# Testosterone Therapy and Bone Quality in Men with Diabetes and Hypogonadism

NCT03887936

Protocol

September 17, 2025


# Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

**Protocol Number:** **H-45062**
Status: Approved
Initial Submit Date: 1/29/2019
Approval Period: 9/17/2025 - 9/17/2026

## Section Aa: Title & PI

### A1. Main Title

TESTOSTERONE THERAPY AND BONE QUALITY IN MEN WITH DIABETES AND HYPOGONADISM

### A2. Principal Investigator

| | | | |
|---|---|---|---|
| Name: | SANJAY MEDIWALA | Phone: | 7137911414 |
| Id: | 691884 | Fax: | 6014291214 |
| Department: | MEDICINE: ENDOCRINOLOGY | Email: | mediwala@bcm.edu |
| Center: | | Mail Stn: | BCM185 |

### A3. Administrative Contact

| | | | |
|---|---|---|---|
| Name: | EMILY MERRELL | Phone: | |
| Id: | 253342 | Fax: | |
| | | Email: | u253342@bcm.edu |
| | | Mail Stn: | |

### 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

| | | | |
|---|---|---|---|
| Name: | MICHAEL LIEBSCHNER | Phone: | 713-794-8973 |
| Id: | 163998 | Fax: | 713-798-3739 |
| Department: | NEUROSURGERY | Email: | mal1@bcm.tmc.edu |
| Center: | | Mail Stn: | BCM650 |
| Name: | RUI CHEN | Phone: | 713 7988764 |
| Id: | 177323 | Fax: | |
| Department: | MEDICINE: ENDOCRINOLOGY | Email: | ruic@bcm.edu |
| Center: | | Mail Stn: | BCM185 |
| Name: | DENNIS VILLAREAL | Phone: | 713-794-7156 |
| Id: | 184416 | Fax: | 713-794-7771 |
| Department: | MEDICINE: ENDOCRINOLOGY | Email: | villarea@bcm.tmc.edu |
| Center: | | Mail Stn: | BCM185 |
| Name: | REINA VILLAREAL | Phone: | 7137947534 |

| | | | |
|---|---|---|---|
| Id: | 184419 | Fax: | 713 7947771 |
| Department: | MEDICINE: ENDOCRINOLOGY | Email: | rvillare@bcm.edu |
| Center: | | Mail Stn: | BCM185 |
| Name: | MARIA LIZA NAVA | Phone: | 7135784300 |
| Id: | 196882 | Fax: | 713 7988764 |
| Department: | MEDICINE: ENDOCRINOLOGY | Email: | mdnava@bcm.edu |
| Center: | | Mail Stn: | BCM185 |
| Name: | SALINA BIENE TEO | Phone: | 7137941414 |
| Id: | 240380 | Fax: | |
| Department: | MEDICINE: ENDOCRINOLOGY | Email: | u240380@bcm.edu |
| Center: | | Mail Stn: | |
| Name: | LINA AGUIRRE | Phone: | 5052651711 |
| Id: | Non-Baylor | Fax: | |
| Institution: | NEW MEXICO VA HEALTH CARE SYSTEM | Email: | LINA.AGUIRRE@VA.GOV |
| Address: | 1501 SAN PEDRO SE, ALBUQUERQUE, NM | | |
| Name: | CLIFFORD QUALLS | Phone: | |
| Id: | Non-Baylor | Fax: | |
| Institution: | UNIVERSITY OF NEW MEXICO | Email: | |
| Address: | CQUALLS@SALUD.UNM.EDU | | |
| Name: | PETER RICHARDSON | Phone: | |
| Id: | Non-Baylor | Fax: | |
| Institution: | VAMC | Email: | Peter.Richardson2@va.gov |
| Address: | | | |

### A5. Funding Source:

Organization: VA CSR&D

### A5a. ESP2 proposal(s) linked to this protocol:

### A6a. Institution(s) where work will be performed:

Baylor College of Medicine -- Alkek Eye Center
Michael E. DeBakey Veterans Affairs Medical Center

### A6b. Research conducted outside of the United States:

Country:
Facility/Institution:
Contact/Investigator:
Phone Number:

If documentation of assurances has not been sent to the Office of Research, please explain:

### 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:
NCT03887936

## Section B: Exempt Request

### B. Exempt From IRB Review

Not Applicable

## Section C: Background Information

An existing mutual influence between testosterone (T) and glucose metabolism has been suggested by studies showing that men with low T have impaired glucose tolerance, while type 2 diabetes mellitus (T2D) is associated with low T production.11 T therapy has been shown to improve the glucometabolic parameters in hypogonadal men.12 Men with high T levels had a 42% lower risk of developing T2D.11 It is estimated that the odds of developing T2D is 1.58 for every standard deviation decrease in T levels13. Thus, it is not surprising that as much as 64% of men with T2D were found to have low T.14;15 Low T is associated with age-associated decline in bone mass, and increase in fractures in men making androgen deficiency an important risk factor for osteoporosis. In fact, T deficiency has been reported in over half of elderly men with a history of hip fracture.16 Through its conversion to estradiol (E2), T treatment is associated with a reduction in markers of bone turnover and a significant in increase bone mineral density (BMD) in young and elderly men with hypogonadism. 17-19 Diabetes mellitus (DM) is associated with low bone turnover and normal or high BMD but paradoxically an increase in the risk for fractures.20 There is even a suggestion to adjust the BMD T-scores of patients with DM by -0.6 for women and -0.4 for men, and to consider treating patients with T2D even if they are slightly below the FRAX-based intervention thresholds.20 To our knowledge, the best approach for treating bone disease in patients with DM remains undefined. Considering the common association between T2D and hypogonadism, whether T (the standard of treatment for hypogonadism) will improve or worsen the skeletal health in men who also have T2D is unclear. We have preliminary data showing that among men with hypogonadism, those with T2D have higher total hip areal BMD (aBMD); higher total volumetric BMD (vBMD), lower bone cross-sectional area (CSA), and lower periosteal and endosteal circumferences compared to those without T2D suggesting smaller bone size and poorer bone quality from poor bone geometry in the former. Bone turnover markers, osteocalcin (OCN) and C-telopeptide (CTX) levels were also significantly lower among those with T2D compared to those without DM. However, T treatment resulted in an increase in CTX and OCN and an increase in bone CSA in men with T2D suggesting an increase in bone turnover and improvement in bone geometry compared to those without diabetes. As T remains the standard of therapy for patients with hypogonadism, whether it will significantly improve parameters of bone quality, more importantly bone strength, in men who have T2D and hypogonadism remains unknown. This project will evaluate the effect of T therapy on bone quality in men who have hypogonadism and T2D. The central hypothesis of this 1-year randomized placebo-controlled study is that T therapy will result in improvement in bone quality owing to improvement in bone remodeling through an increase in osteoblastic differentiation and proliferation21 in patients with hypogonadism and T2D.

## Section D: Purpose and Objectives

The specific aims of this project are: Aim #1: To determine the effect of T therapy on bone strength as measured by finite element analysis (FEA) in men with T2D and hypogonadism compared to placebo. As a secondary outcome, we will assess tissue-level material properties of cortical bone in vivo using microindentation.

Aim #2: To determine the effect of T therapy on bone turnover markers in men with T2D and hypogonadism compared to placebo.

Aim #3: An exploratory aim, to examine the mechanism for the improvement in bone metabolism in response to T therapy in men with T2D and hypogonadism. We hypothesize that the increase in T will result in stimulation of osteoblastic proliferation and differentiation21 leading to activation of the bone remodeling cycle from the cross-talk between osteoblasts and osteoclasts and replacement of old with new bone, and ultimately, in improvement in bone quality. Moreover, the possibility of an increase in osteocyte number, both from an increase in: (1) osteoblast number (which are precursors of osteocytes) and (2) an increase in E2 (due to increase in T available for conversion to E2) which inhibits osteocyte apoptosis, may also contribute to the improvement in bone quality.

## 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:
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:
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.
Randomized double-blind placebo-controlled study using testosterone gel 1.62% 2 pumps daily versus placebo gel.

Subjects will be randomized to either testosterone or placebo at a ratio of 1:1.

Inclusion Criteria:
Male veterans only, 35 to 70 yo with an average fasting morning T level from 2 measurements of <300 ng/dl taken at least a day apart and symptoms of hypogonadism as assessed using the quantitative androgen deficiency in aging male (qADAM) questionnaire. They should have T2D, with an A1C of <11.5 %, a fasting blood sugar of ≤180 mg/dl, body mass index (BMI) <40 kg/m2, and with DM of ≤15 years duration to target men who have relatively less complications from long-term DM.

Rationale for changing A1C criteria from 10.5% to 11.5%: There is an existing mutual influence between testosterone and glucose metabolism as suggested by studies showing that men with low testosterone have impaired glucose tolerance,

while type 2 diabetes mellitus is associated with low testosterone production. As testosterone therapy has been shown to improve the glucometabolic parameters in hypogonadal men, we believe that men with worse diabetes will also benefit from testosterone. Thus, we would like to offer this study to men who have A1Cs higher (i.e. up to. 11.5%) than originally proposed (10.5%). To our knowledge, there is no data showing that patients with poorly controlled diabetes are at risk from complications or deterioration in blood glucose when given testosterone. In fact, some investigators reported that testosterone may actually help in blood glucose control in patients with diabetes.

We will also include people with a history of stroke beyond 6 months from the last event in accordance with the guidelines from the Endocrine Society on patients who are deemed candidates for testosterone therapy and also include patients with mild chronic kidney disease (CKD), up to EGFR of 45/ml/min or more (CKD stage 3a). Newer evidence suggests that the rise in parathyroid hormone which promotes bone loss in patients with CKD occurs primarily in patients with worse CKD starting at CKD3b with bone mineral density negatively impacted in advanced CKD stages (3b to 4-5) (Cailleaux et. al. Kidney Int Rep (2021) 6, 1525–1536). Hence, we do not expect that allowing subjects with EGFR of 45 ml/min or more to participate will materially affect our bone outcomes.

Exclusion Criteria:

Exclusion Criteria :1) history of prostate or breast cancer; 2) history of testicular disease; 3) untreated severe sleep apnea; 4) ongoing illness that could prevent the subject from completing the study; 5) a hematocrit of > 50%;53 6) prostate-related findings as: a palpable prostate nodule on digital rectal exam (DRE), serum PSA of ≥4.0 ng/ml or ≥3.0 ng/ml for African-Americans, International Prostate Symptom Score (IPSS) >19 (severe); 7) on androgen therapy, or selective androgen receptor modulators; 8) on medications that affect bone metabolism such as: estrogen, selective estrogen receptor modulator as raloxifene, aromatase inhibitors, GnRH analogs, glucocorticoids with prednisone equivalent of least 5 mg daily for ≥1 month, anabolic steroids, phenobarbital and Dilantin; 9) use of bisphosphonates (i.e. risedronate, alendronate, zoledronic acid and pamidronate), within two years of study entry; 10) diseases that interfere with bone metabolism as hyperparathyroidism, untreated hyperthyroidism, osteomalacia, chronic liver disease, renal failure with estimated glomerular filtration rate (EGFR) of less that 45 ml/min), hypercortisolism, malabsorption and immobilization; 11) current alcohol use of more than 3 drinks/day and 12) those with a history of deep vein thrombosis, pulmonary embolism or recent diagnosis of coronary artery disease and stroke less than 6 months from the most recent event. Because of the potential of being randomized to placebo, subjects with osteoporosis or a BMD T-score by DXA of -2.5 in the lumbar spine, total femur or femoral neck and those with a history of fragility fractures (spine, hip or wrist) will be excluded. Furthermore, patients with severe symptoms of hypogonadism defined as overall score of <10 in the quantitative ADAM (Androgen Deficiency in the Aging Male) questionnaire for androgen deficiency and those with total testosterone level of <50 ng/dl will be excluded from study participation.

## F2. Procedure

I. Tests/procedures: 1) Baseline A) Medical and social history and intake of medications, will be obtained at baseline. B) Fasting blood for testosterone, luteinizing hormone (LH), follicular stimulating hormone (FSH), prolactin, thyroid stimulating hormone (TSH), drawn between 8 to 10 AM. Two samples will be drawn for testosterone levels at least a day apart and the average T will be calculated. Other blood tests include: comprehensive metabolic panel (CMP) with fasting glucose, hemoglobin A1c (A1c), fasting insulin, fasting lipid panel, complete blood count (CBC), prostate specific antigen (PSA), 25-hydroxyvitmin D (25OHD), parathyroid hormone (PTH), estradiol, sex-hormone biding globulin- all standard of care except for estradiol. We will calculate homeostasis model assessment of insulin resistance (HOMA-IR) according to the formula (fasting insulin (microU/L) x fasting glucose (nmol/L)/22.5. C) Bone turnover markers: osteocalcin (OC), C-telopeptide (CTX) and procollagen I intact N-terminal or P1NP (P1NP)- standard of care Tartrate-resistant acid phosphatase 5b (TRAP5b), Osteoprotegerin (OPG), receptor activator of nuclear factor kappa B ligand (RANKL), sclerostin-not standard of care D) Blood for osteoclast and osteoblast precursors-not standard of care E) Areal bone mineral density (BMD) testing measurement of the lumbar spine and proximal left femur by dual energy x-ray absorptiometry using Hologic Discovery (Hologic Inc., Waltham, MA, U.S.A.).- standard of care F) Bone microarchitecture and volumetric BMD, failure load and stiffness by high-resolution peripheral quantitative computer tomography (HR-pQCT) (XtremeCT II, Scanco Medical AG).- not standard of care. G). Microindentation Testing will be used to determine the effect of testosterone therapy on bone material properties in in men with T2D and hypogonadism compared to placebo. The OsteoProbe reference point indenter (Active Life Scientific Inc., Santa Barbara, CA) is a handheld microindentation instrument designed for in vivo BMS measurements. The testing site (midshaft of the anterior tibia) is determined by calculating the midpoint from the medial border of the tibial plateau to the distal edge of the medial malleolus. After 1% lidocaine, the probe is inserted through the soft tissue and periosteum until residing on the bone surface. While keeping the device perpendicular, the measurement is actuated by slowly compressing the device's outer housing unit, compressing the internal primary spring until the trigger mechanism initiates an impact. The impact mechanism creates a force to drive the probe into bone, while the displacement transducer measures indentation distance increase (IDI, micrometer) from impact. Based on our experience, the procedure causes only minimal discomfort while applying local anesthesia. The actual measurement is painless. This is a secondary outcome, hence, procedure is optional. H) Physical examination with a digital rectal examination (DRE) will be performed. We will obtain height, weight and BMI calculated as weight (kg) divided by the square of the height (m2) -standard of care I) Questionnaires: Androgen Deficiency in Aging Male (ADAM)-standard of care International Prostate Symptom Score (IPSS)-standard of care Food Frequency Questionnaire (FFQ) (Block Brief 2000, Nutritionquest, which is sold for use online) 3-day food record 7-day Physical Activity Recall-not standard of care 2. Follow-up visits will be done as shown at 3, 6 and 12 months.

A) 3 months: A.1 blood tests: testosterone, CBC, PSA, CMP, fasting lipid panel and A1C, fasting insulin, bone turnover markers (OC, CTX, P1NP, TRAP5b, OPG, RANKL and sclerostin), osteoclast and osteoblast precursors. HOMA-IR will be calculated. A.2 Questionnaires (ADAM, IPSS, 7-day physical activity recall and 3-day food record).

B) 6 months: B.1. Physical examination and intake of medications B.2. Blood tests: testosterone, CBC, PSA, CMP, fasting lipid profile, A1C, fasting insulin, 25OHD, PTH, estradiol, sex-hormone binding globulin, bone turnover markers (OC, CTX, P1NP, TRAP5b, OPG, RANKL and sclerostin), osteoclast and osteoblast precursors. HOMA-IR will be calculated. B.3. Areal bone mineral density by DXA B.4. Bone microarchitecture, volumetric BMD and failure load and stiffness by HR-pQCT B.5. Questionnaires (ADAM, IPSS, 7-day physical activity recall and 3-day food record).

C) 12 months: C.1. Physical examination and intake of medications C.2. Blood tests: testosterone, CBC, PSA, CMP, fasting lipid profile, A1C, fasting insulin, 25OHD, PTH, estradiol, sex-hormone biding globulin, bone turnover markers (OC, CTX, P1NP, TRAP5b, OPG, RANKL and sclerostin), osteoclast and osteoblast precursors. HOMA-IR will be calculated. C.3. Areal bone mineral density by DXA C.4. Bone microarchitecture, volumetric BMD and failure load and stiffness by HR-pQCT, and microindentation. C.5. Questionnaires (ADAM, IPSS, 7-day physical activity recall, FFQ, and 3-day food record).

II. Intervention: There will be 2 arms of the study. Participants will be randomized to either testosterone gel 1.62% or a matching placebo for 12 months. II.A. Testosterone therapy (standard of care). Based on previous studies, testosterone gel was able to reduce markers of bone turnover, improve BMD22 and bone microarchitecture13;55 in men with hypogonadism. In this study, we will use Testosterone gel 1.62% at 2 pumps daily (40.5 mg) which is the starting dose suggested by the manufacturer and available at the MEDVAMC pharmacy. The matching placebo will be prepared by the pharmacy. Dosage adjustments will be based on serum testosterone levels, symptoms and the occurrence of side effects and will be performed by a physician co-investigator who is un-blinded to the treatment assignment but will not be involved in baseline or follow-up testing. We will aim to achieve total testosterone levels between 500 to 700 ng/dl which is in the mid-range of normal (264-960ng/dl) in the MEDVAMC laboratory. Dose adjustments will be done by increments or decrements of 1 pump to maintain the target testosterone level. Repeat testosterone measurements will be performed as outlined above from blood samples obtained between 2-4 hours after application. A decrease in the dose by 1 pump will be done for patients who develop a hematocrit of >52%. Testosterone measurement will be performed 2 months after a change in dosage. For those who need adjustment because of elevation in hematocrit, a CBC will also be repeated 2 months after a change in dose. Otherwise the schedule for follow-up testing will be as shown in Table 5. To maintain blinding, the physician making the dose adjustments will direct that a subject in the placebo group be treated similarly. Individuals in the testosterone treatment group who are unable to maintain testosterone levels in the target range despite dosage adjustments will be dropped from the study. In addition, those who have persistently elevated hematocrit levels above 54% despite reduction in the dose of the study drug to as much as 50% of the weekly dose and those who experienced an increase in PSA above 4 ngl/ml, except African-Americans (above 3 ng/ml), will be dropped from the study and will be offered to follow-up at the Endocrine Clinic at the MEDVAMC or referred to their primary care provider for further management and follow-up. II.B. Dispensing of testosterone under double-blind conditions and monitoring of compliance with drug therapy. Subjects will be randomized to testosterone (n=83) and placebo (n=83) using random number generation; randomization list to be provided by the study biostatistician. The study coordinator will inform the MEDVAMC Pharmacy and the biostatistician when a subject is ready for randomization. The T gel 1.62% and placebo gel 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 the unblinded investigator. Lists of the participants and their treatment assignment will be kept by the pharmacy. The pharmacy will dispense the testosterone and placebo to the study patient on a monthly basis and will maintain a record of the dosage dispensed. The study coordinator will contact participants every 2 weeks by phone during the first 2 months to discuss any concern in relation to the medication. The coordinator will document the dose of testosterone that the subject is taking daily and any time the dosage is changed on a standardized form (though the coordinator will be blinded to the treatment status).

Testosterone gel 1.62% is approved by the FDA for treatment of hypogonadism and is available commercially.

II.C. Calcium and vitamin D (standard of care). Subjects will be asked to take calcium carbonate 500 mg twice a day with 800 IU of vitamin D.

Temporarily, due to COVID-19 pandemic and the decision by MEDVAMC and BCM to suspend all study-related activities in human trials, we will be contacting and monitoring participants by phone calls instead of face to face contact. In addition, the 3- month follow-up assessments may be delayed by one-two months. Scheduled follow-ups and assessments will be done as per protocol once all study-related activities are allowed to resume.

## Section G: Sample Size/Data Analysis

### G1. Sample Size

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

Local: 92 Worldwide: 92

Please indicate why you chose the sample size proposed:

In our original power analysis, CTX was the parameter the required the largest sample size (Table 1 in the attachment entitled Revised Sample Size Calculation) ; the original study was based on preliminary data from a prior study on testosterone intervention; that study is now completed and results concerning CTX has been published (Colleluori et.al. J Clin Endocrinol Metab. 2021 Mar 18). However, our main outcome which is Aim1 outcome, is FEA for the tibia and the

radius, with the radius requiring the larger sample size, only requires 34/group to detect a 5.1 %change difference between treatment and placebo with 80% power and alpha=0.05. For CTX, the above published data indicates a smaller standard deviation than we had assumed (56% change instead of 150%). So, the sample size of 34/group is adequate to detect a difference of 42% change between the two groups with 80% power and alpha=0.05, which is better the original power analysis result for CTX. Our anticipated dropout rate of 20% would require recruitment of 43/group to have adequate power. Thus, we will recruit at least 43/group, or a total of 86. We will of course be able to recruit more than this in the current study even with the slower rate of enrollment.

### 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?

Statistical analyses and data interpretation. Treatment associations with changes in the primary outcome, i.e. μFEA, over time will be modeled using linear mixed models with treatment as the grouping factor and measurement times as the repeated factor and will be adjusted for covariates as age, and initial value. Additional covariates considered include pack-years smoking, body mass index, duration of diabetes, medications, presence of diabetes complications, the Charlson index; and changes in A1C, strength, lean mass, 25OHD hormonal levels, and activity. Changes in CTX (aim 2) and circulating osteoblast precursors (aim 3) over time will be analyzed by linear mixed model adjusted for baseline values. Other secondary outcomes as BMSi, aBMD Hr-pQCT parameters (vBMD, bone area, cortical and trabecular thickness), biomarkers (sclerostin, RANKL, and OPG), hormonal levels and circulating osteoclasts will similarly be analyzed with adjustments as appropriate. We will perform follow up post hoc after the linear mixed model shows a significant omnibus test (i.e. p<.05). Log transformations will be considered when they will equalize variances. If we discover that the distributional assumptions required for the above analyses are not met by our data, even after standard data transformation, we will explore the use of more robust semi-parametric or non-parametric tests (e.g. rank tests.). We will employ two powerful statistical methods to deal with the issues of non-compliance and missing values. These will be considered as alternative analyses unless the original analyses are not validated thereby; in which case these analyses will be promoted in importance in our results. First, if non-compliance in either arm results in missing values, we use multiple imputation (MI) to randomly generate 100 complete databases. Our statistical analyses will be repeated for these 100 databases, and the 100 estimates +/- SE will re-combined (MIANALYZE) into one, less biased answer/result. MI and MIANALYZE procedures are available in SAS. Second, if noncompliance results in biased values (not missing values), non-compliance measures; for example, # of prescription refills for T, placebo and diabetic medications, as well as other measures such as age, will be used as predictors in a non-parsimonious propensity scoring in order to adjust for these biases. Typically, the propensity scores (PS, probabilities) are computed as residuals in a (non-parsimonious) logistic regression of two arms, as a binary outcome, on predictors. Weights for each record in the database are computed by a stabilized inverse probability method. Subsequently, our alternative analysis will be the weighted analyses using these weights.] We anticipate that compared to placebo, men randomized to T will have:1) significant increase in μFEA, 2) increases in both markers of bone resorption and formation, and 3) in circulating osteoblast progenitors and osteoclastic precursors supporting the positive effect of T on bone turnover in hypogonadal men with T2D.

## 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:

Risks to Subjects* <. Potential 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 but may range from mild to very serious. Subjects will be monitored carefully for any side effects and may be prescribed medicine to help lessen the side effects if any arise. The potential risks of the study are primarily associated with the testing measures and testosterone therapy as described in the next paragraphs:

Risks and side effects related to testosterone are listed below: o Frequent (Greater than 20%) Side Effects Include: increase in red blood cell count which may result in blood viscosity syndrome. As a result, the participant may need to have blood drawn (phlebotomy) and may need to adjust the frequency and/or dose of testosterone or even suspend the use of this medication. Increased blood thickness may cause headaches, visual disturbances, dizziness, ringing in ears, high blood pressure, heart failure and blood clots. Testosterone may also result testicular shrinkage or infertility (common in young men, usually reversible).

o Occasional (Between 2-20%) Side Effects Include: induction or worsening of sleep apnea, mood disorders (disturbance in a person's feelings or emotions) , acne or oily skin, enlargement of the prostate or growth of prostate cancer. Mild pain, bruising or skin irritation at the site of application. Because of the potential enlargement of the prostate from testosterone, the participant may need to undergo a biopsy of the prostate to make sure the participant does not have prostate cancer, a procedure that would not otherwise be required if not taking testosterone. Mild pain, bruising or skin irritation at the site of application.

o Rare (Less than 2%) Side Effects Include: edema or fluid retention, breast enlargement (usually reversible), skin reactions, change in cholesterol levels increased risk of blood clots, (deep venous thrombosis and pulmonary embolism), myocardial infarction and cerebrovascular events especially in those who had these conditions previously or those who are at risk for these conditions which may lead to death.

Allergic reaction: Symptoms may include but not be limited to trouble breathing, fast heart rate, rash, dizziness, and swelling.

Subjects will also be informed that if they are randomized to placebo they may not experience the potential beneficial effects of testosterone therapy in improving energy, sexual function, muscle mass, muscle strength, bone density and bone strength.

Risks associated with the testing procedures:

o Blood drawing risks: Drawing blood may cause 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.

o 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, as well as from spine X-rays. 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 than the usual daily exposure.

o The microindentation may result in some mild discomfort, bleeding, bruising, scarring or infection. Occasionally some people experience dizziness or feel faint. Risks associated with the injection of the local anesthesia are an allergic reaction (redness and swelling of the skin in the area of the injection, rashes or red bumps on the body, and in very rare instances, difficulty in breathing, low blood pressure, and death). To minimize the discomfort a small amount (2-3 ml) of local anesthetic (1% lidocaine) is injected at the incision site prior to the procedure. Careful sterile techniques are used during the tests to decrease the risk of infection. The bone microindentations are small (375 microns, about the size of the period at the end of this sentence) and are not harmful. Our group routinely performs microindentation testing and have had no complications. It has been our experience that after explaining the purpose and details of the procedure, volunteers in our prior and ongoing studies agree to participate in the microindentation testing and after having the procedure, they also agree in having them done repeated over time.

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

o There are risks related to the loss of confidentiality of the participants health information. Researchers 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.

o 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, it is suggested to avoided pregnancy with 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.

There may or may not be benefit to you from participating in this study. Possible benefits to taking part in the study include potential health improvements from the study intervention, which include improvements in bone mineral density, mood or well-being, energy, strength and muscle mass and sexual function. .

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

To date there is no specific treatment for bone disease in patients with type 2 diabetes mellitus. The information gained from this study may support the benefit of giving testosterone to men with type 2 diabetes mellitus who also have hypogonadism to prevent bone deterioration and fracture.

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 at large, far surpass the risks.Improvement in bone bone quality which we anticipated to occur with testosterone therapy in men with type 2 diabetes mellitus will help the subset of men with type 2 diabetes mellitus who are also hypogonadal, among whom no specific therapy exists. . In addition, improvement in quality of life, increase in muscle mass and improvement in strength are well-known benefits from testosterone.

## 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 CDW data and CPRS/VISTA to determine subject eligibility.

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.

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.

No 38 U.S.C. 7332 information (drug abuse, alcohol abuse, HIV infection and sickle cell anemia) will be used in this research study 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.

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

Biospecimens will be used to screen patients for eligibility into the study, to monitor changes in the outcome parameters and for subject safety.

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.

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 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 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:

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 #:

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?

No

### 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 primarily male veterans attending the Endocrine, Primary Care and Urology Clinics at the Michael DeBakey VA Medical Center, Houston, TX. Active advertisement through posters and flyers, and direct mailings of printed materials to potential subjects will be done. Potential subjects will be identified from direct referral by the attending physicians or from patients referred for consult to the Endocrine Section for low testosterone levels of < 300 ng/ml under the inclusion criteria. The records will be reviewed for exclusion criteria. A member of the staff will then contact potential participants by a letter describing the study and introducing the investigators. Interested patients will be asked to return a postcard. 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.

Individuals who express an interest in participation will undergo a brief (~10 min) telephone interview by a member of the research team. All individuals who express an interest in participating and meet the preliminary inclusion criteria will be invited to visit our facility and discuss their potential participation in greater detail. During a 60 min long orientation session with members of the research team, detailed information will be provided regarding the aims of the study, and all of the tests and measurements that they will undergo if they participate in the study. Verbal and written information about the potential benefits and risks of the study will be provided; their questions will be answered and any concerns that they have will be addressed. If the individual is interested in participating, a screening evaluation will be scheduled. Prior to enrollment and randomization, the volunteers will undergo a detailed medical history and physical examination, and a clinical laboratory testing after a proper consent has been obtained in writing. During this session they will have the nature and purpose of the study explained to them again, discuss their reasons and motivation for participation in the research to determine whether they are realistic and discuss any potential problems, that might interfere with participation and have their questions answered. Informed consent to participate in the study will be obtained in writing by one of the investigators before any tests or measurements are performed. Data which include HIPAA identifiers such as names, date of birth or age, dates of tests and medical record number (first letter of last name plus last 4 digits of social security number) will be collected.

Each subject will be informed that their participation in the study is completely voluntary and they may withdraw by telling the study team that they are no longer interested in participating in the study or they may send in a withdrawal letter. They will also be informed that their choice will not at any time affect the commitment of their health care providers to administer care and that there will be no penalty or loss of benefits to which they are otherwise entitled.

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?
Hard copies of the research data will be maintained at the MEDVAMC building 110, and will be stored in a locked office (room 240) 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

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

No

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-45062

Database location will be on a VA server.

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.

An Accounting of Disclosure (AOD) will be created and maintained for any disclosure of individually identifiable information (III) outside the VA. The electronic spreadsheet will include the participant's name, 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.

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.

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.

## 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.

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:

220

Distribution Plan:

Subjects will be paid $40 at baseline, $20 at 3 months, and $40 at 6 and 12 months. Total payment for completing the study will be $140 per patient. If the subject chooses to participate in the optional microindentation, the subject will receive additional $40 in compensation for each procedure which will be done at baseline and at the end of the study, thus, he will receive a total payment of $220.

## 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 study (see inclusion/exclusion criteria, 2) to monitor blood levels of testosterone, other hormones and biomarkers, 3) to monitor side effects (complete 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 discarde

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?
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.
Participant's 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: TESTOSTERONE

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 is required to evaluate whether testosterone is effective in improving bone quality in men with both type 2 diabetes mellitus and hypogonadism in a double-blind randomized-controlled trial.

Will the research involve a radioactive drug?
No

## Section P: Device Studies

Does this research study involve the use of ANY device?
Yes

Device 1: Oateoprobe

## Section Q: Consent Form(s)

Study on the efficacy of testosterone therapy on bone quality of men with diabetes mellitus and low testosterone

## Section R: Advertisements

### Mode of Advertising: Other: Flyers

Exact language of Advertisement:
MALE VOLUNTEERS NEEDED

This study is looking at the effect of testosterone treatment on the bones of men with diabetes mellitus and low testosterone.

VOLUNTEERS MUST:

Be a Veteran Be age 35-65 Must have diabetes Be able to come for clinic visits Not have osteoporosis Not have prostate cancer Not be on testosterone

Duration: Participation in the study will be 12 months. Test/Procedures: Include phone screening, orientation session, medical examination, strength testing, bone mineral density testing, prostate tests, and simple blood testing. Compensation: Volunteers may receive up to $220.00. For more information please contact Dr. Reina Villareal at 713-791-1414 ext. 24084 or 27534 or Vittoria Russo at ext.23644 H-45062