Testosterone Plus Finasteride Treatment After Spinal Cord Injury

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Abstract

The Institute of Medicine has indicated that short-term, small scale randomized clinical trials (RCTs) should be conducted to establish the efficacy of testosterone replacement therapy (TRT) as a strategy to enhance muscular strength and reduce disability in clinical populations of hypogonadal men. Men with spinal cord injury (SCI) experience a high prevalence of hypogonadism which influences the neural, muscular, skeletal, and body composition deficits that occur after injury. A single *retrospective* analysis has reported that TRT improved motor function in hypogonadal men with incomplete SCI. However, only one small *prospective* (open label) clinical trial has evaluated the safety/efficacy of TRT in men with SCI. This study reported that low-dose TRT improved lower extremity lean mass and reduced risk of sudden cardiac death in men with motor complete SCI, demonstrating that TRT safely improves lean mass even in the absence of voluntary muscle activity. However, body composition was unaltered and bone mineral density (BMD) was not reported in this study likely because these deficits respond only to higher doses of TRT. Despite the potential benefits of TRT, some clinical concern exists regarding the safety of this therapy, with increased hematocrit (which is rarely detrimental), prostate enlargement, and potential cardiovascular risk remaining areas of concern. Interestingly, the 5α-reduction of testosterone to dihydrotestosterone mediates prostate enlargement and may worsen cardiovascular risk, but this conversion is not required for the benefits of TRT. As evidence pharmacologic 5α-reductase inhibition (via finasteride) ablates prostate enlargement in neurologically healthy hypogonadal men receiving TRT, without inhibiting the substantial musculoskeletal and lipolytic benefits of this treatment. However, the safety and efficacy of this novel combination therapy remains to be determined in men with chronic motor incomplete SCI.

For this double-blind placebo-controlled RCT, hypogonadal men >18 years of age with chronic motor incomplete SCI (AIS C/D) who present with ambulatory dysfunction will receive testosterone (125mg/week, i.m.) plus finasteride (5mg/day, p.o.) in FDA approved doses or vehicle/placebo for 12 months. At baseline and 3-6 month intervals, we will assess: BMD and body composition via DXA, thigh muscle cross-sectional area (CSA) via MRI, lower extremity neuromuscular function via dynamometry and muscle activation via twitch interpolation, circulating markers of musculoskeletal and metabolic health and metabolism, and safety measures including prostate health, electrocardiogram (EKG) and cardiovascular symptoms, hematocrit, and other putative health risks associated with TRT. Our primary hypotheses are that TRT plus finasteride will safely 1) regenerate BMD via antiresorptive actions, 2) enhance muscle CSA and improve neuromuscular force production, and 3) improve body composition.

These findings will benefit Veterans with SCI who experience musculoskeletal impairments and may provide the VA with a novel cost-effective therapy able to improve musculoskeletal and metabolic health in this population.

List of Abbreviations

AE – Adverse Events
AIS – ASIA Impairment Scale
BMD – Bone Mineral Density
BRRC – Brain Rehabilitation Research Center
CSA – Cross Sectional Area
CTSI – Clinical and Translational Science Institute
DAV – Disabled American Veterans
DHT – Dihydrotestosterone
DRE – Digital Rectal Exam
DSMP – Data Safety Monitoring Plan
DSMB – Data Safety Monitoring Board
DXA – Dual X-ray Absorptiometry
EKG – Electrocardiogram
EMG – Electromyography
fNIRS – Functional Near Infrared Spectroscopy
HCT – Hematocrit
i.m. – Intramuscular
ISCD – International Society of Clinical Densitometry
KE – Knee Extensors
MRI – Magnetic Resonance Imaging
NF/SG – North Florida/South Georgia
PHI – Protected Health Information
PVA – Paralyzed Veterans of America
RCT – Randomized Clinical Trial
SAE – Serious Adverse Event
SAM – Step Activity Monitor
SCI – Spinal Cord Injury
T – Testosterone
TRT – Testosterone Replacement Therapy
TRUS – Transrectal Ultrasound Sizing
UAP – Unanticipated Problem
UF – University of Florida
VA – Veterans Affairs
VAMC – VA Medical Center
VHS – Veterans Health System

Contents

Protocol Title: 5
1.0 Study Personnel 5
2.0 Introduction 6
3.0 Objectives 9
4.0 Resources and Personnel 9
5.0 Study Procedures 10
5.1 Study Design 11
5.2 Recruitment Methods 17
5.3 Informed Consent Procedures 19
5.4 Inclusion/Exclusion Criteria 19
5.5 Study Evaluations 20
5.6 Data Analysis 25
5.7 Withdrawal of Subjects 26
6.0 Reporting 26
7.0 Privacy and Confidentiality 28
8.0 Communication Plan 28
9.0 References 29

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2.0 Introduction

Relevance to VA: 270,000 individuals currently have a SCI in the US, with an estimated 12,000 new SCIs occurring annually.[2] Of these, 42,000 are eligible for treatment in the VHS,[3] resulting in direct annual medical expenditures exceeding $716 million/year.[4] The average direct/indirect per patient costs associated with the first-year medical treatment of incomplete motor SCIs is $218,000,[5] with subsequent yearly expenditures averaging $21,450 per patient year within the VHS.[4] These costs are exacerbated by the myriad of functional and physiologic deficits that occur following SCI, of which reduced lower limb musculoskeletal integrity, impaired neuromuscular force production, and elevated visceral adiposity are hallmark characteristics.[6] Importantly, these maladaptive changes represent fundamental impediments to rehabilitation strategies intended to restore musculoskeletal and metabolic health after SCI.[7]

Musculoskeletal Deficits after SCI: Neurologic impairment and reduced sublesional load-bearing are the primary factors underlying the musculoskeletal deficits after SCI.[6] These impairments produce a progressive 30-40% reduction in lower limb muscle CSA[2] and impaired voluntary muscle activation[8] that combine to worsen neuromuscular force production and locomotor ability.[8-10] In this regard, the preservation and/or restoration of lower limb muscle strength/power is recognized as an important predictor of ambulatory recovery after motor incomplete SCI.[10, 11] A progressive 50-60% loss of cancellous bone also occurs in the first 2-3 years after SCI and cortical bone loss persists for >10 years.[12] These maladaptive responses result from elevated bone resorption and reduced bone formation,[13] which contribute to the 20- to 100-fold greater fracture risk in those with SCI compared with healthy age-matched individuals.[14] Importantly, each 0.1gm/cm^2 BMD decrement at the femoral neck increases fracture risk by 2.2 times,[15] indicating that even small alterations in BMD strongly influence fracture risk within this population.

Metabolic Consequences of SCI: SCI causes a plethora of metabolic consequences that increase risk for metabolic syndrome,[16, 17] diabetes,[18] and premature cardiovascular disease.[17] Nearly all metabolic syndrome risk factors (i.e., elevated visceral adiposity, high fasting blood glucose, insulin resistance, elevated triglycerides, low HDL cholesterol, and high blood pressure) are exacerbated by SCI.[17] For example, diabetes prevalence is 3 times higher in Veterans with SCI compared to the general population.[18] The pathophysiology underlying these deleterious metabolic consequences is influenced by the reduced energy expenditure and the extensive muscle loss that occur after SCI,[2] because muscle is the largest reservoir of metabolically active tissue and the primary site of postprandial glucose disposal.[19] As evidence, physical rehabilitation strategies that increase energy expenditure[20] or improve muscle mass[21] result in reduced fasting glucose and improved insulin sensitivity in men with SCI. In addition, hypogonadism is a secondary metabolic consequence that occurs in ~40-60% of men with chronic motor incomplete SCI [ASIA Impairment Scale (AIS) C/D].[22, 23] In particular, the median serum T concentration was 220ng/dL (standard reference range 241-827ng/dL) in a large cohort of men whose duration of SCI was upwards of 14 years, with >50% of men with incomplete SCI exhibiting low T;[23] demonstrating the prevalence of hypogonadism after SCI is much higher than the general population.

Testosterone Replacement Therapy (TRT): In neurologically healthy men, low T is associated with reduced BMD[24] and muscle mass,[25] elevated visceral adiposity, increased metabolic syndrome risk[26] [i.e., elevated fasting glucose, insulin, and hemoglobin (Hb)A1c values],[27] and

sexual dysfunction.[28] TRT is commonly prescribed to hypogonadal men[29] because it is the sole FDA-approved agent able to increase BMD and muscle mass and reduce adiposity, and because it improves sexual function in men with low T.[28] However, inconsistency exists in the literature regarding the efficacy of TRT, with some studies reporting only slight musculoskeletal benefit[24, 25] and others reporting more substantial effects;[30] likely because studies utilize a wide range of TRT doses [up to the FDA-approved maximum (200mg/week, i.m.)]. As evidence, meta-analyses indicate more substantial musculoskeletal benefit from higher doses of long-acting T esters (i.e., ≥100mg/week, i.m.)[24, 25] because these formulations produce higher peak T concentrations. In contrast, transdermal patch/gel TRT formulations produce low- or mid-range T values that result in only minor myotrophic[25] effect and no BMD improvement.[24] Similarly, higher dose TRT is required for reductions in visceral adiposity[30] and perhaps for improvements in other metabolic syndrome markers.[31] In this regard, a lesser known effect of T is regulation of glycometabolic control, evidenced by the ability of TRT to reduce insulin resistance and lower blood glucose in men with abdominal obesity[32] and improve several metabolic syndrome risk factors (i.e., insulin sensitivity, fasting glucose, HbA1c, triglycerides, and C-reactive protein) in men with type II diabetes.[33]

TRT After SCI: Members of our research team were the first to report that TRT ameliorates muscle loss in rodents after SCI,[34] results that have been verified by others.[35] Specifically, spinal cord transection reduced hindlimb muscle fiber size by 49% and the percentage of slow fibers in the soleus by >80%. In comparison, animals receiving TRT exhibited a 58% larger fiber size and a 152% increase in the percentage of slow fibers in the soleus,[34] demonstrating T produces robust myotrophic effects in the complete absence of neural input. We have expanded on these findings by demonstrating TRT dose-dependently improves bone and muscle mass in rats receiving severe contusion SCI, with high-dose TRT fully preventing bone loss and partially alleviating muscle loss; while low-dose TRT produced much less profound benefit[36]. Our group[36] and others[37] have also reported that androgens partially restore hindlimb locomotor function after contusion SCI, with animals receiving high-dose TRT exhibiting greater functional improvement than those administered low-dose TRT or placebo.[36] In 2008, Clark et al., published a retrospective analysis reporting that high-dose TRT improved motor function in men with incomplete SCI (AIS C/D), while those with motor complete SCI obtained no functional benefit.[1] The mechanisms through which TRT improved motor function were not examined, but likely involved elevated muscle mass and/or enhanced voluntary muscle activation (which are both impaired after incomplete SCI)[8, 9] and likely occurred via direct androgen-mediated neuroprotection[38] of spinal motor neurons,[39] as observed in rodent SCI models[35] and other nerve injury models.[40-42] Despite this promising evidence, no prospective RCT has examined whether T enhances muscle function in men with motor incomplete SCI.

In 2011, Bauman et al., published findings from a small prospective trial indicating men with motor complete SCI exhibited improved lean body mass and energy expenditure[43] and reduced sudden cardiac death risk due to arrhythmia after 12 months TRT,[44] with no serious (S)AEs reported. Interestingly, relative improvements in lean mass were consistent in all body compartments above (e.g., arm) and below the level of lesion (e.g., leg),[43] providing direct evidence that TRT enhances lean mass even in the absence of voluntary muscle activity (similar to our preclinical findings).[34] While these preliminary results are promising, Bauman et al., administered low-dose transdermal TRT that only slightly elevated circulating T and failed to reduce adiposity.[43] Not surprising, given that higher dose TRT is required for fat loss[30] and bone accretion.[24, 25] Additionally, other measures of metabolic health, such as fasting glucose and insulin sensitivity were not reported. To-date, the above mentioned studies remain the sole analyses evaluating the efficacy of TRT after SCI. As such, prospective RCTs are required to verify whether TRT improves musculoskeletal and metabolic health in this population.

TRT Health Risks: Meta-analyses have confirmed three health risks resulting from TRT: 1) elevated HCT, 2) increased prostate-related AEs[45], and 3) increased cardiovascular-related risk. In most cases, the HCT increase is not detrimental and may benefit some individuals because anemia is common in men with low T[46] and men with SCI.[47] However, a small proportion of men receiving TRT exhibit polycythemia (HCT >54%),[45] which is completely reversible upon discontinuation of TRT. In contrast, the higher incidence of prostate-related AEs produces more serious clinical concern because most men receiving TRT exhibit progressive prostate enlargement,[48] which is suspected of being related to prostate cancer development.[49] However, meta-analyses indicate that TRT does not increase prostate cancer risk nor Gleason grade of prostate cancer (even in men with a history of prostate cancer),[49] suggesting that TRT induces trophic (but not neoplastic) effects on the prostate. Additionally, a higher incidence of cardiovascular-related AEs raises clinical concern for those on TRT.[50] Although, the extent of cardiovascular risk is unknown because conflicting evidence exists in the literature, with several meta-analyses reporting TRT does not increase cardiovascular AEs in elderly men[45, 51, 52] or in heart failure patients,[53] while a recent retrospective analysis reports adverse health outcomes after TRT in Veterans with pre-existing cardiovascular co-morbidities.[54] In contrast, data from a recent meta-analysis[55] and separate retrospective analyses[56] indicate men with low T who are *not receiving* TRT exhibit heightened cardiovascular risk and increased all-cause mortality. In this regard, hypogonadal men with SCI exhibit pathologic cardiac adaptations when compared to eugonadal men with SCI,[57] and TRT has been shown to reduce sudden cardiac death risk after SCI by normalizing cardiac electrophysiology.[44] Regardless, prostate-[58] and cardiovascular-related[56] AEs remain a clinical concern that should be evaluated when administering TRT. Other putative (unproven) risks of TRT include fluid retention (edema), gynecomastia, breast tenderness, elevated liver enzymes, injection site irritation, emotional lability, worsening of untreated sleep apnea, and decreased spermatogenesis;[58] although, the incidence of these putative health risks are quite low and none have been confirmed by meta-analysis.[45]

5α-reductase and Prostate Enlargement: The localized intraprostatic 5α-reduction of T to DHT[59] worsens prostate enlargement[45] and prostate cancer development[60] because DHT is a more potent and longer acting androgen than T.[59] In contrast, pharmacologic 5α-reductase inhibitors prevent prostate enlargement resulting from endogenous T[59] and from TRT[61-63], and are known to reduce prostate cancer risk by >25%.[60] Interestingly, the conversion of T to DHT is not required for the musculoskeletal or lipolytic benefits of androgens[19-21] because bone, muscle, and fat only mildly express 5α-reductase.[59] As evidence, high-dose TRT increases prostate mass in orchiectomized rodents by >50% (resulting from elevated intraprostatic DHT), while co-administration of a rodent 5α-reductase inhibitor prevents prostate growth without inhibiting the musculoskeletal or lipolytic benefits of TRT.[64] Finasteride also blocks prostate enlargement resulting from TRT (in elderly hypogonadal men) without altering the beneficial effects of this therapy on bone, muscle, or adiposity,[61, 62, 65] demonstrating that 5α-reductase inhibitors prevent a prominent health risk resulting from TRT (i.e., prostate enlargement) without reducing the overwhelming benefits of this treatment. This provides rationale for the prophylactic use of finasteride as a safety measure when administering TRT.[63] However, several (infrequent and reversible) side-effects may also result from finasteride, the most prevalent of which is sexual dysfunction (i.e., decreased libido, erectile dysfunction, and ejaculation disorder) that occurs in <5% of men on long-term finasteride treatment.[60] Thus, TRT plus finasteride appears to be a promising means of safely improving musculoskeletal and metabolic health; although the safety and efficacy of this novel combination pharmacologic therapy requires verification prior to clinical implementation in the SCI population.

3.0 Objectives

The purpose of this study is to determine whether TRT plus finasteride will safely improve musculoskeletal health, neuromuscular function, body composition, and metabolic health in men with incomplete SCI. We will conduct a double-blind, placebo-controlled RCT in which hypogonadal men >18 years old with ambulatory dysfunction subsequent to chronic motor incomplete SCI will receive TRT (125mg/week T-enanthate, i.m.) plus finasteride (5mg/day, p.o.) in FDA-approved doses vs. vehicle/placebo for 12 months. This proposal addresses the following three Specific Aims:

AIM 1: Evaluate the effects of 12 months of TRT plus finasteride on bone mineral characteristics and bone turnover in hypogonadal male men with motor incomplete SCI.

Hypothesis 1: **TRT plus finasteride will improve BMD via antiresorptive actions in this population.** The primary outcome will be hip BMD [measured via dual x-ray absorptiometry (DXA)]. Secondary outcomes will be serum markers of bone metabolism.

AIM 2: Determine the effects of TRT plus finasteride on the recovery of muscle integrity and neuromuscular force production in hypogonadal men with motor incomplete SCI.

Hypothesis 2: **TRT plus finasteride will enhance muscle CSA and improve neuromuscular force production in this population.** The primary outcomes will be thigh muscle CSA [via 3D-magnetic resonance imaging (MRI)] and KE torque (via dynamometry). A secondary outcome will be KE voluntary muscle activation.

AIM 3: Examine the effects of TRT plus finasteride on body composition and the pathophysiology underlying metabolic syndrome in men with motor incomplete SCI.

Hypothesis 3: **TRT plus finasteride will improve body composition and risk factors associated with metabolic syndrome.** Primary outcomes will be total body and visceral fat mass (via DXA). Secondary outcomes will be metabolic syndrome risk factors (fasting glucose, hemoglobin A1c, insulin resistance, serum lipids, and blood pressure).

4.0 Resources and Personnel

Recruitment will be handled cooperatively through the NF/SG VHS, James A. Haley VAMC (Tampa, FL), and the University of Florida (UF) Clinical and Translational Science Institute (CTSI). All testing will be conducted at the NF/SG VHS. MRI may also be conducted by trained medical staff at our academic affiliate, University of Florida (UF). The following individuals or VA Services will be involved in data collection:

- Joshua Yarrow, PhD (Study PI, NF/SG VHS) is the Local Site Investigator at NF/SG VHS and will have access to participant protected health information (PHI) and has the responsibilities for all supervisory and regulatory aspects of the study, study management, participant recruitment, screening and consenting, administering survey/interview procedures, performing functional assessments and evaluation of physical function on participants, and data analysis.
- Larissa Nichols, BSN, RN (Study Nurse, NF/SG VHS) will have access to participant PHI and will assist in daily operations of the study and be responsible for CPRS records screening and creation, participant recruitment, screening, and consenting, blood

acquisition, training participants on drug administration, performing health assessments, administering survey/interview procedures, performing functional assessments and evaluation of physical function on participants.

- Dana Otzel, PhD (Research Investigator, NF/SG VHS) will have access to participant PHI and will assist in daily operations of the study and be responsible for CPRS records screening and creation, participant recruitment, screening, and consenting, performing health assessments, administering survey/interview procedures, performing functional assessment, evaluating physical function, knee extensor muscle function, and knee extensor voluntary activation of study participants, and data analysis.
- Kevin White, MD (Chief – Spinal Cord Injury, James A. Haley VAMC) is the Local Site Investigator at James A. Haley VAMC (Tampa, FL) and the Medical Director for this study and will have access to participant PHI. He has the responsibilities of ensuring the safety of all participants and may perform health/safety evaluations of participants if adverse events occur. Dr. White (in conjunction with the Study Physician or other Physicians) will determine participant withdrawal based on established study criteria.
- Robert Sammel, MD (Chief – Spinal Cord Injury Primary Care, NF/SG VHS) will have access to participant PHI and has the responsibility of evaluating the overall health and physical function of study participants.
- Charles Plumlee, MD (Physical Medicine & Rehabilitation (PMR), NF/SG VHS) will have access to participant PHI and has the responsibility of evaluating the overall health and physical function of study participants, for writing prescriptions for study drugs, and may oversee PMR related assessments.
- Anita Wokhlu, MD (Noninvasive Cardiologist, NF/SG VHS) and Cardiology Service (NF/SG VHS) will have access to participant PHI and has the responsibility of evaluating the cardiovascular health of study participants and interpreting cardiovascular-related testing procedures.
- David Clark, PhD (Research Health Scientist, NF/SG VHS) will have access to participant PHI and has the responsibility of evaluating and interpreting physical function, knee extensor muscle function, and knee extensor voluntary muscle activation of study participants.
- Charles Levy, MD (Chief – Physical Medicine & Rehabilitation (PMR), NF/SG VHS) will have access to participant PHI and has the responsibility of writing prescriptions for study drugs and may oversee PMR related assessments.

In addition, Nuclear Medicine Service and Radiology Service (NF/SG VHS) will conduct MRI and DXA scans, respectively, Urology Service (NF/SG VHS) will conduct prostate digital rectal exams (DRE), transrectal ultrasound sizing (TRUS) of the prostate, and prostate biopsy (if required), and Cardiology (NF/SG VHS), will perform EKG. Trained medical staff at UF, our academic affiliate, may also perform MRI.

Statistical analyses will be performed by the University of Florida, Center for Translational Science Institute (CTSI). Preliminary analyses will be performed during years 2 and 3 and the final statistical analysis will be performed during year 4. All data provided for statistical analysis will be coded.

5.0 Study Procedures

5.1 Study Design

Experimental Design
There are four phases to this study: recruiting/screening, testing, treatment, and follow-up. All interventions in this study are for research purposes and none represent standard of care. A brief study overview is included below and an in-depth description of each phase follows.

Study Overview: For this double-blind, placebo-controlled RCT we will recruit men >18 years of age who have experienced a chronic motor incomplete SCI (AIS C/D) between C2-L3 with upper motor neuron signs. Individuals will undergo comprehensive screening and safety assessments to determine eligibility. Men with low serum T (≤325 ng/dL) or low bioavailable T (≤70 ng/dL) and locomotor dysfunction will qualify. Those qualifying (n=30) will be stratified by walking speed to ensure an equal number of persons with a low- and high-level of ambulatory dysfunction are present in each group. Participants (n=15/group) will then be randomized into one of two groups: 1) T-enanthate (125mg/week, i.m.) + finasteride (5mg/day, p.o.) or 2) vehicle (sesame oil, i.m.) plus placebo (p.o.) for 12 months. Prior to beginning the study treatment participants will also undergo testing. Primary outcomes will be hip BMD, thigh muscle CSA, KE torque, and body composition. Secondary outcomes include circulating markers of musculoskeletal and metabolic health, KE voluntary muscle activation, and metabolic risk. 10m walk tests will be performed and blood will be acquired at 1, 2, and 3 months of treatment and at 3 month intervals thereafter and other safety assessments and outcomes testing will be repeated at 3 or 6 month intervals throughout the intervention. The study treatment will be discontinued after 12 months.

Recruitment/Screening: Participants will be recruited from the NF/SG VHS or the James A. Haley VA Medical Center (Tampa, FL), from Paralyzed Veterans of America (PVA), Disabled American Veterans (DAV), Veterans of Foreign Wars (VFW), American Legion Posts, or other Veteran-centric offices or centers located in Florida/Georgia, from local area long-term care centers, rehabilitation centers, or hospitals (e.g., UF Health, the Center for Independent Living of North Central Florida, Brooks Rehabilitation, or others), from other VA hospitals and outpatient clinics throughout Florida/Georgia, or from an existing University of Florida IRB-approved SCI registry of individuals who have agreed to be contacted to query their interest in participating in research studies [access provided by the VA-funded Brain Rehabilitation Research Center (BRRC) Center of Excellence]. We may travel to these locations or phone these locations to engage staff in a brief conversation to explain the study and ensure they will allow placement of VA CIRB approved flyer in their offices. Staff at locations other than NF/SG VHS or Tampa VAMC will not be engaged in participant recruitment or any other aspect of the research. We may also recruit via advertisements in magazines, newspapers, newsletters or other print media and via the websites and email listservs of these print media outlets, on the UF Health Study Listings website (https://ufhealth.org/research-studies-clinical-trials), through the ResearchMatch.org national recruitment database, through posts to the Facebook pages of the NF/SG VHS or the James A. Haley VA Medical Center, through posts to individual Facebook pages or groups that have a veteran or SCI support focus, through advertisements placed on Facebook, or via http://www.clinicaltrials.gov. A separate document outlines our Facebook advertising strategy, including monitoring of Facebook pages and advertisements.

Prescreening: We will prescreen individuals who are interested in participating to determine if they meet criteria to enroll. During the prescreening we will query individuals about their complete medical history and previous six months use of physician prescribed and over-the-counter medications (via phone or in-person) and we will conduct a review of their CPRS medical records (if applicable) to determine if they meet prescreening criteria. If individuals meet prescreening criteria we will obtain informed consent and HIPAA authorization and participants will undergo additional hands-on screening to determine eligibility. We have requested a waiver of informed consent and a waiver of HIPAA authorization (for recruitment and screening purposes) that will ensure that we are able to screen individuals with a high likelihood of qualifying for our study and that we are not placing an undue burden on individuals who may not qualify due to past medical diagnoses that can easily be identified through health history and CPRS reviews. An in-depth description of the prescreening process is included in Sections 5.5 of this document. The prescreening is being done solely for the purposes of research and will take approximately 1 hour to complete.

Screening: Informed consent and HIPAA authorization will be obtained from individuals who meet prescreening criteria and decide to enroll. These participants will undergo additional hands-on screening at the NF/SG VHS to determine whether they qualify. Study Inclusionary/Exclusionary Criteria are explained in-depth in Section 5.4 of this document. If individuals do not meet criteria, they will be considered screen-failures. Individuals qualify they will be invited to participate in the study. The screening is being done solely for the purposes of research and will take approximately 1-2 days to complete.

Testing: Individuals who qualify and decide to participate will undergo testing that is being done solely for the purposes of research. All testing will be performed at the NF/SG VHS. Testing will occur at baseline (before beginning the study treatment) and at 3-6 month intervals thereafter, until completion of the study treatment. Tests will take 1-2 days to complete. Participants will be allowed a 1 month window surrounding the scheduled testing dates to ensure completion of all testing procedures. Tests that are completed during Screening will not be repeated at baseline. A detailed explanation of all testing is included in Section 5.5 of this document.

Treatment: The Study Pharmacist will randomize participants using RanPro® (Applied Logic Associates, Houston, TX) or another similar program into one of the two following treatment groups, with equal allotment (n=15) per group:

- Placebo injection plus placebo tablet for 12 months
- Testosterone injection plus finasteride tablet for 12 months

Study drugs will be administered in FDA approved doses. T-enanthate (125mg/week Delatestryl®) will be administered via i.m. injection into the thigh or buttock because this is the preferred method of administration according to VA formulary. Finasteride (5mg/day Proscar®) will be administered orally according to VA formulary guidelines. T-enanthate will be purchased commercially through the Research Pharmacy at the NF/SG VHS. Matching vehicle (1ml sterile sesame oil/week, i.m.) and placebo (5mg/day pill, p.o.) will be manufactured by an FDA-regulated compounding pharmacy. Finasteride will also be purchased through the above mentioned compounding pharmacy or may be purchased by the VA Research Pharmacy. Medications will be distributed in identical packaging to ensure double blinding is maintained to the Research Nurse for initial administration. In order to reduce travel burden, participants have the option to self-administer the injections and prescription refills may be mailed to participants (both standard VA practices). The Study Nurse will instruct each participant on proper drug administration and

will reinforce procedures via weekly telephone calls to verify that they have administered the drug. Alternatively, the participant can choose to have the Study Nurse administer the once weekly injection which will require travel to the NF/SG VHS. All procedures for the matching vehicle/placebo will be handled in an identical manner. Importantly, i.m. T-enanthate is a common TRT formulary in the VHS and routine clinical practice includes i.m. self-injection. We will also measure the volume of remaining study medications at regular intervals (3 month or less) to evaluate participant adherence. Drug administration is expected to take about 10 minutes per week. The study treatment is being done solely for research purposes and will last 12 months. During the study treatment, the participants will also be asked to undergo regularly scheduled testing that is discussed in detail in Section 5.5 of this document.

Study Completion and Follow-up: At the completion of the intervention the study treatment will be discontinued. We will follow-up with participants monthly (via phone call) and perform a monthly review of their medical records for 3 months to assess potential AEs after study discontinuation. In addition, we will reassess blood values, perform physical exam, and EKG at 6 months following study completion to ensure participant safety. A detailed description of what blood markers will be assessed is included in Section 5.5. Participants will be referred to their Primary Care Provider if AEs appear after study completion. The phone call should take about 10 minutes. The phone call and medical records check are done solely for the purposes of research.

Some participants may report a transient depression of mood following TRT cessation because reduced circulating T occurs after TRT discontinuation. If this occurs, participants have the option of tapering to a lower dose of T (125mg T-enanthate *biweekly*, i.m.) for 4 weeks (administered through the VA Research Pharmacy). This should assist in alleviating symptoms.

Minimization of Risk

We have assembled a strong and experienced Research Team with multidisciplinary backgrounds to ensure participant safety and minimize risk throughout this intervention. The Research Team includes an SCI Physician, Cardiologist, Physical Medicine and Rehabilitation Physician, Research Pharmacist, Exercise Physiologist, and several PhD level Researchers with clinical trial experience. Each member of the Research Team will be focused on monitoring participant safety and minimizing risk throughout the intervention. Specific procedures and monitoring activities are addressed below.

Informed Consent: The PI, Study Nurse, or another member of the research team will obtain a signed informed consent document from all participants prior to study enrollment. A complete description of the study, eligibility criteria, the potential risks and benefits, expected time involvement, and the importance of the knowledge to be gained will be discussed with the participants. An in-depth description of the informed consent process is included in Section 5.3 of this document.

General and Cardiovascular Exclusionary Criteria: We have developed stringent Exclusionary Criteria to ensure participant safety and minimize risk. An in-depth description of the General Exclusionary Criteria and Cardiovascular Exclusionary Criteria are included in Section 5.4 of this document.

Baseline Safety Screening: Individuals who give informed consent will undergo a comprehensive Safety Screening to determine if they qualify. This safety screening is addressed in detail in Section 5.5 of this document.

Follow-up Safety Assessments: Participants will have their blood drawn monthly for the first three months of treatment and at 3 month intervals thereafter to evaluate serum markers of health and will also undergo comprehensive Safety Screenings at 3 or 6 month intervals throughout the study. These safety assessment are identical to that performed at baseline and are outlined in Section 5.5 of this document. In addition, the Study Nurse or another member of the study team will phone participants on a weekly basis to determine their general health / well-being and will perform a monthly formal medical records review to assess for potential AEs. Patients will be interviewed regarding the cardiovascular symptoms of chest pain, edema, palpitations, and dyspnea and other health related issues. To ensure participant safety we have also developed study removal criteria that are addressed in Section 5.7 of this document.

Titration of Testosterone Dose: The dose of T-enanthate will be evaluated monthly for the first three months of treatment and at three month intervals thereafter. The prescribed testosterone dose will be continued if the nadir serum testosterone concentration (assessed one week following injection) remains below the normal upper limit for the VA Clinical Laboratory (869 ng/dL). If the nadir serum testosterone concentration exceeds the normal upper limit, the serum testosterone value will be reevaluated to ensure accuracy of the test. If the reevaluated nadir value remains higher than the normal upper limit, the weekly T-enanthate dose will be reduced by 25 mg/week and nadir serum testosterone value will be reevaluated. At reevaluation, if nadir serum testosterone remains higher than the normal upper limit, the dose of testosterone will be reduced by another 25 mg/week. This titration pattern will continue until nadir serum testosterone is below the normal upper limit. In contrast, if nadir serum testosterone is <400 ng/dL the dose of T-enanthate will be increased by 25 mg/week and nadir serum testosterone will be reevaluated in the manner described above. However, at no point will administered T-enanthate exceed 125 mg/week.

Data Safety Monitoring Plan (DSMP): We have established a comprehensive DSMP that abides to VA RR&D guidelines to ensure participant safety. The Study Nurse or another member of the study team will compile AE incidence and all AEs will be immediately reported to the Study Medical Director and/or Study Physician. If SAEs or deaths occur, they will be immediately reported to the independent DSMB, IRB, and VA RR&D. Other less serious AEs will be compiled and reported at semi-annual intervals to the DSMB, IRB, and VA RR&D. The independent DSMB will consist of one Physician / Subject Matter Expert, one Biostatistician, and one Cardiologist (none of whom are involved in the study). The DSMB will meet at 3-6 month intervals during the first year and semi-annually thereafter, and a charter will be developed prior to beginning participant accrual. DSMB meetings will have two parts: open and closed. In the open meetings, the safety reports will be presented by the PI / Co-Is and discussed. After, the PI / Co-Is will be excused, and the DSMB will write its recommendation, which may include: Continue, Continue with Modifications, or Discontinue the Study. Minutes will be provided after each meeting. Additionally, a list of participant demographics, outcome measures collected, missing data, and participant adherence will be compiled and the total number of participants screened, enrolled, active (and duration of participation), withdrawn, and completed will be reported semi-annually to ensure enrollment proceeds as planned. The DSMB may recommend study discontinuation if a disproportionate number of SAEs occur in one group.

Specific Risks and Risk Aversion Plan

Specific procedures that we will incorporate to minimize risk associated with the interventions and testing involved in this study are described below.

Blood Acquisition: The risks of drawing blood from a vein include discomfort at the site of puncture, possible bruising and swelling around the puncture site, rarely an infection, and uncommonly

faintness from the procedure. The Study Nurse or a phlebotomist will draw blood to minimize risk. We may provide the participant with ice if bruising or swelling occur. The participant will be referred to the Study Physician in the rare instance that an infection occurs at the puncture site.

Functional Assessments: The risks associated with muscle strength testing, assessments of voluntary muscle activation, walking speed assessments, and other assessments of physical function include muscle soreness and rarely musculoskeletal injury. Functional near infrared spectroscopy (fNIRS) sensors may be taped or strapped to the participants' head during walking speed assessments. These fNIRS sensors use harmless infrared light to estimate changes in hemoglobin concentration and pose no risk to the participant. An exercise specialist who is trained in conducting exercise tests will perform the muscle function tests to minimize risk. We may provide the participant with ice if muscle pain occurs. The participant may be referred to the Study Physician in the rare instance that a musculoskeletal injury occurs.

DXA: The risks associated with DXA scan include exposure to ionizing radiation. Radiation exposure in this study is thought to be minor. However, the effects of radiation add up over the life span. Repeated exposures may increase risk of injury or disease. Examples would include x-rays taken for a broken bone or radiation therapy treatments for cancer. The radiation exposure from each scan varies from 0.2 to 1 millirem. For comparison, this exposure is equivalent to 1 day of radiation exposure that people in the United States receive from natural background. The risk from radiation exposure of this magnitude is too small to measure directly and is considered to be low when compared with everyday risks. To minimize risk, all DXA testing will be conducted according to normal clinical guidelines under the supervision of VA Radiology Service. The participant will be monitored during all DXA scans in case any problems occur. We will provide the participant with the contact information for the Radiation Safety Officer at NF/SG VA Medical Center if they would like more information about radiation exposure.

MRI: MRI exposes the participant to a strong magnetic field and radio waves for imaging. There are no harmful side-effects associated with temporary exposure to the strong magnetic field used by MRI scanners. Because MRI acts like a large magnet, it could move iron-containing objects in the MRI room, which could in the process possibly harm the participant. Additionally, there is minor risk of claustrophobia and for hearing loss resulting from MRI noise. To minimize risk, all MRI will be performed according to normal clinical guidelines under the supervision of VA Nuclear Medicine Service or trained medical staff at UF, our academic affiliate. Standard precautions are in place to ensure loose metal objects are not allowed in the MRI room. Participants with metal in their body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, will only be allowed in the MRI room if they pass screening by Nuclear Medicine, which is standard of care. If MRI screening is not passed, participants cannot have an MRI. MRI will not be conducted on individuals with severe claustrophobia. Individuals may be asked to wear earplugs to reduce the minor possibility of hearing loss during MRI.

Prostate Exams: The risks associated with prostate DRE and prostate TRUS are relatively minor and include occasional bleeding from the rectum, especially if hemorrhoids or anal fissures are present. In rare cases, the individual may feel lightheaded and faint. This feeling is called vasovagal syncope and is caused by fear or pain when the doctor inserts his finger into the rectum. Trained medical staff from VA Urology Service will perform the prostate exam to minimize risk. If a prostate nodule/induration (bump) is found, the participant will be referred for a prostate biopsy to check for prostate cancer, which is the standard of care. The participant can refuse to have a prostate biopsy, but will not be allowed to continue in the study if the biopsy is refused. The participant will be referred to VA Urology Service to discuss treatment

options if prostate cancer is found. The participant will be allowed to continue in the study if prostate cancer is not detected.

Study Treatment: Side effects observed in patients receiving TRT include increased hematocrit, increased blood prostate specific antigen (PSA), prostate growth, headache, increased blood pressure, acne, breast enlargement, breast tenderness, baldness, leg swelling, elevated liver enzymes, worsening of sleep apnea, decreased sperm count, thromboembolic events, peliosis hepatitis, hepatic neoplasms, and worsening of congestive heart failure. Rare side effects include pain or swelling at the injection site in the muscle, painful prolonged erection, stroke, or heart attack. There is no evidence that TRT increases prostate cancer or other cancer risk. However, it remains possible that TRT may stimulate undiagnosed prostate cancer risk. Some subjects may experience transient depression of mood following cessation of TRT. Other unknown side-effects may result from TRT.

There are relatively uncommon risks associated with finasteride, including: impotence, decreased libido, reduced volume of ejaculation, ejaculation disorder, gynecomastia, breast tenderness, breast cancer, and rash. Other unknown side-effects may result from finasteride treatment.

The risks associated with co-administration of TRT and finasteride include those listed above. However, studies have reported fewer prostate-related side effects when combining TRT and finasteride.[61-63]

All drugs have the potential to cause allergic reactions. Allergic reactions may be mild to severe, and include the following symptoms: skin rash, itching, difficulty breathing, severe low blood pressure, and even death.

To minimize risk we will administer TRT and finasteride in FDA approved doses, according to VA formulary, and in accordance with the Endocrine Society Clinical Practice Guidelines for Testosterone Therapy in Adult Men.[58] We will also titrate the T-enanthate dose to ensure the nadir serum testosterone does not exceed the normal upper limit. The specific titration pattern for T-enanthate is outlined above in the Section titled “Titration of Testosterone Dose”. Study drugs will be dispensed by the Research Pharmacy at the NF/SG VHS to the Study Nurse who will train participants on proper drug administration procedures. Participants will have the choice of self-administering weekly TRT injections or having the Study Nurse administer injections. All participants will be contacted weekly to ensure compliance with the study protocol, to reinforce proper drug administration procedures, and to evaluate participant health. During the study, participants will receive physical exams, blood tests, and other medical tests to check their prostate, heart, and overall health. A description of all study exams is included in Section 5.5 of this document. Participants will also complete questionnaires that are specific to sexual function. Participants will be removed if they develop side effects that are considered severe or if the Study Physician feels it is within their best interest. Specific withdrawal criteria are discussed in Section 5.7 of this document.

Data Security: As part of this study, medical/health information and blood samples will be collected and stored. There is a slight risk that health information could be revealed inappropriately or accidentally. Depending on the nature of the information, such a release could upset or embarrass you, or possibly affect your insurability or employability. The PI and his staff will be responsible for ensuring that health information and blood samples are protected and that medical information is kept confidential. Only persons involved with this study will have access to your information. Any personally identifiable information will be stored in locked filing cabinets in locked offices or on computer servers with secure passwords, or encrypted electronic storage

devices behind the VA firewall. Blood samples will be linked to a specific participant by a code number rather than a direct identifier to ensure that personally identifiable information is protected. The code will be maintained by the Study Coordinator and/or the Research Pharmacist who are the only study personnel that will have direct access to the code. The code will be maintained by the Study Coordinator and/or Research Pharmacist who are the only study personnel that will have direct access to the code. Access to research study data will be removed for study personnel when they are no longer part of the research team. The ISO and Privacy Officer will be notified within one hour of any improper disclosure.

Financial Risk: Participants will be required to travel to the NF/SG VHS and may be required to take time of work to take part in this study. There will be no cost to participants in this study, for specimen collection, or for storage of specimens. Participants will be reimbursed for gas or another form of travel to offset costs of attending the screening, baseline, 1 month, 2 month, 3 month, 6 month, 9 month, 12 month, and 18 month testing sessions and will receive compensation for their time involvement in these testing sessions. The specific compensation plan is discussed in Section 5.2 of this document. Any overnight stay that is required for these testing sessions will be provided at no cost.

Other Risk: This study may include risks that are unknown at this time.

Potential Benefits
Participants may benefit directly from this study by learning additional information about their musculoskeletal, metabolic, cardiovascular, and prostate health, body composition, and general health. This information would be obtained through physical exams, blood draws, DXA and MRI scans, evaluations of muscle function, EKG, and prostate exams. The participant may also benefit directly by improving musculoskeletal and metabolic health, which may reduce the risk of future bone fracture or other musculoskeletal related health conditions or may reduce metabolic syndrome risk.

The findings of this research study may benefit Veterans and non-veterans with SCI who are not involved in the study. Specifically, persons with SCI who exhibit low BMD, low muscle mass, or elevated visceral adiposity may benefit from this research because it is intended to delineate the safety/efficacy of a combination pharmacologic therapy intended to improve musculoskeletal and metabolic health.

The VHS and Department of Veterans Affairs may benefit from this study because it is intended to evaluate a cost-effective means of improving BMD, muscle mass, physical function, and body composition. If successful, the strategy evaluated in this study could be implemented to safely improve musculoskeletal and metabolic health in Veterans with SCI.

The PI, his staff, and the Department of Veterans Affairs may benefit if the results of this study are presented at scientific meetings or in scientific journals because presenting research helps the career of a scientist and the reputation of an institution.

Risk/Benefit Analysis
The risks associated with this study occur infrequently and are relatively minor. As such, the benefits of this intervention outweigh the potential risks.

5.2 Recruitment Methods

Recruitment

Recruitment will be handled cooperatively through the NF/SG VHS, the James A. Haley VAMC (Tampa, FL), and the UF CTSI. We will prescreen up to 500 individuals. Of these, we will enroll up to 200 participants in order to find 30 participants who qualify. Prescreening and enrollment will be completed once we have identified 30 participants who qualify. Participants who qualify will be randomized into two groups (n=15/group). Participants will be recruited beginning at the initiation of funding (following development of the DSMB Charter) and continuing until recruitment is completed. Participants will be recruited by physician referral, verbally (in person) in the above hospitals, by flyers posted in the above hospitals, or by direct mailings to potentially eligible individuals seen in the above hospitals. In addition, we will recruit individuals through PVA, DAV, VFW, and America Legion Posts, other Veteran-centric offices or centers located in Florida/Georgia, local area long-term care centers, rehabilitation centers, or hospitals, and from other VA hospitals and outpatient clinics located in Florida and Georgia through flyers posted in these offices and through use of a University of Florida IRB-approved SCI registry that lists individuals who have agreed to be contacted to query their interest in participating in research studies. The referring physician from NF/SG VHS or James A. Haley VAMC will instruct potential participants to contact the PI or his staff directly via phone or in-person (no cold calls will be made) and the referring physician will not directly consent the potential participant. We may also travel to the locations listed above or phone these locations to engage staff in a brief conversation to explain the study and ensure they will allow placement of VA CIRB approved flyers in their offices. Staff at these locations will not be engaged in participant recruitment or any other aspect of the research. Under all other circumstances the initial contact will be made by the potential participant. We may also recruit via advertisements in magazines, newspapers, newsletters, or other print media and via the websites of these print media outlets and their email listservs, on the UF Health Study Listings website (https://ufhealth.org/research-studies-clinical-trials), through the ResearchMatch.org national recruitment database, through posts to the Facebook pages of the NF/SG VHS or the James A. Haley VA Medical Center, through posts to individual Facebook pages or groups that have a veteran or SCI support focus, through advertisements placed on Facebook, and via www.clinicaltrials.gov. A separate document outlines our Facebook advertising strategy, including monitoring of Facebook pages and advertisements.

Compensation and Reimbursement

Significant participant time involvement is required for this RCT due to the comprehensive evaluations we propose. We will inform participants of the estimated time involvement prior to enrollment. This includes: screening, baseline, 3 month, 6 month, 9 month, and 12 month testing sessions (~8 hours/visit), ~1 hour visits at 1 month, 2 month, and 18 month, and ~1 hour of home care per week, including drug administration and weekly phone calls from the Study Nurse. Participants will receive compensation for their participation in the study. Total compensation for the study will be $400, which will be disbursed in $80 increments during baseline, 3 month, 6 month, 9 month, and 12 month testing sessions. We will reimburse participants for transportation expenses at a rate of $0.415 per mile for the screening, baseline, 1 month, 2 month, 3 month, 6 month, 9 month, 12 month, and 18 month testing sessions. Any overnight lodging required for study participation in the screening, baseline, 1 month, 2 month, 3 month, 6 month, 9 month, 12 month, and 18 month testing sessions will be provided for free. Payment for participation will be provided through the VA Finance Office and will be pro-rated for study participation. The VA Finance Office will issue payment by direct deposit to the participant's bank account. If it is not possible for the participant to receive payment by direct deposit, they may have payment sent to a pre-paid debit card or they may decline payment for participation. Participants will not receive travel reimbursement, compensation, or overnight lodging for any other study visit. If the

participant chooses to have the Study Nurse provide the weekly injection, they will not receive any travel reimbursement, compensation, or overnight lodging.

5.3 Informed Consent Procedures

Individuals who contact us and are interested in participation will undergo prescreening to determine if they meet criteria to enroll. We have requested a Waiver of Informed Consent and a Waiver of HIPAA Authorization for purposes of recruitment and prescreening. Prescreening will be conducted by the PI, Study Nurse, or another member of the study team over the phone or in-person. We will query interested individuals about their complete medical history and conduct a review of their CPRS medical records (if applicable) to determine if they meet prescreening criteria. An in-depth description of the prescreening procedures is included in Section 5.5 of this document. We will obtain informed consent and HIPAA authorization from those individuals who meet prescreening criteria. Informed consent will be obtained by the PI, Study Nurse, or another member of the study team. Referring physicians will not be involved in the informed consent process.

5.4 Inclusion/Exclusion Criteria

Participants who meet prescreening criteria and provide informed consent and HIPAA authorization will undergo additional hands-on screening to determine eligibility. An in-depth description of the prescreening and screening process is included in Section 5.5 of this document. Participants who meet Inclusionary Criteria or who do not exhibit Exclusionary Criteria will be allowed to continue in the study. Those who do not meet criteria will be considered screen failures and will not continue in the study. The Inclusionary and Exclusionary Criteria for this study are listed below.

<u>Inclusionary Criteria</u>

- Men >18 years of age.
- SCI >12 months prior to enrollment.
- Motor incomplete SCI (AIS C/D) between C2-L3.
- Low serum total T (≤325ng/dL) or bioavailable T (≤70ng/dL).
- Ambulatory dysfunction, defined as self-selected gait speed between 0.10 m/s – 1.30 m/s on 10m walk test, and/or impaired gait parameters, as identified by a trained observer.
- Diagnosis of first time SCI including etiology from trauma, vascular, or orthopaedic pathology.
- Medically stable condition that is asymptomatic for bladder infection, decubiti, cardiopulmonary disease, or other significant medical conditions that will interfere with study design.
- Documented medical approval from the from the Study Physician and/or Medical Director verifying medical status.
- Persons using anti-spasticity medication may participate; however, the medication dosage must have been stable for the preceding 3 months and remain stable throughout participation.

<u>Exclusionary Criteria</u>

- Currently participating in another research protocol that may influence study outcomes.

- Life expectancy <1 years.
- History of or current congenital SCI (e.g., Chiari malformation, myelomeningocele, intraspinal neoplasm, Frederich's ataxis) or other degenerative spinal disorder (e.g., spinocerebellar degeneration, syringomyelia) that may complicate the study procedures.
- Multiple sclerosis, amyotrophic lateral sclerosis, or other neurologic impairment/injury.
- Any poorly compensated or uncontrolled cardiovascular disease (see next section).
- History of venous thromboembolism within the last 6 months, specifically deep venous thromboembolism and pulmonary embolism, history of recurrent venous thromboembolism or known hereditary thrombophilia.
- Current prostate, breast, or other organ cancer.
- History of prostate, breast, or other organ cancer, with the exceptions of completely resolved basal or squamous cell carcinoma for a duration of >24 months or completely resolved melanoma for a duration of >24 months.
- Serum PSA >3.0ng/ml.
- Benign prostate enlargement (BPE) >40cc, evaluated via TRUS.
- HCT >49%.
- Liver enzymes (AST / ALT) above normal upper limit.
- Creatinine level >1.4mg/dl.
- Serum calcium >10.5mg/dl.
- Gynecomastia.
- Mental state that precludes understanding of the protocol.
- Diagnosed, but untreated moderate or severe sleep apnea.
- High risk for malnutrition (score >15 on Spinal Nutrition Screening Tool).
- Severe claustrophobia that precludes MRI testing.
- Current anticoagulant therapy (contraindication for i.m. injections).
- Use of any of the following pharmacologic agents that alter sex-steroid metabolism in the previous 3 months (i.e., TRT, leuprolide, androgenic hormones, growth hormone, oral androgen precursors, 5α-reductase or aromatase inhibitors).
- Use of anti-resorptive or bone anabolic drug therapy in the previous 6 months.
- Known allergy to sesame oil

Cardiovascular Exclusionary Criteria Include:

- Any major cardiovascular event within the last 12 months (defined as a history of acute myocardial infarction, any cardiac revascularization procedure including angioplasty, stenting, or coronary artery bypass grafting, hospitalization due to unstable angina, transient ischemic attack, or stroke).
- Any angina that is not controlled on a current medical regimen (Canadian class II, III, or IV).
- Poorly compensated congestive heart failure (NYHA class III or IV).
- Poorly controlled hypertension (consistently measured systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg).
- Poorly controlled arrhythmia.
- Severe valvular heart disease.
- LDL cholesterol >160 mg/dl with known history of any major cardiovascular event, as defined above, within the last 12 months.
- Baseline EKG findings such as left bundle branch block or marked EKG abnormalities that would preclude serial screening evaluations for occult ischemic events.

5.5 Study Evaluations

Prescreening

We will prescreen individuals who contact us and are interested in participating to determine if they meet criteria to enroll. This is necessary in order to determine whether interested individuals meet the stringent inclusionary/exclusionary criteria to qualify for our study (discussed above in Section 5.4). We have requested a Waiver of Informed Consent and a Waiver of HIPAA Authorization, which will be used for recruitment purposes and prescreening. During the prescreening we will query individuals about their complete medical history and previous six months of physician prescribed and over-the-counter medications (via phone or in-person) and conduct a review of the CPRS medical records (if applicable) to determine if they meet prescreening criteria. Additionally, we will collect the following identifiers:

- Names
- Social security numbers
- Telephone numbers
- State, City, Zip Code, Address
- Age
- Date of birth
- Date of past medical procedures/diagnoses
- Medical records number

Informed consent and HIPAA authorization will be obtained from individuals who meet prescreening criteria. These individuals will then undergo additional hands-on screening to determine eligibility.

Safety Screening

Individuals who give informed consent will undergo a Safety Screening and Functional Assessment prior to study enrollment to determine eligibility. All screening and assessments will take place at the NF/SG VHS and will be conducted over a 1-2 day period to reduce participant transportation, time, and travel burden.

The Safety Screening includes the following:

- Comprehensive physical exam
- CPRS medical records review (if applicable) and health history questionnaire encompassing the complete medical history including cardiovascular disease history and review of systems
- Fasting blood collection
- Comprehensive prostate exam
- Electrocardiogram (EKG)
- Questionnaire evaluating previous six months use of physician prescribed and over-the-counter medications
- Spinal Nutrition Screening Tool assessing nutritional status
- Questionnaires assessing perceived erectile quality [International Index of Erectile Function (IIEF)] and sexual function [Brief Sexual Function Inventory (BSFI)]

The Study Nurse and/or Study Physician will perform the comprehensive physical exam and administer questionnaires. Fasting blood samples will be acquired twice (between 0:700-10:00am, separated by 30 minutes) by the Study Nurse and/or a VA hospital phlebotomist which is standard practice when measuring serum T. The VA Clinical Lab will evaluate blood samples for total T, complete blood count (CBC), comprehensive metabolic panel, lipid panel, fasting insulin and glucose, HbA1C, C-reactive protein, erythropoietin, and PSA (a serum marker of

prostate growth). Urology Service will perform the prostate exam, which includes DRE to evaluate for prostate nodules/indurations and prostate TRUS to assess prostate volume according to standard clinical guidelines. If prostate nodules are detected via DRE, participants will be referred to VA Urology Service for prostate biopsy, which is standard of care. The participant can refuse to have a prostate biopsy, but will not be allowed to continue in the study if the biopsy is refused. The participant will be referred to VA Urology Service to discuss treatment options if prostate cancer is found. The participant will be allowed to continue in the study if prostate cancer is not detected. Cardiology Service will perform EKG to evaluate cardiac abnormalities. The questionnaires will be completed by the participant and assistance will be provided if necessary.

The Functional Assessment will evaluate (self-selected) walking speed during 10m walk tests that are performed with and without brief cognitive tasks. Examples of the brief cognitive tasks include listing words starting with the letter "A", performing basic math calculations like continuously adding or subtracting by 7, or other similar tasks. During the 10m walking tests sensors may be taped or strapped to the participants' head to allow us to estimate brain activity via fNIRS, which uses harmless and non-invasive infrared light to estimate changes in blood flow by determining changes in hemoglobin concentrations. Individuals with gait speeds between 0.10 m/s – 1.30 m/s on 10m walk test and/or impaired gait parameters, as identified by a trained observer, will qualify for the study because these values are below typical healthy adult preferred walking speed and common to the AIS C/D population. Furthermore, individuals who fit these criteria will have sufficient KE motor function to engage in the proposed muscular strength assessments. Additionally, we will perform the following assessments which are standard in SCI rehabilitation trials and which will allow us to appropriately classify participant functional, cognitive, and emotional status:

- Modified Ashworth Scale for lower limbs spasticity
- Spinal Cord Independence Measure (SCIM) III
- Berg Balance Scale
- Walking Index for Spinal Cord Injury (WISCI) II
- Craig Handicap Assessment & Reporting Technique (CHART) Questionnaire
- Veteran Rand 12 Item Health Survey (VR-12)

Participants who meet the above inclusionary criteria will be allowed to continue in the study and will undergo Baseline Testing. Those who do not meet the above criteria will be considered screen failures and will not continue in the study.

Baseline/Follow-up Testing: Participants who qualify for the study will undergo Baseline Testing to assess:

- Total body and region-specific bone mineral density (BMD) and body composition
- Blood markers of musculoskeletal and metabolic health and metabolism
- Thigh musculoskeletal and adipose cross-sectional area (CSA)
- Neuromuscular function and voluntary neuromuscular activation
- Daily activity
- Metabolic syndrome risk

Tests that are completed during Screening will not be repeated at baseline. Follow-up testing will occur at 3-6 month intervals and will include all Safety Screening and Baseline Testing measures. The table below illustrates when testing will occur. Additionally, 10m walk tests and blood tests will occur at 1, 2, and 3 months of treatment and at 3 month intervals thereafter. Participants will

be allowed a 1 month window surrounding the scheduled testing dates to ensure completion of all testing procedures. A specific explanation of all tests follows.

Table 1. Testing Schedule

Test	*Rationale*	*Baseline*	*3 month*	*6 month*	*9 month*	*12 month*
Physical exam	*Safety*	X	X	X	X	X
Blood collection	*Safety*	X	X (1-3)	X	X	X
EKG	*Safety*	X	X	X	X	X
Questionnaires	*Safety*	X	X	X	X	X
Functional status	*Safety*	X	X	X	X	X
Prostate exam	*Safety*	X		X		X
BMD / body composition	*Aim 1 & 3*	X		X		X
Blood measures	*Aim 1*	X	X	X	X	X
Thigh CSA	*Aim 2*	X		X		X
Neuromuscular function	*Aim 2*	X	X	X	X	X
Daily activity	*Aim 2*	X	X	X	X	X
Metabolic syndrome	*Aim 3*	X	X	X	X	X

Body Composition and Bone Assessments: VA Radiology Service will perform total body DXA (for body composition) and region-specific DXA to evaluate bone mineral characteristics according to established ISCD guidelines.[66] Scans will be performed on DXA densitometer with software for evaluation of both standard and non-standard regions of interest (e.g., distal femur). The DXA is calibrated daily using multi-stage hydroxyapatite and soft-tissue phantoms. Participants will arrive fasted and will be placed supine for the total body scan, as previously reported[62]. Care will be taken to ensure identical body positions during each scan. Region-specific BMD scans will be performed on the non-dominant hip/knee, unless surgical hardware or previous fracture is present. Hip DXA will be performed with knee stabilized in full extension at ~20° internal rotation of the hip. For the distal femur, the knee is stabilized in full extension with 0° internal rotation against a 90° support and the region of interest is determined according to published protocol.[67] Participants will remain supine for the lumbar scan with the lower limbs stabilized on a box to allow 90° hip and knee flexion with back flat on the scanning surface. The lumbar scan is performed in the anterior-posterior (A-P) direction.[68]

Circulating Markers of Musculoskeletal and Metabolic Health and Metabolism: Circulating markers of musculoskeletal and metabolic health and metabolism will be evaluated on previously collected blood samples in order to determine potential mechanisms through which testosterone alters these measures. These analyses may be performed by the VA Clinical Lab or a commercial lab subcontracted by the VA Clinical Lab to complete such analyses when in-house assessments are not possible (e.g., Quest Diagnostics), which is standard practice at NF/SG VHS. Alternatively, these analyses may be performed in the PIs laboratory, who is experienced in these techniques, because some tests are not standard in the VA Clinical Laboratory or available in VA-subcontracted labs. These will include circulating markers of: bone formation (e.g., osteocalcin and bone alkaline phosphatase), bone resorption (e.g., C-telopeptide and tartrate resistant acid phosphatase 5b), bone metabolism (e.g., osteoprotegerin, RANKL, sclerostin), muscle metabolism (e.g., myostatin, brain-derived neurotrophic factor, adiponectin, leptin), and perhaps others. All samples will be linked to a specific participant by a code number rather than a direct identifier to ensure that personally identifiable information is protected, as described in Sections 5.0 “Minimization of Risks / Data Security” and 7.0 “Privacy and Confidentiality”. Unused samples will be returned to VA for storage or will be destroyed.

Musculoskeletal and adipose cross-sectional area: The Nuclear Medicine Service at NF/SG VHS or trained medical staff at UF, our academic affiliate, will perform MRI screening and testing according to standard clinical guidelines. Briefly, MRI will be used to quantify maximal CSA of the flexor and extensor compartments of the thigh. Participants will remain in a supine position for approximately 30 minutes prior to MRI. Padding will be provided to limit pressure sores/ulcers. MRI will be performed using either a body coil or a standard quadriture extremity coil and should take approximately 30 minutes.

Neuromuscular function: Neuromuscular assessments will be supervised by a trained Exercise Physiologist. Participants will undergo a warm-up and familiarization prior to beginning testing. Subsequently, participants will perform submaximal and maximal effort contractions of knee extensor and flexor muscle groups. Isometric and dynamic force production will be measured by a Biodex dynamometer. During these assessments, participants will be instructed to contract the muscle as forcefully and rapidly as possible and hold the contraction for up to 5 seconds. Neuromuscular activation will be assessed using surface electromyography (EMG), which is a non-invasive technique that measures the bioelectrical signals associated with muscle contraction. EMG electrodes will be taped to the skin over the muscle(s) of interest. For proper application of electrodes, it may be necessary to shave hair from the skin and clean the site with an alcohol wipe. To evaluate spasticity and abnormal co-activation between agonist/antagonist muscle groups we will quantify the co-activation index as the ration of agonist/antagonist EMG magnitude.

Voluntary Neuromuscular Activation: Voluntary neuromuscular activation will be assessed by the twitch interpolation technique. Short bursts (i.e., < 1 second) of electrical stimulation will be used to evoke activation of the knee extensor (quadriceps) muscle group. This is a safe and well tolerated procedure that is performed with specialized equipment that is designed for use with human subjects. Electrical stimulation will be delivered using a Grass-Telefactor square pulse stimulator and Model SIU5 stimulus isolation unit (Astro-Med, West Warwick, RI). Two stimulating electrodes coated with non-allergenic electrode gel will be placed over motor nerve. Optimal positioning of the stimulating electrodes will be determined by palpation and visual observation of muscle contractions during low-intensity stimulation. Stimulation will be delivered at rest and during voluntary muscle contractions. For proper application of some electrodes, shaving hair from the skin and wiping with alcohol may be necessary. To familiarize the participant with the sensation of the stimulation, a series of four to five trials will be delivered with gradually increasing intensity. We will ensure the participant is comfortable with the sensation and willing to proceed before moving on to the next trial. During testing, stimulation will be delivered during maximal and submaximal muscle contractions. An estimated total of about 25 stimulations will be performed. The participant will be reminded that they are free to end the testing session at any time if they are uncomfortable with the sensation of the stimulation, or for any other reason.

Metabolic Syndrome Risk: We will assess metabolic syndrome risk according to the American Heart Association criteria, which considers men with ≥3 of the following conditions at-risk for metabolic syndrome: abdominal obesity; systolic blood pressure ≥130mmHg; diastolic blood pressure ≥85mmHg; serum triglycerides ≥150mg/dL; HDL cholesterol <40mg/dL (in men); fasting glucose ≥100mg/dL; or presence of insulin resistance [Homeostasis model assessment (HOMA)]. Blood pressure will be obtained during the physical exam, blood markers will be evaluated by the VA Clinical Lab using previously collected samples, and total body and trunk/android fat mass (assessments of visceral adiposity) will be measured via DXA, as previously discussed. HOMA will be determined with the following equation:

HOMA-IR = FASTING GLUCOSE x FASTING INSULIN
22.5

Daily Activity Assessment: We will assess daily activity using the Stanford 7-Day Physical Activity Recall (PAR) questionnaire, which is a valid and reliable research tool for assessing cumulative daily activity. This PAR assesses a variety of physical activities, such as aerobic exercise, work-related activities, gardening, walking, recreation, and leisure-time physical activities that occurred over the previous 7 days, as recalled by the participant.

Safety Assessments: Participants will also undergo comprehensive Safety Screenings at 3 or 6 month intervals throughout the intervention and additional blood tests at 1, 2, and 3 months of study treatment and 3 month intervals thereafter. These assessments will be identical to that outlined above in the Participant Safety Screening section above. In addition, the Study Nurse will phone participants on a weekly basis to determine their general health / well-being and will perform a monthly formal CPRS medical records review to assess for potential AEs. Patients will be specifically interviewed regarding the cardiovascular symptoms of chest pain, edema, palpitations, dyspnea, and other health-related matters.

Study Completion: Participants will be referred to their VA or non-VA Primary Care Provider at the completion of the RCT. Some participants may report a transient depression of mood following TRT cessation because reduced circulating T occurs after TRT discontinuation. If this occurs, participants have the option of tapering to a lower dose of T (125mg T-enanthate biweekly, i.m.) for 4 weeks (administered through the VA Research Pharmacy). We will also provide participants with information for their Primary Care Provider to assist in deciding whether continuing TRT is appropriate. We will follow-up with participants monthly (via phone call) and perform monthly medical chart reviews for 3 months to assess potential AEs after study discontinuation. In addition, we will reassess blood values, perform a physical exam, EKG, and 10m walk tests at 6 months following study completion to ensure participant safety and to evaluate patient safety measures and persistence of any walking changes after discontinuation of study medication. Blood will be collected and blood tests will be performed in an identical to that previously discussed. Participants will be referred to their Primary Care Provider if AEs appear after study completion.

5.6 Data Analysis

Statistical Methods: Statistical analysis will be performed by the Study Statistician through the UF CTSI. All data will be provided to the statistician in a coded form. Preliminary analyses will be performed during years 2 and 3 and the final statistical analysis will be performed during year 4. All data provided for statistical analysis will coded. The primary analysis will be a repeated measures ANOVA using the SAS 9.3 PROC MIXED software, with dependent variable change from baseline, independent variables time (6 Mo vs. 12 Mo) and subject (random effect), and a compound symmetric covariance structure. The contrast of primary interest is the arithmetic mean of the 6 month and 12 month changes. The relative efficiency of the repeated measures analysis is 133% compared to using only the change from baseline to 12 months. If there is no missing data, the mixed model and two-sample t-test using the mean of the 6 and 12 month differences from baseline on each subject will lead to identical point estimates and asymptotically equivalent standard errors. However, the mixed model handles missing data more efficiently. Secondary analyses*:* We shall also present descriptive statistics and confidence intervals for changes from baseline for each treatment (2) by time (2), and provide Satterthwaite corrected t-tests comparing the treatments for changes from baseline at each of

the two time points. Other variables will be analyzed in like manner, but the following six are the primary outcomes for which the study was powered: Total hip BMD, lumbar spine BMD, knee extensor force production, total body fat mass, visceral fat mass, thigh muscle CSA.

Sample Size/Power Analysis: Our *a priori* power analysis indicates that the repeated measures method has 80% power to detect a difference of 1.15 standard deviations in the change from baseline for all primary outcomes in Aims #1-3 at P=0.05 (two-sided) with n=10 completers per group. In order to provide sufficient power for all primary outcomes we will recruit n=15 per group (to account for potential participant dropouts that are characteristic of long duration RCTs), which exceeds that indicated by our power analysis by 50%. It is difficult to determine the anticipate rate of screen failures; although, we conservatively estimate that we will need to screen up to 200 individuals to find 30 participants who qualify.

5.7 Withdrawal of Subjects

Participants may be withdrawn from the study for medical reasons:

- HCT >52%
- Hemoglobin >17.5 g/dL
- Serum PSA >4.0ng/ml
- Increase in serum PSA of >1.4ng/ml vs. baseline
- Liver enzymes (AST / ALT) >1.5 times normal upper limit
- Serum calcium between 10.5 – 11.2mg/dL with symptoms of hypercalcemia
- Serum calcium >11.2mg/dL (whether symptomatic or asymptomatic for hypercalcemia)
- Gynecomastia
- Prostate, breast, or other organ cancer development
- Development of severe peripheral edema, as classified as 2+ or higher
- Occurrence of any of the following adverse cardiovascular events: acute myocardial infarction, acute coronary syndrome, congestive heart failure (new onset), newly diagnosed flow-limiting coronary artery disease, any cardiovascular-related hospitalization, stroke, or cardiac arrest, and the development of new significant ischemic findings or symptoms during the course of the study (including development of new major abnormalities on serial EKGs or symptoms of typical angina)
- Development of any other SAE that the Medical Director feels necessitates study withdrawal for participant safety

Treatment will be immediately discontinued for those experiencing any AE listed above and participants will be referred to the Study Physician and/or Medical Director for monitoring and reevaluation of laboratory values. Participants will be withdrawn from the study if aberrant results are verified upon rescreening, with the exception of elevated PSA or HCT (see below). If serum calcium is elevated the Study Physician and/or Medical Director will determine whether the participant is symptomatic or asymptomatic for hypercalcemia. If asymptomatic for hypercalcemia and serum calcium is between 10.5 – 11.2 mg/dL, the participant will be allowed to continue in the study and if symptomatic for hypercalcemia and serum calcium is >10.5 mg/dL the participant will be withdrawn from the study. The Study Physician and/or Medical Director may order additional testing (as needed) to assist in the decision regarding participant withdrawal and may consult with other Physicians (as needed). Prostate withdrawal criteria: In the unlikely instance that a prostate nodule is detected via DRE or that elevated PSA occurs, participants will discontinue TRT and will be referred to VA Urology Service for reevaluation and monitoring. While

undergoing reevaluation, participants will remain enrolled, but will not receive TRT. Participants will be assessed for prostatitis and lower urinary tract infection (standard-of-care), which can occur due to intermittent urinary catheterization, and will be offered treatment if infection is noted. The participant will remain enrolled if they choose to receive treatment but will not receive TRT until PSA renormalizes and study physician re-approves TRT. The participant will be withdrawn if they choose not to receive treatment or if elevated PSA persists for >4-weeks, as extended TRT withdrawal may compromise study validity. If prostate nodule is verified upon reevaluation, participants will be referred to VA Urology Service to undergo prostate biopsy to assess for prostate cancer, which is standard of care. The participant can refuse to have a prostate biopsy, but will not be allowed to continue in the study if the biopsy is refused. The participant will be referred to VA Urology Service to discuss treatment options if prostate cancer is found. The participant will be allowed to continue in the study if prostate cancer is not detected, with approval from study physician. HCT withdrawal criteria: If HCT >52% is noted, participants will discontinue TRT and will be referred to the study physician for reevaluation and monitoring. While undergoing reevaluation, participants will remain enrolled, but will not receive TRT. Participants can resume TRT if HCT renormalizes within 4-weeks, with approval of the study physician. Participants will be withdrawn if elevated HCT persists for >4-weeks because extended TRT withdrawal may compromise study validity. Participants experiencing any other SAE will be immediately referred to the Study Physician and/or Medical Director for monitoring and additional testing (as needed) or to Urgent Care for unexpected potentially life-threatening emergencies. The Medical Director may withdraw participants who experience SAEs if they feel this is necessary to ensure participant safety. Under all conditions described above, participants will be followed until resolution of AEs.

Participants may also be withdrawn from the study for the following reasons:

- Failure to comply with the study protocol
- Use of anticoagulant medications that are contraindications for i.m. injections
- Use of any pharmacologic agent that alters muscle/bone metabolism or sex-steroid metabolism (defined in Exclusionary Criteria)

Participants also have the option to discontinue study participation at will and without consequence. If they choose to do so, they will be asked to contact the PI or Study Nurse to schedule an end of study visit for the purposes of evaluating potential safety concerns and obtaining any final testing. For 3 months after study discontinuation we will follow-up with participants monthly (via phone) and perform monthly medical chart reviews to assess potential AEs after study discontinuation. Participants will be referred to their Primary Care Provider if AEs appear in the follow-up period after study completion and will be followed until resolution of AEs.

6.0 Reporting

We have established a comprehensive Data Safety Monitoring Plan (DSMP) to ensure participant safety and reporting of potential unanticipated problems (UAPs), SAEs, and protocol deviations. The Study Nurse or another member of the study team will compile AE incidence and all AEs will be immediately reported to the Study Medical Director and Study Physician. If SAEs, deaths, or protocol deviations occur, they will be immediately reported to the independent DSMB, IRB, and VA RR&D. Other less serious AEs will be compiled and reported at semi-annual intervals to the DSMB, IRB, and VA RR&D. The independent DSMB will consist of one Physician, one Biostatistician, and one Cardiologist (none of whom are involved in the study). The DSMB will meet at 3-6 month intervals during the first year and semi-annually thereafter, and a charter will

be developed prior to beginning participant accrual. DSMB meetings will have two parts: open and closed. In the open meetings, the safety reports will be presented by the PI / Co-Is and discussed. After, the PI / Co-Is will be excused, and the DSMB will write its recommendation, which may include: Continue, Continue with Modifications, or Discontinue the Study. Minutes will be provided after each meeting. Additionally, a list of participant demographics, outcome measures collected, missing data, and participant adherence will be compiled and the total number of participants screened, enrolled, active (and duration of participation), withdrawn, and completed will be reported semi-annually to ensure enrollment proceeds as planned. The DSMB may recommend study discontinuation if a disproportionate number of SAEs occur in one group. Once the charter has been developed it will be provided to IRB.

Participants will be immediately notified (in person or via telephone) if any AE occurs that may affect their health or welfare. Participants will be referred to the Study Physician and/or Medical Director for monitoring and reevaluation of laboratory values. Participants will be removed from the study if aberrant results are verified upon rescreening. The Study Physician or Medical Director may also order additional testing (as needed) to assist in their decision regarding whether participants need to be removed from the study, including consulting other Physicians. In the unlikely event that prostate nodules / indurations are detected, participants will be referred to VA Urology Service for prostate biopsy to assess for prostate cancer. Participants will be immediately withdrawn from the study if prostate cancer is detected, but will be allowed to continue participation if prostate cancer is not found. Participants experiencing any other SAE will be immediately referred to the Study Physician and/or Medical Director for monitoring and additional testing (as needed) or to Urgent Care for unexpected potentially life-threatening emergencies. The Medical Director may withdraw participants who experience SAEs if he feels this is necessary to ensure the safety of the participant. Under all conditions described above, participants will be followed until resolution of AEs.

7.0 Privacy and Confidentiality

This study will collect and use PHI. The PI and his staff will be responsible for ensuring that health information and blood samples are protected and that medical information is kept confidential. Individuals will only be allowed access to PHI if necessitated by the study protocol. All personnel with access to PHI will complete the necessary training as required by VA. Data and samples will be linked to a specific participant by a code number rather than a direct identifier to ensure that personally identifiable information is protected. While the data may contain some protected health information, only someone possessing the code can link the data to a particular participant. The code will be maintained by the Study Coordinator and/or Research Pharmacist who are the only study personnel that will have direct access to the code. In the case of SAEs/UAPs, the code may be provided to the Medical Director to ensure participant safety. Any personally identifiable information will be stored in locked filing cabinets in locked offices or on computer servers with secure passwords or encrypted electronic storage devices behind the VA firewall. Access to research study data will be removed for study personnel when they are no longer part of the research team. The ISO and Privacy Officer will be notified within one hour of any improper disclosure.

8.0 Communication Plan

We will recruit participants from the NF/SG VHS and James A. Haley VA Medical Center and through other approved methods, but all testing and follow-up will be completed at NF/SG VHS under the supervision of the PI and his staff. This plan greatly simplifies the communication plan and ensures the study will be conducted according to the IRB approved protocol. In particular, the PI and his staff will be responsible for recruiting, screening/consenting, enrollment, and data collection. The PI and his staff will inform the local site investigators of any changes to the protocol, informed consent, and HIPAA authorizations via email immediately following IRB approval and at regularly scheduled semi-annual meetings. The PI and his staff (in cooperation with the local site investigator) will be responsible for ensuring all required local site approvals are obtained and that facilities remain engaged. If necessitated, the PI or his staff may contact the local site investigator at James A. Haley VA Medical Center to ensure the facility remains engaged in recruiting. All SAEs, UAPs, and interim results will be immediately reported to the local site investigator at James A. Haley VAMC. Additionally, SAEs/UAPs will be reviewed semi-annually at regularly scheduled meetings. The LSI at James A. Haley VAMC will remain engaged throughout the completion of this study because he is the study Medical Director and will be notified by the PI or his staff upon completion of the study.

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