardiovascular testing, blood tests, body composition testing, mood/cognition, and muscle biopsies

Interventions: Supervised weight loss and exercise training program ± testosterone therapy

Compensation: may receive up to \$ 400.00

Dr. Dennis Villareal Principal Investigator HRRC No. Please contact the study office at telephone no. (713) 578-4300 for more information

Mode of Advertising: Other

Exact language of Advertisement:

OLDER VETERANS NEEDED

To participate in a study looking into the effect of weight loss, exercise training, and meformin on physical function, body fat, muscle, bone, memory and thinking, and mood..

Duration: Participation in the study will be ~ 8 months.

Tests/Procedures include medical examination, assessment of physical function, cardiovascular testing, blood tests, body composition testing, mood/cognition, and muscle biopsies

Interventions: Supervised weight loss and exercise training program $\pm$ testosterone therapy

Compensation: may receive up to \$ 400.00

Dr. Dennis Villareal Principal Investigator HRRC No. Please contact the study office at telephone no. (713) 578-4300 for more information

Mode of Advertising: BCM Clinical Trials Website

Exact language of Advertisement:

OLDER VETERANS NEEDED

To participate in a study looking into the effect of weight loss, exercise training, and metformin on physical function, body fat, muscle, bone, memory and thinking, and mood..

Duration: Participation in the study will be ~ 8 months.

Tests/Procedures include medical examination, assessment of physical function, cardiovascular testing, blood tests, body composition testing, mood/cognition, and muscle biopsies

Interventions: Supervised weight loss and exercise training program $\pm$ testosterone therapy

Compensation: may receive up to \$ 400.00

Dr. Dennis Villareal Principal Investigator HRRC No. Please contact the study office at telephone no. (713) 578-4300 for more information