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Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

Protocol Number: H-41814
Status: Approved
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Approval Period: 3/9/2026 - 2/10/2027

Section Aa: Title & PI

A1. Main Title

AROMATASE INHIBITORS AND WEIGHT LOSS IN SEVERELY OBESE MEN WITH HYPOGONADISM

A2. Principal Investigator

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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

A4. Co-Investigators

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A5. Funding Source:

Organization: NATIONAL INSTITUTES OF HEALTH (NIH)

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?
Yes

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 trail is required as a term and condition of the reward by the funding agency.

ClinicalTrials.gov Identifier:
NCT03490513

Section B: Exempt Request

B. Exempt From IRB Review

Not Applicable

Section C: Background Information

The syndrome of hyperestrogenemia-induced hypogonadotropic hypogonadism (HHG) in obese men has been described over 3 decades ago.1-3 In this syndrome, the increased conversion of androgen precursors to estrogens, i.e. testosterone (T) to estradiol (E2) and androstenedione to estrone, from an expanded adipose tissue volume and the consequent hyperestrogenemia, is hypothesized to result in a negative feedback to the hypothalamic-pituitary-gonadal (HPG) axis, leading to low luteinizing hormone (LH) and follicle stimulating hormone (FSH), and reduced T production.4 Multiple studies have shown that weight loss (WL) leads to increase in T level which is proportional to the amount of WL.5-7 However, the ability of WL by lifestyle changes to increase T is at best modest,8 and in severely obese hypogonadal men may not be enough to raise T to the mid-eugonadal range.5;7 In addition, weight regain is quite common after WL.9 Studies on the use of aromatase inhibitors (AIs) in aging- and obesity-associated HHG have consistently shown reversal of the hormonal abnormalities with increase in LH and serum T and reduction in E2 levels. 10-13 However, the few studies that investigated the effect of this hormonal reversal on clinical outcomes reported inconsistent results. A very recent study in older men reported improvement in lean mass and strength with no significant decrease in bone mineral density (BMD) with AI therapy for 1 year.14 However, in a study of 37 elderly men with low or borderline low serum T, anastrozole for 12 weeks did not significantly improve quality of life, and sexual function.10 There were no significant adverse effects on hematocrit (HCT), prostate symptoms, bone metabolism and cardiovascular risk factors.15;16 In a bigger population of older men, anastrozole for 1 year also resulted in no significant differences in the changes in hypogonadal symptoms, strength, body composition, HCT and prostate-specific antigen (PSA) compared to placebo.17,18 Yet, there was a small but significant reduction in spine BMD although there was no difference in changes in trabecular bone volume.18 But nonobese older men have a different mechanism for low T than those with HHG from obesity. Since obesity-associated HHG is due to hyperestrogenemia from increased conversion of androgens to estrogens suppressing the HPG axis, AIs would likely be more useful in this setting. The only study, to our knowledge, that investigated the effect of AIs on clinical outcomes in obese men with HHG, found no significant changes in the body composition, psychometric parameters, BMD, and markers of bone turnover after 6 months of letrozole therapy.13 However, issues relating to study design in this proof-of-concept study which included escalating doses of letrozole and subjects on variable doses of letrozole, limit our interpretation of the results. Thus, despite available data showing that AIs can reverse HHG in obese hypogonadal men, the consequence from this reversal on clinical outcomes remains unknown. In addition, the increase in T from non-surgical WL is quite modest8 and may not be enough to significantly improve clinical outcomes in severely obese hypogonadal men, requiring alternative treatment strategy. We hypothesize that WL and AIs each can lead to improvement in hormonal profile but the reversal of hormonal abnormality in obesity-associated HHG from enhanced aromatase inhibition by the additive effects of AI+WL will result in greater improvement in muscle strength and hypogonadal symptoms than WL alone, with minimal adverse effects on body composition (and metabolic risk factors) and bone.

Section D: Purpose and Objectives

1. To evaluate the effect of an AI plus WL (AI+WL) compared to WL alone on the changes in hormonal profile in severely obese men with HHG. 2. To evaluate the effect of an AI+WL compared to WL alone on the changes in muscle strength and muscle mass, and symptoms of hypogonadism in severely obese men with HHG. 3. To evaluate the effect of an AI+WL compared to WL alone on the changes in body composition and metabolic risk factors in severely obese men with HHG. 4. To evaluate the effect of an AI+WL compared to WL alone on the changes in BMD, bone markers, and bone quality in severely obese men with HHG.

As secondary aim, we will elucidate the mechanism for the anticipated positive effects of AI+WL on obesity-associated HHG. We propose that the consistently higher and stable T levels, the increased lean/muscle mass and the changes in mediators (IGF-1, follistatin, myostatin, irisin) are responsible for the proposed efficacy and safety of AI+WL as treatment of obesity-associated HHG.

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:
Male

Age:
Adult (18-64 yrs), Geriatric (65+ yrs)

Ethnicity:
All Ethnicities

Primary Language:
English

Groups to be recruited will include:
Asymptomatic patients with chronic conditions, healthy

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?

Does the study enroll or collect personal data from individuals residing in any of the following countries: European Union (EU) countries, European Economic Area (EEA) countries, the United Kingdom, or Switzerland?
No

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:
y) Drug, Phase IV, Single Center

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.

To achieve robust and unbiased results, this study will be a randomized, double-blind, placebo-controlled study of severely obese men with HHG to establish the effects of the combination of an AI and WL compared to WL alone for 12 months on the following outcomes: 1) hormonal profile, 2) muscle strength, muscle mass and symptoms of hypogonadism, 3) body composition and metabolic profile, 4) bone density and bone quality and 5) circulating mediators (insulin growth factor-1 [IGF-1], myostatin, follistatin, irisin and circulating osteogenic progenitors). This 5-year project has 4 Specific Aims and one Secondary Aim that will be carried out in parallel and in the same patient population, using highly validated methods of assessments likely to lead in reproducible results.

Dr. Clifford Qualls is a staff at the New Mexico VA Health Care System, the University of New Mexico School of Medicine, and the Biomedical Research Institute of New Mexico. His e-mail is CQualls@salud.unm.edu. He is relying on the University of New Mexico School of Medicine IRB and will not be relying on BCM IRB.

Dr. Nicola is a staff at Washington University. His e-mail is nnapoli@wustl.edu He is relying on the Washington University IRB and will not be relying on BCM IRB.

Inclusion Criteria:

Inclusion criteria and Rationale: Our preliminary results suggest that men with the BMI of 35kg/m2 or more did not derive optimum benefits from T therapy, thus we will target this population of male hypogonadal patients. We will recruit men between 35-65 yo who are severely obese men with BMI of 35 kg/m2 or more who have an average fasting T level from 2 measurements taken between 8 to 10 AM on 2 separate days within 1 month of less than 300 ng/dl,48 with LH of less than 9.0 mIU/L, E2 of 14 pg/ml or more and with symptoms consistent with androgen deficiency as assessed by the quantitative Androgen Deficiency in Aging Male (qADAM) questionnaire.

Exclusion Criteria:

Exclusion criteria: 1) clinical/biochemical evidence of pituitary or hypothalamic disease, 2) drugs affecting gonadal hormone levels, production and action or bone metabolism (bisphosphonates, teriparatide, denosumab, glucocorticoids, phenytoin), 3) diseases affecting bone metabolism (e.g. hyperparathyroidism, untreated hyperthyroidism, osteomalacia, chronic liver disease, significant renal failure, hypercortisolism, malabsorption, immobilization, Paget¡¯s dis.), 4) prostate carcinoma or elevated serum PSA> 4 ng/ml, 5) HCT more than 50%, 6) untreated severe obstructive sleep apnea, 7) Cardiopulmonary disease (e.g. recent myocardial infarction or MI defined as MI within 6 months at the time of study entry, 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), 7) History of deep vein thrombosis or pulmonary embolism, 8) severe lower urinary tract or prostate symptoms with International Prostate Symptom Score (IPSS) above 19, 9) excessive alcohol or substance abuse, 10) unstable weight (i.e.+/-2 kg) in the last 3 months, 11) condition that could prevent from completing the study, and 12) a screening BMD T-score of less than -2.0 at the spine, femoral neck or total femur, history of osteoporosis or fragility fracture, 12) Diabetes Mellitus with a fasting blood glucose of more than 160 mg/dl, and/or Hemoglobin A1c (A1C) more than 9.5%

F2. Procedure

A. Initial screening and baseline evaluation. Screening blood tests for T will be obtained from fasting samples drawn between 8-10 AM to control for diurnal variation in hormone levels and performed twice on 2 separate days within 1 month. Other screening tests include a comprehensive metabolic panel (CMP), HCT, PSA, LH, FSH, prolactin, E2, and other hormones to rule-out a pituitary problem such as adrenocorticotropic hormone (ACTH), cortisol, Insulin growth factor-1 (IGF-1), thyroid stimulating hormone (TSH), free T4 and prolactin. An Electrocardiogram will be performed at Baseline visit.

Medical, social and medication history; body weight and height will be obtained; and a physical examination with a digital rectal examination (DRE) will be performed at baseline, 6 months and 12 months. For patients who may have risk factors for CAD basing on their medical history, we will send a letter to their primary care physician asking them for a signature that the patient can participate in a supervised moderately-strenuous exercise program associated with the study (see attached document entitled "PAR_PCP_CLEARANCE"). In case the PCP does not send the form back, another form will be sent or the PI will personally contact the PCP and will obtain permission on the phone for patient participation. Proof of the conversation will be saved in the patient's records. If these efforts fail, the subject will be or will not be allowed to participate on the discretion of the PI as determined after an exhaustive review of the patient's past and present medical history and careful physical examination in relation to the subject's ability to safely perform supervised moderately-strenuous exercise program.

B. Follow-up visits: Schedule of tests and follow-up visits are as shown in Table1. All of the visits, testing and behavioral interventions will be conducted at the Center for Translational Research on Inflammatory Diseases (rooms 209, 226, 242A, 262 and 262A), 2nd floor of Building 110, MEDVAMC. Blood samples will be obtained, processed immediately and labeled with the participants ID number and stored in triplicate aliquots at -80 degrees C.

C. Intervention: Subjects will be randomized to 2 groups: 1) placebo+WL, and 2) anastrozole+WL. Intervention will be conducted for 12 months. 1) Placebo+WL group will receive a placebo plus a program of diet modification and exercise training. Diet modification will be achieved through group behavioral therapy sessions designed to have the subjects acquire positive weight-control skills and attitudes, and practice weight management skills. We have successfully used this approach in our previous studies. Participants will attend weekly group sessions (10-15 persons) in the first 3 months, lasting ~75-90 min. Visit frequency will be decreased to every two weeks from 3 to 12 months to prevent treatment fatigue. These sessions will be provided by a dietitian experienced with lifestyle and behavioral therapy. Subjects will be instructed on behavioral strategies for modifying eating habits: goals setting and self-monitoring, stimulus control techniques, problem-solving skills, identification of high-risk situations and relapse prevention. To enhance lifestyle change and retention, subjects will also be provided individual motivational interviewing at least once a month or as needed that last 10 minutes. A balanced diet will be prescribed to provide a deficit of 500-750 kcal/day from daily energy requirement. EXERCISE TRAINING: You will exercise on 2 nonconsecutive days per week for approximately 45 minutes per session at our exercise facility, at your community fitness center, or at home for the 12 months duration of the study. Each session will be performed following the physical therapist/exercise trainer's recommendations and will include exercises to improve flexibility, strength, endurance, and balance. Participants will receive phone calls twice a week and lifestyle maintenance meetings to discuss topics such as how to maintain the exercise program, enjoy healthy meals/snacks, avoid food traps, monitor weights regularly, stick to a healthy weight plan, and create a support network. These calls will last 10 minutes. The level of exercise will be based on the American Heart Association and American College of Sports Medicine (ACSM) for optimizing cardiovascular fitness in adults, and the ACSM recommendation for appropriate physical activity strategies for weight loss. The supervised aerobic training will be ~45 minutes in duration and involve walking on a treadmill and

stationary cycling. After a brief warm-up, the participants will exercise so that their heart rate will be 65% of heart rate reserve (HRR) and gradually increase to 70-85% of HRR. In addition, the participants will participate in supervised resistance training on 2 non-consecutive days per week. The resistance training will involve nine upper-extremity and lower extremity exercises with the use of weight-lifting machines. The participants will perform 1-2 sets at a resistance of ~65% of their one repetition maximum (1-RM), with 8-12 repetitions of each exercise; they will gradually increase the intensity to 2-3 sets at a resistance of ~80% of their 1-RM. The home-based exercises will involve ground walking, or treadmill walking, or stationary bike if available at a rating of perceived exertion (RPE) of 12-14, as well as resistance exercise using body weight (e.g. abdominal crunches), resistance bands, and ankle weights at a RPE of 15-16. To improve retention, interventionist will interact individually with the volunteers, and programs will be made flexible to account for illness, vacation, etc. Compliance to this exercise program in our previous studies was 82-83%. These subjects will receive extensive education and instructions on behavioral modification to promote adherence to lifestyle change and continue the techniques learned even after they are finished with the study.

2) Anastrozole+WL group will be randomized to the AI, anastrozole, plus the diet and exercise intervention detailed above. Prior studies showed that anastrozole 1 mg/day is effective in increasing T levels in men with low T to within the mid-normal range with minimal or no side effects. Dosage will be adjusted based on serum T, E2 and HCT levels, symptoms and the occurrence of side effects and will be performed by a physician co-investigator who is unblinded to the study randomization. We will aim to achieve a total T level between 500 to 800 ng/dl which corresponds to the mid-normal range for a young adult male at the Mayo Clinic laboratory (300-1200 ng/dl), E2 equal to or more than 10 pg/ml and HCT less than 54%.60 T and E2 level will be checked 6 weeks (1.5 months) after starting therapy. Dose adjustments will be done by increments or decrements of 1 mg/week (not to exceed 1 mg/day) to maintain the target T, E2 and HCT. For HCT, we will start reducing anastrozole dose by 1 mg/week once HCT reaches equal to or more than 52% with repeat T, E2 and HCT measurement done 2 months after a change in dose. Otherwise schedule for follow-up testing will be as shown in Table 1. To maintain blinding and avoid bias, the physician making the dosage adjustments will direct that a participant in the placebo group be treated similarly. Those who are unable to maintain T and E2 in the target range and HCT of less than 54% despite dosage adjustments will be dropped from the study. Dispensing of anastrozole under double-blind conditions. Subjects will be randomized to anastrozole 1 mg daily (n=70) or placebo daily (n=70) using random number generation; randomization list to be provided by the study biostatistician with experience in clinical trials (Dr. Clifford Qualls). The study coordinator will inform the Michael E. DeBakey VA Medical Center (MEDVAMC) research Pharmacist and the biostatistician (Dr. Qualls) when a subject is ready for randomization. Placebo will be provided in an identical form and dispensed by the MEDVAMC pharmacy. The pharmacy will complete a group assignment form, copies of which will be provided to Dr. Qualls and Dr. Rui Chen (unblinded investigator). Lists of the participants and their treatment assignments will be kept by the pharmacy. The pharmacy will dispense the drug/placebo to the study coordinator on a monthly basis, and will maintain a record of the dosage that will be dispensed. The study coordinator will be responsible for giving the study drug to the participants and meet with them every 2 weeks for the first 2 months to discuss questions that may arise in relation to the medication.

All subjects will be provided supplements to ensure an intake of ~1200 mg of calcium/day and ~1000 IU vitamin D/day. Additional vitamin D supplements will be provided to those with 25-hydroxyvitamin D (25OHD) level of less than 30 ng/ml to maintain the target 25OHD level of equal to or more than 30 ng/ml.

D. Tests: 1) Hormone studies: T and E2 (and free hormones), FSH, and LH will be measured as by liquid chromatography/mass spectroscopy (LC/MS) and SHBG by ELISA (Alpco Diagnostics, Salem, NH); and will be measured at baseline, 1.5, 3, 6, and 12 months. 2) Muscle strength testing: Knee flexion and knee extension will be tested at baseline, 6 months, and 12 months by isokinetic knee extensor and flexor strength and will be evaluated using a Biodex System 4 dynamometer (Shirley, NY) and will performed on the right leg at an angular velocity of 60°/s. The best of the three maximal voluntary efforts for each of the knee flexion and extension will be used as the measure of absolute strength and reported as peak torque at 60° in Newton meter (Nm) units. 3) Thigh muscle volume will be measured at baseline and 12 months by magnetic resonance imaging (MRI) of both thighs using a 1.5-T superconducting MRI instrument (Siemens, Iselin, NJ) and a T1-weighted pulse sequence as described previously by our group. Muscle volume and cross-sectional area will be quantified in each slice by Analyze Direct software (version 10.0; Mayo Clinic, Rochester, MN), which distinguishes muscle from other tissues. Muscle size data are reported as the sum of values from the right and left thighs. This test will be done at baseline and 12 months. 4) Questionnaires will be administered at baseline, 6, and 12 months. We will use validated questionnaires. The ADAM questionnaire 63 is widely-used as screening tool for androgen deficiency. A modified version, (quantitative ADAM (qADAM)) was developed 49 to enhance specificity to the standard ¿yes¿ or ¿no¿ answer to the 10 questions related to androgen lack in the original ADAM. The qADAM asks subjects to grade each symptom from 1 to 5, with 1 being ¿terrible¿ and 5 being ¿excellent¿. Other questionnaires include: International Index of Erectile Function scoring system (IIEF) to detect changes in erectile function; International Prostate Scoring System (IPSS) to assess changes in urinary symptoms; Short Form 36 (SF-36) for changes in quality of life; and Stanford physical activity 7 days recall (PAR) for changes in physical activity. In addition, we will ask to the participants the amount of alcohol they drink per week which they will report in terms of glasses/cans or bottles. 5) Body composition by dual energy x-ray absorptiometry (DXA) using Hologic Horizon (Hologic Inc., Bedford, MA, U.S.A.). will be done at baseline, 6 months and 12 months. The DXA instrument is used to distinguish soft tissue from bone and to distinguish fat from non-bone lean tissue. Regional measurement of the lower extremity (LE) will also be made by using a line bisecting the femoral neck. Please see attachment entitled "Continuation F2_Procedure" for the rest of the testings associated

Section G: Sample Size/Data Analysis

G1. Sample Size

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

Local: 140 Worldwide: 140

Please indicate why you chose the sample size proposed:

Our power analyses were based on our own data in multiple published papers,(8;19-21) and on a new, small clinical trial on AI therapy (14). Basing on these studies, we propose to recruit 140 subjects and randomize 70 subjects in each arm. Since in this calculation we assume a 1 year 20% dropout rate as in our T study, we anticipate there will be remaining 56 subjects per group (assuming the drop-out of 14 individuals per group -20%-). Using Bonferroni correction in the power analyses for the main outcomes in aims #1-3 and adjusting the alpha to á=0.05/3=0.0167, this sample size is adequate to detect a 1) 29% change in T levels with 80% power, feasible due to the addition of an AI, 2) 13.5 N-m change in knee extension strength, and 3) 1.1 kg difference in lean mass between the 2 arms. .

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?

Treatment associations with measures of hormone profile, muscle strength, body composition and BMD (by DXA) over time will be modeled using Repeated measures (RM) ANOVA with treatment as the grouping factor and measurement times (baseline, 1.5 months, 3 months, 6 months, and 12 months of intervention as appropriate) as the repeated factor and will be adjusted for adherence and baseline values, the presence of co-morbid conditions (e.g. diabetes mellitus, metabolic syndrome) or the use of medications, e.g. metformin which has been shown to inhibit aromatase activity and selectively for certain covariates as 1) degree of WL for outcome change in T, 2) age for change in muscle strength 3) age and physical activity for change in body composition and 4) age, degree of WL and physical activity for BMD change. If distributional assumptions for the above analyses are not met even after standard data transformation, we will use more robust semi-parametric or non-parametric tests (e.g. rank tests). Similar analysis will be performed for changes in sexual function, quality of life measures, VAT volume, metabolic risk factors, thigh muscle mass by MRI, bone turnover markers, bone quality measures and mediators. Simple/partial correlation and multiple regression analyses will be performed to determine which hormonal/metabolic factors and substances are important mechanistic mediators of the observed changes in the different outcomes. These will be performed using SAS. Intent to treat (ITT) analysis. RM ANOVA (our overall analysis) in SAS uses all available data and handles missing data well. This solves the problems caused by missing data, as loss of degrees of freedom and bias. SAS Procedure Multiple Imputation (MI) is used 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 reputations. MRI scans of the thigh will be analyzed using ¿Mayo Analyze Software¿. 10 scans of the thigh, starting from the third scan after the superior edge of the patella, will be analyzed. First, the background noise will be removed and x-min values will be used to discriminate between muscle tissue and fat tissue. The following region of interest will be analyzed: fat mass, muscle mass, and intramuscular fat mass.

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 you may experience in this study are small and primarily associated with the testing measures and anastrozole therapy as described in the next paragraphs:

Risk related to aromatase inhibitors administration: available data regarding potential risks and discomfort due to the use of aromatase inhibitors refer to women. Thus, these potential risks and discomfort from aromatase inhibitor administration do not necessarily apply to you. In addition, different from postmenopausal women who have low levels of estrogens, your condition of hypogonadism or low testosterone which is caused by obesity is characterized by having high levels of estrogens. Decrease in bone mineral density or calcium in the bones was also reported primarily in women taking the medication for breast cancer. Although, a decrease in bone mineral density was also reported in a study conducted on elderly men, this group of men is different from the men we are recruiting in our study. You will be instructed to report all of the possible discomfort to the research team.

Below are the signs and symptoms reported to be associated with the use of aromatase inhibitors from studies in women with breast cancer:

Among the less serious but more common side effects (more than 10% risk) include: weakness; headaches; hot flushes; sweating; stomach pain, nausea and vomiting; heartburn; joint, bone or muscle pain; cough and sore throat, . While diarrhea; constipation; breast pain; difficulty of falling asleep or staying asleep; nervousness; dizziness; pain, burning

numbness of tingling of hands or feet, sinus inflammation, increase in fat or cholesterol in your blood, dry mouth and hair thinning which could range from mild, moderate, to severe hair thinning and may even include severe hair loss, loss of appetite, weight loss or weight gain, swelling of hands, blurred vision are considered less serious and less common side effects.

There are also some possible side effects that could be considered as serious and may be more common (more than 10% risk) such chest pain mostly among those with a history of heart disease; and osteoporosis or thinning of the bones; mood changes; depression and widening or expansion in the size or the diameter of blood vessels which could result in a drop in blood pressure. Other serious but less common side effects (from 1 % to less than 10 %) include broken bones; heart attack; high blood pressure; fever, chills or swollen glands or other signs of infection; swelling of hand or arm; difficult, painful, or urgent urination; blood clots; stroke; yellowing of the skin or eyes and pain in the upper right part of the stomach; inflammation of air passages in the nose and air passages in the lungs; and severe allergic reaction characterized by hives; itching; difficulty of breathing; swelling of the eyes, face, lips, tongue, and throat,

A rare but serious type of severe skin reaction is Steven-Johnson Syndrome. It is characterized by fever, flu-like symptoms, and blisters and may result in death. It can happen with any medication.

Risks related to blood drawing: possible temporary pain and discomfort from the needle stick, occasional bruising and or bleeding at the site of needle insertion, sweating, feeling faint or lightheaded and in rare cases infection.

Risk related to radiation (x-ray) risks: This research involves exposure to radiation from the dual energy x-ray absorptiometry (DXA) and high-resolution peripheral quantitative computed tomography (HR-pQCT) for bone mineral density and body composition measurements. The amount of radiation from these tests when averaged over our entire body is less than 3% of the allowable annual dose to a radiation worker (for example, X-ray technicians). The risk from the radiation exposure in this study is too small to be measured and not more thanthe usual daily exposure.

Risk related to lifestyle intervention: A modest muscle and bone density loss associated with weight loss can occur. However, this is prevented by exercise which we propose to combine with weight loss. A rare risk of weight loss is the formation of gallstone.

The MRI procedure may be harmful for people with metal implants in their bodies, and may cause discomfort in people with claustrophobia (fear of closed spaces). This procedure will not be performed if you have certain types of metal implants, and will be discontinued if you become claustrophobic.

The risk of participating in an exercise program includes fractures, sprains, falls, tendon injury, and sore muscles, and joints on different parts of the body. However, these complications will be minimized as you will be doing warm-up and cool-down exercises and you will receive close monitoring to reduce the risk of these complications.

Exercise training and testing is associated with a slight risk of developing serious disturbances in heart rhythm, temporary drop in blood pressure, or, very rarely, heart attack and death. Disturbances in heart rhythm are typically reversible. A physician will be available should a medical emergency arise.

There are risks of stress, emotional distress, and inconvenience associated with participating in a research study. You may experience emotional discomfort when answering some questions in the questionnaires. You will be encouraged to discuss the importance and the need to answer these questions with a member of the research team. If you remain uncomfortable in answering these questions despite the above efforts, you will be given the option not to answer them.

There are risks related to the loss of confidentiality of your health information. We may use, disclose or release for this research is past and present medical and mental health information, alcoholism or alcohol abuse information, medications, tests including diagnostic laboratory, pathology results, imaging such as x-rays, MRIs scans, dates of tests, demographic information such as name, date of birth, age, home address, phone number, last four SSN, race, dates of tests and test results, completed research questionnaires and records of study drug received. These sensitive information may be disclosed unintentionally in the course of the study. However, study personnel will make every effort to minimize the risk.

Unknown risks: The experimental treatments may have side effects that no one knows about yet including potential death. They may also have unknown risks to a fetus or embryo. Since the effect of the medication on a developing fetus or embryo is unknown, we suggest avoiding pregnancy in your wife or partner by using birth control methods. In addition, because there are no studies on the safety of the fetus with use of these drugs in men, we suggest avoiding pregnancy in your wife or partner by using birth control methods throughout the duration of the study and to continue for 6 months after stopping the medication.

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 â€“ 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.
POTENTIAL BENEFITS: Patients may or may not benefit from participating in this study. Improvement in quality of life and hypogonadal symptoms including muscle strength, sexual function, mood, and body composition, may be experienced by subjects participating in this study. Weight loss and related metabolic improvement may also occur.

Describe potential benefit(s) to society of the planned work.
The information gained from this study may help identifying the best way of treatment for the obesity-related hypogonadotropic hypogonadism : its different physiopathology necessitates an effective therapy able to act the the root of the disease and thus improve hypogonadal symptoms and muscle strength. According to our preliminary data, this subgroup of hypogonadal obese subject do not benefit from testosterone therapy.

Do anticipated benefits outweigh potential risks? Discuss the risk-to-benefit ratio.
The benefits to the subjects studied in this research protocol, and to society are large, and far surpass the risks. In addition to having weight loss, improvement of symptoms related to hypogonadism may result from a combination of weight loss and anastrozole in severely obese subjects who are likely not to respond to testosterone treatment. On the other hand among the side effects, erythrocytosis, increase in Prostate Specific-Antigen and prostatic enlargement are well-recognized side effects of increased levels from testosterone administration. Furthermore, recent studies reported an increase in the risks of myocardial infarction and stroke associated with testosterone treatment. Although we plan to monitor our subjects closely, these events have not been reported in studies using AIs. Bone loss has been reported in postmenopausal women with breast cancer and in elderly men hypothesized to be due to profound estrogen deficiency resulting from AI use. However, we do not foresee this as a problem for severely obese men who have elevated levels of estrogen at baseline. Thus, we believe that the benefits outweigh the risk with this treatment regimen which if found to be effective, may potentially become the standard of care for severely obese patients.

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)
Chart review to determine subject eligibility (for screening purposes only).

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.
For potential veteran participants, 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. We will also access CDW data and vital status files through the Data Access Request Tracker (DART) to include real SSNs 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 (S 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: S 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.

The purpose of collecting information covered under 38 U.S.C. 7332 is to conduct scientific research and no personnel involved in this study will identify, directly or indirectly, any individual patient or subject in any report of such research.

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

All members of the research team will be issued an individual password. We plan to protect identifiers from improper use or disclosure. 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, 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. Once permission has been obtained from their providers to contact patients, files containing identifiers will be kept for 6 years after the study closure as per VA guidelines.

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. The identifiers will be destroyed at the earliest opportunity according to VA guidelines.

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.

We need to access the data of a large number of patients most of whom may not qualify for the study. Given the limited manpower allowed in the study, an access and use of potential patient¿s medical record would streamline the number of patients we will screen to those who qualify by age, weight and prior serum testosterone levels and don¿t have the exclusion criteria listed in the protocol.

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

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. Please also see our response to (a) above.

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

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.

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:

Yes

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 #:

No

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.
As the waiver is for identification of potential subjects only, there would not be information to disclose to subjects that they would not already be aware of and we are not obtaining new tests or results during the medical record reviews. The information we review from the database to screen potential subjects are already part of their medical record system in the VA, for which they are getting ongoing medical care through their VA health care providers.

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.
We will obtain verbal consent from subjects who are screened over the phone. This waiver is requested only for the purpose of screening potential study participants.

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.
We will recruit male attending the Endocrine, Primary Care and Urology Clinics at the Michael DeBakey VA Medical Center, Houston, TX and clinics associated with Baylor College of Medicine. Recruitment will be performed through active advertisement using1) posters; 2) flyers; 3) direct mailings of printed materials to potential subjects or 4) from direct referral by attending physicians of patients that may qualify; 5) 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. Postcard will contain the study contact phone number allowing for potential participants to express interest in the study; 6) 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 eligible subjects for recruitment purposes. CDW data are part of VA Informatics and Computing Infrastructure (VINCI), an initiative to improve researcher's access to VA data and to facilitate data analyses while ensuring Veteran's privacy and security. The data were collected for administrative/clinical reasons. Guidelines that allow data to be released as identified can be found in the DART user guide, which outlines an extensive 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.

Records will be reviewed for exclusion criteria by the research team, including the research coordinator and the PI. For subject interested in participating who directly contact the research team (recruitment methods 1, 2 and 3). Interested patients will be asked to return a postcard.

For patients who may have risk factors for CAD basing on their medical history, we will send a letter to their primary care physician asking them for a signature that the patient can participate in a supervised moderately-strenuous exercise program associated with the study (see attached document entitled "PAR_PCP_CLEARANCE". In case the PCP does not send the form back, another form will be sent or the PI will personally contact PCP and will obtain permission on the phone for patient participation. Proof of the conversation will be saved in the patient's records. If these efforts fail, the subject will be or will not be allowed to participate on the discretion of the PI after an exhaustive review by the PI of the patient's past and present medical history and careful physical examination in relation to the subject's ability to safely perform supervised moderately-strenuous exercise program.¿ Please see the rest of the description in the attachment entitled "Section J2".

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:
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

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

Where is the data being used for this research currently stored and at what institution?

Institution: Michael E. DeBakey VA Medical Center Source: Electronic Health Records; Database; Other, description:

At what institution will the physical research data be kept?
Hard copies of the research data will be maintained at the MEDVAMC building 110, and will be stored in a locked office (room 210) inside a locked file cabinet, located in a restricted area.

How will such physical research data be secured?
Only the PI and research staff will have access to the room and cabinet where the information will be stored and they will take care of locking both at all time of usage.

At what institution will the electronic research data be kept?
Electronic data will be stored on the secure MEDVAMC S drive (restricted shared drive permission) in a subfolder of the main research folder.

The exact location of the electronic data is S:\Research\Villareal, Reina\H-41814

Database location will be on a VA server

De-identified MRI data will be stored on the secure BCM Z:drive (restricted shared drive permission) in a subfolder of the main research folder.

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):
Electronic data will be stored on the secure MEDVAMC S drive (restricted shared drive permission) in a subfolder of the main research folder .The exact location of the electronic data is S:\Research\Villareal, Reina\H-41814

Database location will be on a VA server.

De-identified MRI electronic data will be secured via BCM IT services provided secured network (Non-Portable device 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:
People who ensure quality from the institutions where the research is being done, federal and other regulatory agencies will have access to all of the research data such as Food and Drug Administration (FDA) and Data Monitoring Committee (DMC). The purpose of collecting information covered under 38 U.S.C. 7332 is to conduct scientific research and no personnel involved in this study will identify, directly or indirectly, any individual patient or subject in any report of such research. There is no plan to disclose or otherwise grant access to VINCI/CDW data to entities outside or within VHA other than described in this protocol. Only authorized personnel will have access to the data and personnel who no longer need the information will have their access removed.

Please describe the methods of transmission of any research data (including PHI, sensitive, and non-sensitive data) to sponsors and/or collaborators.
All 18 HIPAA identifiers will be removed prior to sending data outside the VA

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.

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

Yes

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.

We will obtain information on the amount of alcohol intake as affects one of our outcome measures, i.e. changes in bone density. We are not interested on the information about alcohol abuse, thus, would have no need for certificate of confidentiality.

Will information about the subject's participation be included in subject's medical records?

Yes

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

We now rectified the issue by checking "yes" on the appropriate box. In addition, we will send a letter to those subjects affected stating that the information regarding their study participation will be included in their medical records. We will send the letters to patients affected by this error only after approval by the IRB.

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 are not responsible for any costs related to participation in the research.

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:

120

Distribution Plan:

Subjects will be paid 40$ at baseline, 20$ at 3 months, 20$ at 6 months, and 40$ at 12 months. The total payment for completing the study will be 120$ per patient. If the subject needs to pay for a gym membership while is part of the study, the participant will receive the additional reimbursement for the cost of the gym up to $50 monthly after submitting the invoice under the subject's name.

Section M: Genetics

How would you classify your genetic study?

DNA diagnostic 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.

Since the type of genetic variations that this study is investigating are common genetic variations in the population, we foresee no consequences on the patients employablity, immigration status, educational opportunities or social stigma and not useful in establishing paternity.

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?

No, subjects will not be offered any type of genetic education or counseling. There is not the possibility that a family's pedigree will be presented or published. The results of the genetic testing will not be given to the subjects. As the patients blood sample will not be linked to the patients identity, we plan to match the subjects identity with their DNA results with a study code assigned to each subjects DNA results which can only be interpreted with a special decrypting file.

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 study (see inclusion/exclusion criteria, 2) to monitor blood levels of testosterone, estradiol, LH, FSH, other hormones and biomarkers and side effects on blood count and PSA 3) overall safety monitoring while in the study. Samples will be collected directly from the study participant in the research lab or in the clinical lab.

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

A total of 4 tablespoons of blood at baseline, 6 and 12 months, and 3 tablespoons at 1.5 and 3 months. Total amount of blood collected for participating in the study 18 tablespoons.

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?

Yes, to BCM collaborators. All samples will be coded using random numbers not linked to SSN.

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?

Yes, sample will be banked at the Michael DeBakey VA Medical Center for 10 years .

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?

If the patient withdraws from the study, samples will not be destroyed and will be stored anonymously. If the subject revokes authorization, the 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 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?

Yes

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

Standard test results that are done at VA lab and have clinical use are reported in CPRS, or 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 through the CPRS which are shared with their VA primary care physicians. Depending on the urgency of the abnormal findings, the PI may directly contact the primary care provider by phone to discuss the abnormal findings

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

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: anastrozole

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.
The placebo controlled trial is required to evaluate which is the best approach for the treatment of hypogonadotropic hypogonadism in severely obese men: life style intervention induced weight loss alone (placebo group) or life style intervention induced weight loss combined with anastrazole therapy (active group). IND # 126696

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

None