Title: **Effect of a Multimodality Intervention to Improve Function and Metabolism in Spinal Cord Injury**

Protocol Number:

National Clinical Trial (NCT) Identified Number: NCT03576001

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Funded by: National Institutes of Health

Version Number: 3.2

Date: 8/9/2024

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Effect of a Multimodality Intervention on Function and Metabolism in Spinal Cord Injury
Study Description:	The proposed phase 2 trial a randomized, placebo-controlled, parallel group trial in persons with cervical or thoracic SCI, AIS grade A, B, C, or D, 6 months or later after injury. The trial will test the hypothesis that a Home-Based Multimodality Functional Recovery and Metabolic Health Enhancement Program that addresses multiple pathophysiologic factors in SCI and includes functional electrical stimulation during leg cycling (FES-LC) plus arm ergometry and an androgen will be more efficacious than functional electrical stimulation during leg cycling (FES-LC) plus arm ergometry plus placebo in improving aerobic capacity, function, metabolism, bone health, and wellbeing.
Objectives:	Primary Objective: • To determine whether the multimodality intervention is more efficacious in improving peak aerobic capacity, and muscle mass and strength than placebo plus functional electrical stimulation during leg cycling (FES-LC) plus arm ergometry alone. Secondary Objectives: • To determine whether the multimodality intervention is more efficacious than placebo plus functional electrical stimulation

during leg cycling (FES-LC) plus arm ergometry in improving metabolic health, as reflected in fasting glucose, hemoglobin A_{1C}, insulin sensitivity, fat mass and distribution, plasma lipids, and inflammation markers.

- To determine whether the multimodality intervention is more efficacious than placebo plus functional electrical stimulation during leg cycling (FES-LC) plus arm ergometry in improving volumetric and areal bone density, bone microarchitecture, and bone strength.

  To determine the efficacy of the multimodality intervention in improving self-reported physical function (using SCI-FI AT and wellbeing, mood, anxiety, pain, loneliness and life satisfaction)

- To assess safety by structured monitoring of adverse events, and determining the proportion of participants experiencing injury, erythrocytosis, or other androgen-related or exercise-related adverse events.

Endpoints:

Primary Endpoint:

Our primary outcome is **peak aerobic capacity** because it is an excellent marker of overall health, physical function, and mortality. Aerobic capacity is closely related to metabolic health, insulin sensitivity and cardiovascular outcomes. It can be measured accurately in SCI patients and would be expected to improve with the proposed interventions.

Secondary endpoints.

Whole body skeletal muscle and fat mass and intraabdominal fat will be assessed by magnetic resonance imaging (MRI), using the Dixon method for separation of water/ fat signals. Body composition will also be measured by DEXA.

Maximal voluntary strength and **muscle fatigability** in the upper extremity will be assessed using the 1-repetition maximum in chest press.

Total, trabecular and cortical volumetric bone density; trabecular and cortical microarchitecture, both measured using high resolution peripheral quantitative computed tomography (HR-pQCT) at the ultradistal tibia, proximal tibia, and ultradistal radius.

Estimated bone strength of the ultradistal tibia and radius, assessed using microfinite element analysis of the HR-pQCT data.

Areal bone mineral density of the hip and lumbar spine using dual-energy X-ray absorptiometry (DEXA). (aBMD will be measured because DEXA is a clinically used and accepted measure of bone density, and aBMD is predictive of fracture risk.)

	Serum bone turnover markers, including markers of bone formation (osteocalcin, bone specific alkaline phosphatase (BSAP), (PINP) and bone resorption (CTX). **Spinal Cord Injury – Functional Index (SCI-FI)** will be used to assess self-reported function and mobility. SCI-FI is specific for persons with SCI that assesses functional capacity in basic mobility, ambulation, self-care, and fine motor function, and wheelchair ambulation. **Measures of Metabolism**: Fasting glucose, A1C; insulin sensitivity using HOMA-IR; IL-6 and hsCRP as inflammation markers; and plasma lipids, apolipoproteins B, C and A, and lipoprotein particles as markers of atherogenicity – all measured in the Brigham Research Assay Laboratory. Visceral fat will be assessed using Dixon MRI technique. **Wellbeing:** We will assess mood, anxiety, pain, and life satisfaction as measures of wellbeing. Mood will be assessed using Patient Health Questionnaire (PHQ-9), a 9-item scale that assesses mood and depressive symptoms. We will assess anxiety using GAD-7. Modified Brief Pain Inventory (BPI), a validated measure of pain in SCI, assesses pain intensity (sensory dimension) and interference with function (reactive dimension). Satisfaction with Life Scale is a 5-item scale that assesses happiness with life. Loneliness will be assessed using the Three-Item Loneliness Scale.
Study Population:	This proof-of-concept trial will enroll 84 community dwelling men and women with SCI, 19 to 80 years of age, motor cervical and thoracic, AIS A, B, C, or D, 6 months or later after a SCI. The trial plans to randomize 84 eligible subjects at a single trial site.
Phase:	Phase 2
Description of Sites/Facilities Enrolling Participants:	This is a single site study that will take place at the Brigham and Women's Hospital in Boston, MA.
Description of Study Intervention:	The Home-Based Multimodality Functional Recovery and Metabolic Health Enhancement Program includes training at home consisting of FES-LC plus arm ergometry plus testosterone undecanoate. Testosterone injections will be administered by study staff in the research clinic or by a visiting nurse in the participant's home. The control group will receive FES-LC plus arm ergometry plus placebo injections.
Study Duration:	Approximately 54 months
Participant Duration:	Approximately 46 weeks (14 weeks for screening, 6 weeks for baseline studies, up to 4 weeks to start exercise training, 16 weeks of intervention, and up to 6 weeks of end of study assessments)

SCHEMA

Screening - Within 14 weeks of Day 1

The subject will arrive in a fasting state (fasting for at least 8 hours)

- Obtain written informed consent
- Medical history including a menstrual history
- Physical examination including AIS score
- Vital signs, height and body weight
- Concomitant medications
- Complete blood count, blood chemistry, PSA (men only), HbA1c
- EKG
- Pregnancy test in women
- Mini Mental Status Exam (MMSE)
- Check conformity to eligibility criteria

Due to the COVID-19 Pandemic, some study procedures will be done via phone or Enterprise Zoom (a Partners approved tool) that will minimize the participants time in the clinic. The calls will not be record on Zoom and the chat feature in Zoom will not be used. Study staff could go over the consent form prior to the subject's screening visit and answer any questions the subject may have over Zoom or phone call. The day of the in-person screening visit, the subject will sign the consent form. Study staff could also go over the consent form in person and answer any questions subjects may have. Study staff will ask subjects to provide a medical history and medications list to minimize the time in the clinic.

Subject's eligibility will be determined based on the results of the medical history, physical examination, BMI calculation and blood tests. AIS score will be obtained from the subject's medical record whenever possible. If AIS score cannot be obtained from the record, a study clinician may perform an exam to obtain AIS score, or the subject may be asked to return to the clinic for an exam for AIS grading.

Subjects found to have a urinary tract infection with fever, leukocytosis (WBC count > 10,000/cmm) or sepsis will be sent to their primary providers for evaluation and treatment. Once treatment of urinary infection is complete, these subjects will be considered eligible.

The ability to comply with the study-specific prohibitions and restrictions will also be assessed. The Principal Investigator or a designated Study Physician will sign the eligibility checklist to verify conformity to inclusion and exclusion criteria.

Baseline Studies - Within 6 Weeks Prior to Day 1

Subjects who meet all the inclusion criteria and none of the exclusion criteria will be invited for baseline studies, which will be performed during the 6-week window prior to randomization. These studies may occur over 2-6 visits over the course of 6 weeks. The planned baseline assessment schedule may be modified as necessary to meet scheduling needs of the participant. Aerobic capacity and muscle performance testing may be performed on the same day after an appropriate resting period. The following baseline studies will be performed.

The following study procedures may be done via phone call or in the clinic, depending what subjects prefer:

- Administer questionnaires: SCI FI AT; wellbeing questionnaires for pain, anxiety, mood, loneliness and life satisfaction.

The subject will arrive in a fasting state (fasting for at least 8 hours)

- Complete blood count, blood chemistry, PSA, and bone markers
- Interim Health Status
- Check and concomitant medications
- Record AE/ SAEs
- Serum lipids, apolipoproteins, and lipoprotein particles, A1C, inflammation markers will be measured in all.
- The maximal aerobic capacity
- Metabolic outcomes – Glucose, insulin and HOMA-IR
- Whole body MRI scan using the Dixon technique
- HR-pQCT and DEXA scan
- Muscle strength and fatigability

Randomization - Day 1

The subject will be randomized by the Data Management System and assigned a unique randomization number. The Investigational Drug Services will dispense the prescribed dose of the study medication (testosterone undecanoate or placebo) based on the randomization number. Interim Health status check will be performed. Concomitant medications and AE/SAEs will be recorded. A skin check will also be performed. The study personnel will administer the first injection of the blinded study medication. After the injection, the subjects will be observed for 30 minutes.

The subject will receive familiarization and training in the use of the exercise equipment. The initial exercise training sessions will take place in the Laboratory of Exercise Physiology and Physical performance as described in detail under research procedures. Subjects have up to 4 weeks after their day 1 injection to start the 16-week exercise training. Delays sometime occur due to machine delivery and set-up time with study staff scheduling etc. Testosterone undecanoate stays in the body for up to 10 weeks so the timeline for the injections will remain the same, administered at week 1, 4 and 14.

Supervised Exercise Training Sessions During the First Week

During familiarization, an exercise physiologist will orient each subject and the caregiver, if available, to the equipment and proper technique for use at home. The subjects will perform practice sessions in the exercise laboratory wherein they will attempt to exercise continuously for 20 min at 50% WRpeak. If 20 min continuous exercise is not possible, the subject will be instructed to cycle as long as possible followed by a 4 min rest period until 20 total exercise minutes are accumulated. During baseline visits or after day 1 injection, the equipment will be installed in the subject's home for the remainder of the exercise training.

Home-Based Exercise

The first two subjects to enter the study will receive all training sessions in the exercise laboratory. Other enrolled subjects, with living situations amenable to home-based training, will perform the exercise intervention at home during Weeks 1, 2 or 3 through 16. Study staff will visit each subject in his or her home to assist the subject and the caregiver, if one is available,

to make sure the machine is set up correctly when the machine is dropped off at the subject's home. Subsequently, periodic two-way communication via audio or video monitoring (telephone call, Skype for Business, Zoom, or another Partners-approved tool) will enable live supervision of the home exercise session by the exercise physiologist (if needed). In the event that we encounter software issues with the FES-LC machine and cannot resolve it over the phone, a member of the study team will go to the subject's home to resolve the issue.

Table. 1. 16-week progressive exercise training using functional electrically stimulated leg cycling (FES-LC) and arm ergometry (AE).

Study Week	Weeks 1-2	Weeks 3-6	Weeks 7-10	Weeks 11-16
Location	Exercise Physiology Laboratory and/or Home	Home		
Duration FES-LC	10-20 minutes (in intervals as needed)	20-25 minutes	25-30 minutes	30-40 min as tolerated
Duration Arm Ergometry	20 minutes (in intervals as needed)	20-25 minutes	25-30 minutes	30-40 min as tolerated
Frequency FES-LC and AE	1-3 days/wk	3 days/wk	3 days/wk	4 days/wk as tolerated
Intensity FES-LC and AE	40-50% WRpeak (RPE: 11-13)	50-60% WRpeak (RPE: 12-14)	60-70% WRpeak (RPE: 13-15)	70-80% WRpeak (RPE: 13-16)
AE = arm ergometry; WRpeak = peak work rate; RPE: rate of perceived exertion. Frequency, duration, and intensity adjusted according to exercise tolerance. The frequency of training in the exercise laboratory will be determined by the Exercise Physiologist and the subject's knowledge of using an FES-LC machine.				

Study Assessments During Week 4 +/- 1 week

The subject will arrive in a fasting state (fasting for at least 8 hours).

- Record AE/SAE
- Interim Health Status Check and record concomitant medications
- Perform skin checks
- Complete blood count and blood chemistries, PSA, and bone markers
- Compliance check and motivational interviewing to encourage adherence to the prescribed exercise training
- Administration of second dose of study medication (subject will be observed for 30 minutes post-dose)

Study Assessments During Week 8

The following study procedures will be done via Zoom or phone call to minimize clinic visits:

- Record AE/SAE
- Interim Health Status Check and ~~r~~ecord concomitant medications
- Compliance check and motivational interviewing to encourage adherence to the prescribed exercise training
- Administer questionnaires: SCI-FI AT; wellbeing questionnaires for pain, anxiety, mood and life satisfaction
- Have subjects perform a skin check

Study Assessments During Week 12

The following study procedures will be done via Zoom or phone call to minimize clinic visits:

- Record AE/SAE
- Interim Health Status Check and ~~r~~ecord concomitant medications
- Compliance check and motivational interviewing to encourage adherence to the prescribed exercise training
- Have subjects perform a skin check

Study Assessments During Week 14 +/- 2 weeks

The subject will arrive in a fasting state (fasting for at least 8 hours).

- Record AE/SAE
- Interim Health Status Check and record concomitant medications
- Perform skin checks
- Complete blood count, blood chemistries
- Compliance check and motivational interviewing to encourage adherence to the prescribed exercise training
- Administration of third dose of study medication (subject will be observed for 30 minutes post-dose)

End-of-Study Assessments During Week 17- 22 + 2 weeks

The following study procedures will be done via phone call or in the clinic, depending what subjects prefer.

- Administer questionnaires: SCI-FI AT; wellbeing questionnaires for pain, anxiety, mood, loneliness and life satisfaction

The subject will arrive in a fasting state (fasting for at least 8 hours). These studies may need to be scheduled on 3-6 separate days.

- Record AE/SAEs
- Interim Health Status Check and record concomitant medications

- Physical exam including skin checks.
- Complete blood count, blood chemistry, PSA, and bone markers
- MRI using Dixon technique
- HR-pQCT and DEXA scan
- Maximal aerobic capacity
- Muscle strength and fatigability
- Metabolic outcomes- Glucose, Insulin and HOMA-IR
- Plasma lipids, apolipoproteins, and lipoprotein particles, A1C, inflammation markers will be measured in all.

End-of-Study Assessments in Participants who are Discontinued from the Study Before Week 17-22 + 2 weeks

Every effort will be made to retain the participants in the trial and to complete all study procedures regardless of whether the study medication is discontinued. If the participants decline to continue with study procedures, every effort will be made to complete the end-of-study procedures at that time. To the extent possible, effort will be made to complete all end-of-study procedures, prioritizing the safety assessments and the primary outcome:

The subject will arrive in a fasting state (fasting for at least 8 hours).

- Record AE/SAEs
- Interim Health Status Check and record concomitant medications
- Physical exam including skin checks.
- Complete blood count, blood chemistry, PSA and bone markers
- Maximal aerobic capacity
- MRI using Dixon technique
- HR-pQCT and DEXA scan
- Muscle strength and fatigability
- Metabolic outcomes - Glucose, insulin and HOMA-IR
- Plasma lipids, apolipoproteins, and lipoprotein particles, A1C, inflammation markers will be measured in all.

Allowed Time Windows for Study Procedures

Because the study is being conducted on patients who have a physical disability and who often experience multiple complex medical issues and transportation challenges, it is likely that they may not be able to come for some blood draws and study procedures within the scheduled time windows due to conflicts with illness, transportation, personal life, or other exigencies. If a blood sample or a study procedure is not performed within the specified time window, the study team will make an effort to obtain the blood sample or perform the study procedure at the next available opportunity. For the same reason, we also have expanded the time windows for various visits.

1.2 ADMINISTER QUESTIONNAIRES: SCI FI AT; WELLBEING QUESTIONNAIRES FOR PAIN, ANXIETY, MOOD, LONELINESS AND LIFE SATISFACTION) SCHEDULE OF ACTIVITIES (SOA)

Table 2. Schedule of Events

	Week -14	Week -6	Day 1	Week 4	Week 8	Week 12	Week 14	Week 17-22
Consent	•							
Screening	•							
Baseline Studies		•						
Interim Health Status/ AE monitoring/ Concomitant medications		•	•	•	•	•	•	•
Randomization			•					
Testosterone undecanoate/ Placebo injections*			.•	•			•	
Exercise training			←	—	—	—	—	→
Maximal Aerobic Capacity		•						•
MMSE questionnaire	•							
MRI using Dixon technique		•						•
HR-pQCT scan		•						•
DEXA scan		•						•
Muscle strength and fatigability		•						•
Metabolic outcomes: HOMA-IR		•						•
Wellbeing (Pain, mood, anxiety, satisfaction with life) and SCI-FI AT questionnaires		•			•			•

Loneliness questionnaire		•						•
Electrocardiogram (EKG)	•							
Physical Exam	•							•
Skin Check	•			•	•	•	•	•
AIS Score	•							
CBC, chemistry panel	•	•		•			•	•
Plasma lipids, apolipoproteins, and lipoprotein particles, A1C, inflammation markers		•						•
PSA	•	•		•				•
Bone Markers		•		•				•

Legend: * IM injections will be administered at Day 1, week 4 and week 14 by study personnel; SCI-FI AT, adaptive technology version of Spinal cord injury functional index; AE, adverse events; CBC, complete blood count, PSA (prostate specific antigen); Bone Markers (BSAP, osteocalcin, P1NP, CTX), DEXA scan is hip, spine and body composition.

2 INTRODUCTION

2.1 STUDY RATIONALE

Approximately 18,000 Americans suffer a spinal cord injury (SCI) each year[1,2], which results in a marked decline in mobility and wellbeing, and a substantial increase in cardiometabolic morbidity and mortality[3-6]. Multiple physiologic derangements, including the loss of neuromuscular stimulation and muscle contractility; alterations in bone metabolism, deficits of anabolic hormones; autonomic dysfunction; and chronic inflammation contribute to a substantial loss of aerobic capacity, sublesional osteoporosis, whole body and visceral fat accumulation, insulin resistance, and cardiometabolic dysregulation, resulting in impaired mobility, increased risk of fractures, increased cardiometabolic mortality, and poor quality of life[3-6]. In recognition of the profound deleterious effect of chronic SCI on an individual's health, the National Center for Medical Rehabilitation Research (NCMRR) has deemed "*pharmaceutical, stimulation, and exercise…strategies to improve the motor function and health of SCI patients"* a priority area of research. The NCMRR has further emphasized efficacy trials of *multicomponent interventions*, as this application proposes to accomplish.

The proposed phase 2 trial a randomized, placebo-controlled, parallel group trial in persons with cervical and thoracic SCI, AIS grade A, B, C, or D, 6 months or later after injury. The trial

will test the hypothesis that a Home-Based Multimodality Functional Recovery and Metabolic Health Enhancement Program that addresses multiple pathophysiologic factors in SCI and includes Functional electrical stimulation – leg cycling (FES-LC) plus arm ergometry, and an androgen will be more efficacious than FES-LC plus arm ergometry plus placebo in improving aerobic capacity, function, metabolism, and wellbeing.

2.2 BACKGROUND

SCI causes a profound loss of muscle mass and mobility[3-6]. Physical inactivity, recurrent infections, and chronic inflammation contribute to whole body and visceral fat accumulation, attenuation of cardiovascular fitness and insulin sensitivity, and the development of pro-atherogenic dyslipidemia[5-7]. Two-thirds of SCI patients are overweight, one third obese[8-10], nearly 40% have insulin resistance, and 12-20% have diabetes[7,11]. Thus, there is clustering of cardiometabolic risk factors in persons with SCI[12,13]. Even as the mortality during the first year after SCI has decreased due to improved acute care, mortality rates after the first year have not changed appreciably. Heart disease and metabolic disorders have emerged as the leading contributors to long term excess morbidity and mortality[12,13]. Depressive symptoms, anxiety, and chronic pain contribute to poor wellbeing and life satisfaction[14].

Sublesional osteoporosis is a nearly universal complication of spinal cord injury (SCI) [(1-5)]. Patients with SCI suffer from high incidence of low trauma fractures [(5-7)] and impaired osseous healing due to reduced mechanical loading and subsequently altered bone metabolism. Bone fractures contribute to pain, further limitation of mobility, and increased risk of decubitus ulcers and venous thromboembolism. Single interventions, such as arm cycle ergometry and electrical stimulation, although individually efficacious, have had limited impact on overall function and health outcomes. Systematic reviews by Hicks[15], Valent[16], and others[17,18] have highlighted the low quality of much of the evidence; most intervention trials have not been randomized, or have not included a matched control group, or have been limited by a small sample size[15,17,18]. Furthermore, most intervention trials have been conducted in a Spinal Cord Center or a Rehabilitation unit, constraining the ability of mobility-limited subjects to adhere to the exercise regimen and scalability of these regimens into clinical practice. Recognizing the limited efficacy of single interventions and the difficulty of scaling laboratory-based interventions into clinical practice, we propose here a randomized, controlled trial of a Home-Based Multimodality Functional Recovery and Metabolic Health Enhancement Program, in alignment with the research priorities established by NCMRR.

Arm ergometry exercise training has been shown to be feasible, but only modestly efficacious in improving musculoskeletal health and metabolic outcomes[15,17,18]. Guidelines recommend that exercise should be performed at moderate (3-6 metabolic equivalents, METs) to vigorous (>6 METs) intensity to achieve benefits in exercise tolerance, metabolic profile, and body composition[15-18]. Unfortunately, “arms only” exercise does not produce sufficiently high intensity for the desired health benefits.

Functional Electrical Stimulation (FES) training programs have been shown to be modestly efficacious in reversing muscle atrophy after SCI and improving mobility and general health[7,19-22]. The quadriceps and the tibialis anterior adapt to electrically stimulated cycling by induction of muscle fiber hypertrophy and muscle regeneration[21]. Physical exercise, especially weight bearing exercise, is known to increase bone density, trabecular architecture, cortical thickness, and bone strength in the general population [(13-17)]. While weight-bearing is difficult to achieve after SCI, FES-LC has made it possible to exercise the lower extremity muscles. Several animal and small human studies have shown beneficial changes in bone turnover markers even after short term FES-LC indicating reduced bone resorption and new bone formation [(18-

[22)]. A recent report demonstrated the feasibility of a home-based FES – leg cycling (FES-LC) program for people with SCI[19]. The major limitation of the FES-LC is the relatively low work rate intensities that can be generated by FES-LC alone. However, substantially greater work rates can be generated when FES-LC is combined with arm ergometry than with either intervention alone[20,22].

Circulating **testosterone levels** decline after SCI and nearly half the men with SCI have testosterone levels below those expected for age[23,24]. The use of opioids, chronic illnesses, inflammation, and denervation of the testis contribute to low testosterone levels[25]. Androgen deficiency contributes to the loss of muscle mass and strength, bone loss, sexual dysfunction, low mood, fatigue, and metabolic dysregulation[25]. The lowering of testosterone levels in men either experimentally or by androgen deprivation therapy for prostate cancer is associated with muscle loss, insulin resistance, and increased risk of diabetes and cardiovascular disease[26-31]. Androgens exert potent anabolic effects on muscle mass and strength even in patients with SCI[32-38]. Our dose response studies have shown that the anabolic effects of testosterone on muscle mass and strength are related to testosterone dose and increments in testosterone levels[39-42]. Thus, raising testosterone levels in men whose levels are low, low normal, or even normal induces further gains in muscle mass and strength. Androgens induce hypertrophy of type I and II fibers[43]. Testosterone promotes myogenic differentiation of mesenchymal progenitors by activating Wnt β-catenin pathway[44,45]. Two nonrandomized trials have reported significant gains in lean body mass in patients with SCI after testosterone treatment.

Testosterone therapy is associated with increases in bone density and bone mass. Testosterone therapy of healthy, young, hypogonadal men is associated with significant increases in vertebral bone mineral density [(28-30).] A meta-analysis of randomized trials found a significantly greater increase in lumbar bone mineral density with testosterone treatment than with placebo [(31).] In the Bone Trial of the Trials, we found significant increases in volumetric bone mineral density and estimated bone strength in the testosterone arm compared to placebo. In addition to its effects on bone mineral density, testosterone might reduce fall propensity because of its effects on muscle strength and reaction time.

We will use intramuscular injections of testosterone undecanoate which is an FDA-approved long-acting formulation of testosterone. The safety and efficacy of testosterone undecanoate has been shown in registration trials as well in peer-reviewed publications.

We and others have shown that **the anabolic effects of testosterone on the muscle are augmented by exercise training**[36]. Accordingly, combined administration of testosterone undecanoate with hybrid exercise training (FES-LC plus arm ergometry) would be expected to induce greater gains in muscle mass and strength than can be achieved with hybrid exercise. Testosterone increases hemoglobin, 2,3 BPG, tissue capillarity, mitochondrial biogenesis and mitochondrial quality[47], all of which should improve tissue O2 delivery and aerobic capacity.

Small non-randomized studies of FES in SCI patients have yielded promising results on the effects of short-term FES on bone turnover and bone density. The effects of testosterone supplementation on vBMD, bone architecture and bone strength have not been previously studied in persons with SCI. However, published data on the effects of FES on the bone from small nonrandomized studies in SCI and from well-designed randomized trials of testosterone treatment in other populations of hypogonadal young and older men support the premise that the multimodality intervention that includes hybrid exercise plus testosterone together would be more efficacious in improving vBMD, bone architecture and estimated bone strength than hybrid exercise alone.

Additionally, androgens improve mood in hypogonadal men[48,49], ameliorate depressive symptoms in HIV-infected men[50] and improve pain sensitivity in opioid-induced androgen deficiency[51]

Reflecting a nationwide trend away from extended in-patient rehabilitation, from 1973 to 2008, the median **length of stay** declined from 84 to 42 days for persons with complete paraplegia, and from 142 to 59 days for people with complete tetraplegia. Thus, there is an urgent need for home-based interventions that are likely to enhance adherence and patient convenience, and lower overall cost than hospital-based interventions.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The potential risks of the study include the risks of administering the study medication; exercising with FES-LC and arm ergometry; assessing peak aerobic capacity and muscle strength; performing MRI scans; drawing blood; and, of administering questionnaires. These risks are outlined in more detail below:

Potential Risks of Blood Drawing

The risks of blood drawing include pain, bleeding, and/or a bruise where the needle was inserted. Serious complications such as blood clots or infection are very rare when proper precautions are taken.

Potential Risks of Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a procedure that uses a combination of a large magnet, radiofrequencies, and a computer to produce detailed images of organs and structures within the body. Unlike *X-rays* or *computed tomography* (CT scans), MRI does not use ionizing radiation. MRI scans last from 30 minutes to two hours.

Due to the use of the strong magnet, special precautions must be taken to perform an MRI on patients with certain implanted devices such as pacemakers or cochlear or other types of metal implants that may contain a magnetic material. The MRI technologist will obtain information from the participant regarding the implanted device, such as the make and model number, to determine if it is safe to have an MRI. Patients who have internal metal objects, such as surgical clips, plates, screws or wire mesh, might not be eligible for an MRI.

Some participants may feel claustrophobic inside the MRI scanner. The participants will be advised that they can ask their physician to provide them with anti-anxiety medication to take prior to the MRI examination.

To date there is no information indicating that MRI is harmful to an unborn child, however MRI testing during the first trimester is discouraged. Pregnant women will not be enrolled in the trial.

Potential Risks of Dual-energy X-ray absorptiometry (DEXA) The radiation exposure during a DEXA scan is 10.8 µSv and is approximately equivalent to what would be received in 2-3 days of exposure to natural background radiation.

As a result of your participation in this study you will be exposed to radiation from one or more x-ray exams of your hip, lumbar spine and whole body. Please note that this radiation is not necessary for your medical care and is for research purposes only. The radiation you will receive from participation in this study is estimated to be 10.8 µSv per scan. A mSv is a unit of radiation dose. For comparison, everyone receives radiation exposure from natural background sources from the earth and the sky. The dose that you receive from participation in this research study is about the same as you would normally receive in 4-6 days from these natural sources. Scientists disagree on whether radiation doses at these levels pose significant

health risks. A possible effect that could occur at doses associated with this study is a slight increase in the risk of developing cancer later in life

Potential Risks of HR-pQCT

Ionizing Radiation exposure: Bone scanning by HR-pQCT exposures the subject to ionizing radiation. The overall total effective radiation dose for HR-pQCT imaging studies is estimated to range from 15 µSv to 45 µSv. This amount of radiation about the same as the natural background radiation one is exposed to from the earth and sky for 2-7 days.

Subjects will be informed about the study ionizing radiation exposure level described above so that they may make informed choices about participation. Study protocols will use the minimum radiation required to achieve the study objectives.

As a result of your participation in this study you will be exposed to radiation from one or more x-ray exams of your ultradistal tibia and radius. Please note that this radiation is not necessary for your medical care and is for research purposes only. The radiation you will receive from participation in this study is estimated to range from 15 microSieverts (µSv) to 45 µSv. A µSv is a unit of radiation dose. For comparison, everyone receives radiation exposure from natural background sources from the earth and the sky. The dose that you receive from participation in this research study is about the same as you would normally receive in 4 - 14 days from these natural sources. Scientists disagree on whether radiation doses at these levels pose significant health risks. A possible effect that could occur at doses associated with this study is a slight increase in the risk of developing cancer later in life.

Potential Risks of Performing Peak Aerobic Capacity and Muscle Strength and Fatigability Assessments

The risks of assessment of aerobic capacity and muscle strength and fatigability include muscle soreness, fatigue, and injury. This risk of injury is greater in patients who have incurred a spinal cord injury. The risk will be minimized by properly instructing the participants, and by using standardized protocols, warm-up, gradual increase in workload, and careful supervision of the subjects during their testing by trained and experienced exercise physiologists. We will provide detailed instructions and practice sessions so that subjects become familiar with the procedures and the equipment.

The investigating team has extensive experience in the measurements of peak aerobic capacity and muscle strength from our studies in persons with spinal cord injury, older adults, older persons with COPD, patients with end stage renal disease, and older men with mobility limitation (Please, see biosketches of Drs. Storer, Latham, and Bhasin). We have conducted these tests in young and older adults with a variety of disabling conditions and in persons with spinal cord injury without incidence for over 25 years. We attribute this remarkable safety record in part to the general safety of these tests, the application of rigorously standardized testing procedures, and stringent supervision. We will conduct strength testing with Keiser pneumatic equipment that allows as little as one pound increments in resistance, thus maintaining the ability to make appropriately small increments in resistance, as required. This equipment has been used extensively in research studies, and shown to be safe when used even in the frail elderly and persons with SCI.

Potential Risks of Arm Ergometry

Potential risks of arm ergometry include muscle soreness, fatigue, and injury. These risks can be reduced by appropriate screening of the participants, optimal training in the correct technique, and by slow progression of exercise intensity, as tolerated. Furthermore, the subjects will undergo initial training in the Laboratory for Exercise Physiology and Physical Performance.

Potential Risks of Functional Electrical Stimulation – Leg Cycling (FES-LC)

The potential risks of FES-LC include skin irritation, skin tear, muscle soreness and injury. These risks will be minimized by appropriate training of study participants in the use of FES-LC, periodic inspection of skin, and by appropriate rotation of electrode application site.

Potential Risks of Questionnaires

The instruments used for the assessment of function, mood, pain, anxiety, loneliness and life satisfaction ask about personal details that the subjects might find embarrassing. Although we encourage subjects to answer all the questions, they have the option of not answering any or all the questions that they might find embarrassing. All the questionnaires are coded and confidentiality will be maintained by the use of systematic data processing methods.

Potential Risks of Study Medication

In this trial, we propose to use testosterone undecanoate by intramuscular injection or a matching placebo. The drug will be obtained by the IDS at the Brigham and Women's Hospital from ENDO Pharmaceuticals and stored in the IDS at the Brigham and Women's Hospital using procedures that are FDA-compliant under an IND held by the Principal Investigator. As discussed below, testosterone undecanoate has been approved by the US Food and Drug Administration in the USA and used clinically for over 50 years.

Many androgens, including testosterone esters, have undergone numerous randomized trials in older men and women with a variety of chronic conditions, including HIV-associated wasting, end stage renal disease, chronic obstructive lung disease, osteoporosis, and hip fracture. These trials have demonstrated the safety and of testosterone administration in men and women. Administration of testosterone esters and other androgens increases lean body mass, maximal voluntary strength, and some measures of physical function in patients with HIV-associated weight loss, chronic obstructive lung disease (COPD), end stage renal disease and in persons receiving maintenance hemodialysis. These trials have reported low frequency of drug-related adverse events with testosterone undecanoate administration.

Potential adverse effects include breast tenderness and enlargement, erythrocytosis, irritability, leg edema, suppression of spermatogenesis, and acne. Intramuscular testosterone esters have had little effect on liver enzymes. In women, testosterone administration might cause hair growth, voice change, and clitoris enlargement, although in previous trials in women with hip fracture, chronic obstructive lung disease, and HIV-associated weight loss, the frequency of virilizing side effects with androgen administration has been very low at comparable or higher doses of testosterone esters. Subjects may experience symptoms of sexual dysfunction, fatigue, and low mood after stopping the medication.

Serious pulmonary oil microembolism reactions and anaphylaxis (POME) characterized by cough, shortness of breath, sweating, throat tightening, chest pain, dizziness, or syncope have been reported outside the USA during or immediately after the injection of testosterone undecanoate 750 mg (3 mL volume). These events are rare. The majority of these events lasted a few minutes and resolved with supportive care; a few required hospitalization and emergency care. Therefore, the participants will be observed for a period of 30 minutes in order to provide appropriate medical treatment in the event of a serious POME reaction or anaphylaxis. The participants who experience a POME or a hypersensitivity reaction to the study medication will not be re-treated with the medication.

2.3.2 KNOWN POTENTIAL BENEFITS

Because this is a research project, there are no specific benefits to individual participants. However, the knowledge to be gained from this trial has important societal benefits and therapeutic implications.

Despite improvements in acute surgical and medical management of SCI, which has reduced mortality in the first year after spinal cord injury, long term outcomes in persons living with spinal cord injury have not changed appreciably. Poor mobility, depressed mood, and increased cardiometabolic morbidity contribute to increased risk of disability, poor wellbeing, and increased mortality. The proposed trial is an important proof-of-concept trial of a multimodality function promoting strategy, which also has the potential to improve metabolic health and wellbeing. In light of the high burden of mobility problems and metabolic disorders after a spinal cord injury, the development of multicomponent therapies that improve function, metabolic health and wellbeing, has important therapeutic and health policy implications. The project addresses an important public health problem with enormously grievous outcomes for the patient, the care-giver, and the society.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The intervention trial has moderate level of risk to the participants. The proposed trial is an important proof-of-concept trial of a multimodality function promoting strategy, which also has the potential to improve metabolic health and wellbeing. In light of the high burden of mobility problems and metabolic disorders after a spinal cord injury, the development of multicomponent therapies that improve function, metabolic health and wellbeing, has important therapeutic and health policy implications. The project addresses an important public health problem with enormously grievous outcomes for the patient, the care-giver, and the society. Therefore, in aggregate, we believe that the benefit to risk ratio is favorable.

We have incorporated multiple strategies to minimize the potential for harm. The participants will be screened thoroughly to exclude those persons who are at increased risk of adverse events to androgen administration, or in whom arm cycle ergometry or FES-LC would be unsafe or unfeasible. After each testosterone undecanoate injection, the subjects will be observed for 30 minutes in order to provide appropriate medical treatment in the event a serious POME or anaphylactic reaction does occur. The risks of testosterone will be minimized by close monitoring with serial physical examinations, hemoglobin and hematocrit, and PSA levels. We have incorporated all the procedures recommended by the Expert Panel of the Endocrine Society (4), ISSAM (5) for monitoring of men receiving an androgen. Although these guidelines were developed for testosterone therapy, they are appropriate for following men receiving testosterone undecanoate. We have incorporated in this trial several additional measures to minimize risk:

a. We have established *a priori* stopping rules
b. We will designate an unblinded Medical Safety Officer to monitor safety data at all sites.
c. An independent DSMB, established in discussions with the NIH staff, will oversee the study after its initiation

All subjects will be monitored by physical examination, blood counts, chemistries and PSA levels (males) at baseline. We will follow hematocrit and hemoglobin, plasma lipids, blood chemistries, and PSA (males). Also, study staff will record all adverse events reported by the subjects at least every 4-weeks.

The risks of blood drawing will be minimized by having only experienced practitioners perform phlebotomy.

The risk of injury from participating in arm ergometry and FES-LC will be minimized by several safety measures. The subjects will be instructed in proper technique and the risks minimized by careful supervision. The likelihood of musculoskeletal injury from exercise will be minimized by providing a warm-up period preceding each exercise session. The intensity, duration and frequency will start at a low level and increased gradually, as tolerated. Further, an experienced exercise trainer will periodically oversee exercise sessions using audio or video monitoring as described above.

Minimizing Risks from MRI

Some participants may feel claustrophobic in the MRI scanner. The participants will be advised that they can ask their physician to provide them with anti-anxiety medication to take prior to the MRI examination.

Also, the study staff will use a standardized questionnaire to ask the subjects if they have an implantable device that contains a magnetic substance. The MRI technologist will further verify this information.

Termination Criteria

The following Termination Criteria will be used:

- An increase in hemoglobin level above 18.0 g/dL would warrant discontinuation of treatment.
- Myocardial infarction or stroke
- Diagnosis of prostate or breast cancer
- Serious hypersensitivity reaction to study drug administration

We recognize that other unexpected adverse events can occur. Therefore, we have instituted a comprehensive plan for structured monitoring to ensure early detection of adverse events. The Data Safety Monitoring Board will be empowered to discontinue treatment in one or more subjects, or halt the study, should the occurrence of adverse events so warrant.

Follow-Up of Patients Whose Hemoglobin Rises Above 18.0 g/L

If the hemoglobin level rises above 18.0 g/L, and this increase is confirmed by repeating the measurement, the intervention will be discontinued and the participant will be referred to his/her primary care provider for further management. If the participant has neuro-occlusive symptoms, a therapeutic phlebotomy may be performed. The hemoglobin level will continue to be followed on a weekly basis until hemoglobin level has fallen to a safe level (<165 g/L).

Follow-up of Patients with PSA Elevation

PSA levels may fluctuate simply because of inter-assay variability. An expert panel of the Endocrine Society suggested urological consultation for evaluation of confirmed PSA increments > 1.4 ng/ml after initiation of androgen therapy[25]. This recommendation is based on observations that increases in PSA levels after testosterone therapy in androgen-deficient men in excess of 1.4 ng/ml over a 3- to 6-month period are unusual. The 90% confidence limit for

the change in PSA levels between two tests performed 3 to 6 months apart in a study of men with benign prostatic hyperplasia was 1.4 ng/ml. In a systematic review, the average PSA increase after initiation of testosterone therapy was 0.3 ng/ml in young, hypogonadal men and 0.44 ng/ml in older men[25]. Therefore, if a PSA elevation above baseline exceeds 1.4 ng/mL and is confirmed, intervention will be discontinued and the participant will be referred to a Urologist for further evaluation.

3 OBJECTIVES AND ENDPOINTS

3.1.1 Primary Objective

- To determine whether the multimodality intervention is efficacious in improving peak aerobic capacity, and muscle mass and strength more than placebo plus exercise alone.

3.1.2 Secondary Objectives

- To determine whether the multimodality intervention is more efficacious than placebo plus FES-LC plus arm ergometry in improving metabolic health, as reflected in fasting glucose, A1C, insulin sensitivity, fat mass and distribution, plasma lipids, and inflammation markers.
- To determine whether the multimodality intervention is more efficacious than placebo plus functional electrical stimulation during leg cycling (FES-LC) plus arm ergometry in improving volumetric and areal bone density, and bone microarchitecture, and bone strength.
- To determine the efficacy of the multimodality intervention in improving self-reported physical function (using SCI-FI AT) and wellbeing (mood, anxiety, pain, loneliness and life satisfaction)
- Safety will be assessed by structured monitoring of adverse events, the proportion of participants experiencing injury, erythrocytosis, or other androgen-related or exercise-related adverse events.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine whether the multimodality intervention is efficacious in improving peak aerobic capacity more than placebo plus FES-LC plus arm ergometry alone.	Peak aerobic capacity	Our primary outcome is peak aerobic capacity because it is an excellent marker of overall health, physical function, and mortality. Aerobic capacity is closely related to metabolic health, insulin sensitivity and cardiovascular outcomes. It can be measured accurately in SCI patients and would be expected to improve with the proposed interventions.
Secondary		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
• To determine whether multimodality intervention is more efficacious in increasing skeletal muscle mass. • To determine whether the multimodality intervention is more efficacious than placebo plus FES-LC plus arm ergometry in improving muscle strength and fatigability. • To determine whether the multimodality intervention is more efficacious than placebo plus functional electrical stimulation during leg cycling (FES-LC) plus arm ergometry in improving volumetric and areal bone density, and bone microarchitecture, and bone strength. • To determine whether the multimodality intervention is more efficacious than placebo plus FES-LC plus arm ergometry in improving metabolic health, as reflected in fasting glucose, A1C, insulin sensitivity, fat mass and distribution, plasma lipids, and inflammation markers. • To determine the efficacy of the multimodality intervention in improving self-reported physical function (using SCI-FI AT) and wellbeing (mood, anxiety, pain, loneliness and life satisfaction) • To determine the safety of	Whole body skeletal muscle and fat mass and intraabdominal fat will be assessed by magnetic resonance imaging (MRI), using the Dixon method for separation of water/ fat signals. Body composition will also be measured by DEXA. Maximal voluntary strength and muscle fatigability in the upper extremity will be assessed using the 1-repetition maximum in chest press. **Total, trabecular and cortical volumetric bone density; trabecular and cortical microarchitecture,** both measured using high resolution peripheral quantitative computed tomography (HR-pQCT) at the ultradistal tibia, proximal tibia and ultradistal radius. **Estimated bone strength** of the ultradistal tibia and radius, assessed using microfinite element analysis of the HR-pQCT data. **Areal bone mineral density** of the hip and lumbar spine using dual-energy X-ray absorptiometry (DEXA). (aBMD will be measured because DEXA is a clinically used and accepted measure of bone density, and aBMD is predictive of fracture risk.) **Serum bone turnover markers,** including markers of bone formation (osteocalcin, bone specific alkaline phosphatase, PINP) and bone resorption (CTX).	MRI scanning using Dixon technique is noninvasive and offers greater accuracy and precision in assessing whole body skeletal muscle mass and whole body and regional at mass than DXA. The use of HR-pQCT for measuring volumetric bone density, bone architecture and bone strength is ideal in the SCI population for several reasons. First, in a large multi-national prospective study (>7000 individuals), we recently showed that bone microarchitecture and strength measurements from HR-pQCT predict incident fracture independently of DXA-aBMD, providing strong evidence for their clinical relevance (45). Second as the peripheral skeleton (e.g., distal femur, tibia) is the most common site for fractures in SCI patients (6-8), it is logical to examine the response to this multimodal intervention at the distal tibia and distal radius, standard sites for HR-pQCT. Fourth, unlike DXA-aBMD, HR-pQCT is able to distinguish the trabecular and cortical compartments (45), thereby providing key information about the structural mechanisms contributing to improved bone strength following the proposed multimodal intervention. DEXA will be used to measure areal BMD of the lumbar spine and proximal hip. This assessment is proposed, despite its

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
home-based Multimodality Intervention	Measures of Metabolism: Fasting glucose, A1C; insulin sensitivity using HOMA-IR; IL-6 and hsCRP as inflammation markers; and plasma lipids, apolipoproteins B, C and A, and lipoprotein particles as markers of atherogenicity – all measured in the Brigham Research Assay Laboratory. Visceral fat will be assessed using Dixon MRI technique. Safety Assessments. Adverse event recording; CBC, blood chemistries, PSA, physical exams, menstrual history in women	limitations, because it is the current standard clinical method of diagnosing osteoporosis and predicting fracture risk. Safety assessment will include a listing of all adverse and serious adverse events**;** injuries, including those incurred during exercise training; number of persons with erythrocytosis; number of persons referred for prostate biopsy; prostate-related adverse events; major adverse cardiovascular events. Events will be classified according to MedDRA and SOC coding system and tabulated as absolute number of events and number and proportion of participants experiencing one or more event.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Hypothesis: This phase 2 efficacy trial will test the hypothesis that a Home-Based Multimodality Functional Recovery and Metabolic Health Enhancement Program that addresses multiple pathophysiologic factors in SCI and includes FES-LC plus arm ergometry and an androgen will be more efficacious than FES-LC plus arm ergometry plus placebo in improving aerobic capacity, function, metabolism, bone health, and wellbeing.

This proof-of-concept trial will be a 16-week, randomized, placebo-controlled, double-blind parallel group trial in community dwelling adults with SCI, 19 to 80 years of age, cervical and thoracic, AIS A, B, C, or D, 6 months or later after a SCI.

This phase 2 trial will be conducted at a single trial site.

Randomized allocation. The participants will be randomly assigned to one of two intervention groups, using a computer-generated concealed block-randomization scheme with randomly varying blocks of 4 and 6, and stratification for sex (male, female), and age (19 to 44, 45 to 80 years), and AIS score (A, B, C or D):

Group A: Multimodality intervention: home-based training (FES-LC and arm ergometry) plus testosterone undecanoate IM.

Group B: home-based training (FES-LC and arm ergometry) plus or placebo injections IM.

No interim analysis are planned. However, the trial's DSMB will review the safety data and trial's progress every 6 months.

Blinding

The participants and the study staff will be blinded to the study medication. Treatment assignment will be known only to the Data Coordinating Center and the Investigational Drug Pharmacy. The syringes containing the testosterone undecanoate and the placebo injections will be masked to maintain blinding.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The control group will receive the exercise training and injections of a matching placebo intramuscularly.

Rationale for intervention duration. We weighed the advantages and disadvantages of shorter (up to 12 wks.) and longer intervention duration (12 months). We selected a 4-month duration because the effects of androgen, arm exercise, and FES-LC on aerobic capacity, muscle mass, strength, and insulin sensitivity become manifest within this period. Longer durations are associated with higher attrition rates, reduced compliance, and higher costs. A 4-month intervention duration provides the best trade-off.

As described in detail under Sample Size Estimation and Statistical Power, the trial plans to randomize 84 eligible subjects. This sample size estimate was based upon the following assumptions: 1. Two-sided type-I error probability 0.05; 2. randomization in a 1:1 ratio and stratification by sex (male, female), age (19-44, 45-80), and (A, B, C or D): 3. a loss-to-follow-up rate of up to 20%; primary analysis utilizing all subjects based on their randomized assignment; 90% statistical power to test the primary hypothesis; power analysis utilizing multiple imputations, consistent with theory and prior experience.

4.3 JUSTIFICATION FOR DOSE

The testosterone undecanoate dose for men is based on data showing that these doses are safe and efficacious in increasing lean mass and strength, and are within the range of doses approved by the FDA. The use of testosterone undecanoate has many advantages: 1. Because of its long duration of action, only 3 injections will be required during the entire trial reducing participant burden and increasing compliance; 2. Substantial data are available on the safety and efficacy of testosterone in men and women from our own trials and other published literature; 3. The injections will be administered by the study personnel, ensuring adherence.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of

Activities (SoA), Section 1.3. The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1. Men and women, 19 to 80 years
2. Confirmed cervical and thoracic, AIS A-D who are at least 6 months post-injury and who use a wheelchair as their primary mobility mode
3. Medically stable, able to follow directions
4. Able to provide informed consent.
5. For females of reproductive potential who are sexually active: use of highly effective contraception for at least 1 month prior to Day 1-and agreement to use such a method during study participation and for an additional 12 weeks after the end of intervention.

5.2 EXCLUSION CRITERIA

1. Upper extremity musculoskeletal conditions (such as advanced rotator cuff pathology or carpal tunnel syndrome) or neurological disorder that in the assessment of the study investigator would prevent the participant from performing the prescribed arm ergometry.
2. Current fractures in the upper and lower extremity
3. In accordance with the Endocrine Society and ISSAM Guidelines[25,52], we will exclude individuals with a contraindication for androgen use:
    - History of prostate or breast cancer
    - Prostate nodule or induration on digital rectal examination (DRE)
    - Prostate specific antigen (PSA) > 4 ng/ml or > 3 ng/ml in individuals at high risk of prostate cancer such as African Americans or those with family history of prostate cancer in first degree relatives, unless there has been a negative prostate biopsy within 3 months
    - Hematocrit > 50%
4. Conditions that would render exercise and FES unsafe or unfeasible such as severe autonomic dysreflexia, severe pressure sores, severe spasticity and severe pain.
5. Body mass index (BMI) > 45 kg/m^2
6. Renal dysfunction as indicated by GFR of <50 ml/min, estimated by using the Modification of Diet in Kidney Disease (MDRD) Study equation, in accordance with K/DOQI guidelines
7. Use of testosterone or other anabolic therapies, including DHEA and androstenedione, or rhGH in the preceding 6 months
8. Active cancer requiring therapy and which may limit life expectancy to less than 5 years
9. Uncontrolled and untreated Psychosis, bipolar disorder, or major untreated depression

10. Dementia (Mini-Mental Status Exam [MMSE] <24)
11. Myocardial infarction (MI) or stroke within 3 months of entry
12. Pacemaker
13. ALT and AST > 3 x upper limit of normal
14. Poorly controlled diabetes as indicated by hemoglobin (Hb)-A1c greater than 9.0% or diabetes requiring insulin therapy
15. Blood thinners such as Coumadin, heparin, rivaroxaban (Xarelto), dabigatran (Pradaxa), lovenox (subcutaneous heparin), apixaban (Eliquis) **(aspirin, plavix and other anti-platelet agents are allowed)**
16. Systolic blood pressure (BP) > 170 or diastolic BP > 100 mm Hg
17. Current grade 2 or greater pressure ulcers at relevant contact sites
18. Pressure sores or open wounds on the areas that restricts their participation
19. Because the safety of testosterone has not been established in pregnancy and lactation, we will exclude pregnant or lactating women and women of childbearing potential who are sexually active but are unwilling or unable to use a reliable form of contraception. We will perform a urine test to exclude pregnancy at the time of enrollment.
20. Participation in a structured exercise program currently or in the past 2 months and unwilling to stop the structured exercise program if ongoing at time of screening. Specifically, participation in a structured exercise program, currently or in the past 2 months, that involves progressive resistance exercise training of moderate to high intensity or regular endurance exercise of moderate to high intensity, and unwillingness to stop the structured exercise program if ongoing at time of screening.
21. Inability or unwillingness to participate in the exercise training or the assessments of muscle performance and physical performance

5.3 LIFESTYLE CONSIDERATIONS

- The participants will be advised not to participate in any other exercise program other than that prescribed in the study protocol. The participants will be advised not to participate in any other structured progressive resistance exercise training of moderate to high intensity or regular endurance exercise of moderate to high intensity other than that prescribed in the study protocol.

- The participants will be advised not to make major changes in their dietary intake, such as starting a weight loss diet or using a high protein supplement

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. Minimal information including nonidentifying demographic information and reasons for screen failure will be recorded. Individuals who do not meet the criteria for participation in this trial (screen failure) because of a specify modifiable factor may be rescreened. Rescreened participants will be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment Plan:

As described in detail below, for maximal efficiencies in recruitment activities, we will utilize several existing resources: 1. Patients receiving care at Spaulding-New England Regional Spinal Cord Injury Center's (SNERSCIC) at the Spaulding Hospital and the Spine Center at the Brigham and Women's Hospital; 2. The database of the Spaulding-New England Regional Spinal Cord Injury Center's (SNERSCIC) Patient Registry; 3. The use of the electronic medical records of the Partners Healthcare System (PHS) using the Research Patient Data Registry (RPDR) and an IRB-approved search process; distribution of informational materials to persons with SCI through the National Spinal Cord Injury Association (NSCIA) to facilitate recruitment, through its support groups, Peer Visitors, newsletter articles, magazine public events, and mailings to members. In addition, study flyers and posters will be displayed in clinics and community organizations that serve persons with SCI. Similarly, informational materials will also be distributed through the patient registry and network maintained by the Spaulding-Harvard SCI Model System Program.

Community dwelling adults with SCI who meet the eligibility criteria will be recruited from the Spaulding-New England Regional Spinal Cord Injury Center's (SNERSCIC) at the Spaulding Hospital and the Spine Center at the Brigham and Women's Hospital.

The Spaulding Rehabilitation Hospital Boston and the Brigham and Women's Hospital's Spine Center cater to nearly a 1000 patients with SCI annually. As described in Preliminary data, the NERSCI Model System's patient registry has nearly 670 participants.~~,~~ We will also reach out to members of the Spaulding Research Registry. This registry is separate from the Model List and is comprised of Spaulding patients who've given consent to be contacted for research studies. An additional large pool of SCI patients is available through the Partners' Electronic Medical Records using the RPDR search engine.

Also, the National Spinal Cord Injury Association (NSCIA) works closely with the NERSCI Model System program in facilitating recruitment, through its Peer Visitors, newsletter articles, and mailings. Therefore, recruiting 24 patients each year should not be difficult.

In addition, Restorative Therapies, the manufacturer of the equipment used for the intervention, will distribute IRB approved information about the study to customers who've expressed an interest in receiving updates and other information related to SCI. We may also advertise on Craigslist, Research Match, Partners Healthcare System Rally, Partners RSVP, and on our Research Unit's website (hosted by Partners Research Computing Core.) In addition, we may place advertisements in local newspapers or on online media platforms such as Facebook. Only IRB-approved text will be used for advertising.

To evaluate the feasibility of recruiting patients, who meet the eligibility criteria for the proposed RCT, we reviewed the electronic medical records of the Partners Healthcare System (PHS) using the Research Patient Data Registry (RPDR) and an IRB-approved search process. Of 15,384 unique patients, who were seen or hospitalized with a diagnosis of SCI from 2000 to 2017 within the PHS, 95% were 20 to 59 years of age. 72% were White, 7.1% Black, 7.4% Hispanic, and 2.4% Asian. 32.5% had cervical injury, 46.6% thoracic, 20.9% lumbar, and 33.8% had injury affecting more than one level. 11.6% had died; 26.0% had

disqualifying co-morbid conditions such as recent myocardial infarction, cancer, autonomic dysreflexia, or poorly controlled diabetes. Overall, 6,393 (41%) were potentially eligible to participate.

Additionally, we queried the database of the Spaulding-New England Regional Spinal Cord Injury Center's (SNERSCIC) Patient Registry; this search yielded 856 persons, 19 to 70 years, who had incurred an SCI 6 months or earlier. Among these 856 age-eligible persons, who had consented to be a part of patient registry, 376 (44%) had AIS grade A, B or C, and an additional 176 patients (19%), who were seen prior to advent of AIS grading, had an equivalent Frankel grade. 375 out of the 856 (44%) patients had C7-T12 level injury. Overall, 38% met major eligibility criteria, consistent with the results of the RPDR survey. We recognize that the patients who are enrolled in the registry are likely to be more motivated in participating in the trial than those found through the RPDR search. Furthermore, new patients with SCI are being added to the pool each year. In light of the large pool of potentially eligible patients identifiable through the RPDR, and an additional pool of motivated patients within the SNERSCIC's Registry, recruitment of 24 patients per year is feasible.

Minority Enrollment

Enrollment table summarizes the aggregate racial and ethnic background of the potential participants. Based on our experience in previous trials in persons with spinal cord injury and the demographics of the catchment area, 9% of participants at the trial sites are expected to be African-Americans, 7% Hispanics, and 2% Asians and others. Thus, minority participants will constitute over 18% of the overall sample participants, higher than in most published trials in spinal cord injury and higher than in the general population of Massachusetts.

Previous research has identified barriers to the participation of minorities in clinical trials, including cultural social-context of patients' lives; fear of participating in research studies, mistrust of the medical community and the burden associated with trial participation. Facilitators to trial participation included physician enthusiasm and good communication skills, a good provider-patient relationship and trust in the study staff, having a perceived benefit, and feelings of altruism. Based on this literature, staff training in cultural sensitivity, securing buy-in from the participant's usual healthcare provider, securing endorsement of community leaders and local church, and minimizing the burden of participation by methods described above should facilitate recruitment of minorities in the trial.

Subject Retention Plan

We have incorporated multiple steps to enhance subject retention:

1. Home-based intervention: The intervention will be administered in the person's home making it easier for the participant to stay in the trial;
2. Provide assistance with transportation. A major challenge in the lives of persons with SCI is getting to the medical center. Therefore, the study staff will assist the participants in arranging transportation for their visits to the clinical research center. The study also will reimburse the participants for their transportation expenses. To further minimize the participant burden, the intervention is being implemented in the participant's home to the extent possible.

3. Scheduled video or audio monitoring sessions will enable the study staff to stay in close contact with the participant on a regular schedule throughout the course of the trial, ascertain whether the participant is experiencing difficulties with the intervention.
4. Study staff will hold regular video conferencing sessions, through Zoom, with participants to create an exercise class that any participant will be allowed to join. Participants will be at their home using the RT300 machine. The classes are meant to increase exercise adherence with participants and allow them to connect with each other. The classes would be held by study staff at least once a week, when several subjects are available during a given time. The Zoom will not be recorded.
5. The study staff will make regularly scheduled phone calls to keep the participants engaged and to remind the participants about upcoming study visits and procedures, and to keep them engaged.
6. A consultant will train study personnel in the use of motivational interviewing to keep the participant engaged in the study. The consultant will engage with study staff only and will not have access to subjects or subject data.
7. The study will offer the participants open label androgen therapy at trial's end to those in control group, should they wish to do so. This will reduce the burden of participation in a randomized blinded trial for subjects who may wish to receive the active intervention.
8. A motivated, well-trained study staff is an important contributor to participant retention. Our retention rates in previous randomized trials have been high, reflecting the high degree of professionalism and dedication of our study staff; in a recent feeding study in functionally-limited older persons, that required eating a custom-prepared diet for a period of 6 months and weekly visits to our research center, our retention rates were greater than 85%; adherence to the prescribed diet varied from 81 to 86% and adherence to study medication was nearly 99%.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Stretching Exercises:

Exercise physiologists will lead participants through a five-minute stretching routine prior and post testing. This routine will be continued throughout their 16-week training program. The stretching exercises will be used to maintain shoulder health and prevent overuse of shoulders.

The Home-Based Multimodality Functional Recovery and Metabolic Health Enhancement Program includes exercise training at home consisting of FES-LC plus arm ergometry plus testosterone undecanoate or placebo. Study staff will administer testosterone undecanoate injections in the clinical research unit under observation. The use of testosterone undecanoate has many advantages: 1. Because of its long duration of action, only 3 injections will be needed for the entire duration of the trial. 2. It is amenable to administration by the study personnel assuring adherence and safety; 3. Previous trials have reported the safety of testosterone in men and women.

Exercise training: Functional Electrical Stimulation leg cycling **(**FES-LC) and arm cycle ergometry (AE) will be performed in the subjects' homes on the RT300 leg and arm system (Restorative Therapies, Inc. (RTI), Baltimore, MD, Support letter) with an AE customized for simultaneous integrated together with the RT300 frame. Functional Electrical Stimulation is an established rehabilitation modality used to stimulate lower motor neurons in individuals who may have lost all or some voluntary control of nerves connecting the spinal cord to peripheral skeletal muscle. Stimulating these nerves evokes patterned movement of the legs such as for leg cycling. Electrical stimuli will be conducted to the quadriceps, hamstrings, and gluteii of both legs via surface electrodes. Visual feedback on leg cycling stimulation level, speed, distance, work rate are presented to the user on a display and transmitted to a secure server in real time via the RTILink data acquisition system. Study staff may access these data either in real time or at any time after a training session. The FES-LC and AE exercise device may be used with the participants' wheelchair which is securely attached to the bottom of the device frame. Arm ergometry is also a well-established training modality in both spinal cord injured as well as able bodied people.

After baseline testing, all subjects will have the opportunity to complete their initial exercise training sessions in the exercise laboratory under the direct supervision of a staff exercise physiologist. Training will be tailored specifically to each individual and appropriately adjusted and programmed for each individual according to the schedule outlined in Table 1. Subjects and their caregivers, if available, will be given detailed instructions on electrode application and removal, skin care, and proper use of the FES-LC and AE device used for training. During the 1-2 weeks of training, subjects will be guided to become independent in use of the exercise device. Subjects will attempt to exercise continuously for 20 min at 50% peak work rate (WRpeak) achieved in incremental the test for aerobic capacity (Section 8/1). If 20 min continuous exercise is not possible, the subject will be instructed to cycle as long as possible followed by a 4 min rest period until 20 total exercise minutes are accumulated. Around the day 1 injection and the start of the subjects' first week of training, study staff will visit each subject in his or her home to drop off and set up the machine. Subsequently, remote audio or video monitoring will commence using Skype for Business, Zoom, or another Partners-approved video monitoring tool. Study personnel will ask subjects about problems and will remind subjects to do regular skin checks. Subjects will be given a diary to fill out based on the Borg rating of perceived exertion (RPE). Subjects will note their mid-point RPE scale for each exercise session during the 16-week program.

All FES-LC exercise training sessions will start with a 3-min motor-assisted warm-up with no electrical stimulation. Subjects will perform arm cycling at 50 rpm with no resistance. Stimulation parameters for FES include frequency, pulse width, and amplitude. Since subjects will have varying time since injury (months to several years) and different lesion levels, we will apply the stimulation parameters with a range chosen to accommodate not only entry characteristics but also changes in responsiveness to the stimulation over the 16-week training periods. We will apply frequencies of 20 Hz to a maximum of 100 Hz. Higher frequencies increase force production but also increases fatigue which can limit training duration. Low frequencies are more tolerable in more recently injured individuals as well in those who are initially unresponsive. Pulse width will range between 150 and 500 microseconds. Longer pulse widths evoke greater torque production and can result in tetanic contractions facilitating

joint movement. Higher pulse width used with lower frequencies can lead to maximizing torque while minimizing sensation. Amplitude is the intensity of the stimulation. Greater amplitude increases the size of the activated muscle and torque production. However, some spinal cord injured people cannot tolerate pain associated with higher amplitudes. Amplitude will be set in a range of 0-140 mA per channel adjusted automatically along with flywheel resistance to maintain the target peak work rates. If the target duration cannot be performed continuously we will allow shorter intervals interspersed with rest to accumulate the exercise duration target. After warm-up, the resistance will then be increased to the target work rate for both FES-LC and AE and sustained continuously as tolerated for the target durations in each of the four training phases. As with FES-LC, individuals who are unable to maintain continuous arm exercise will be allowed to finish the target duration in interval fashion. Subjects will be instructed to inform staff exercise physiologist about difficulties in performing continuous exercise for the target duration. In addition, daily review of training data will alert the exercise physiologists to this difficulty followed by appropriate revisions of training routine.

Training progression. Progression in duration, intensity, and frequency of FES-LC and arm ergometer is described in Table 1. Over the course of the study, duration will increase from 20 minutes to 40 minutes, intensity from 50% to 80% of baseline peak work rate, and weekly training frequency will increase from 3 d/wk to 4 d/wk. As noted in Table 1, the actual targets for duration, intensity and frequency may be adjusted as tolerated by each subject. If a subject misses or is unable to complete an exercise session (s) according to the 16 week schedule outlined in Table 1, make-up exercise sessions may be performed. Study staff will liaise with the subject to confirm the specific duration, frequency and intensity of any make-up exercise sessions.

Table. 1. 16-week progressive exercise training using functional electrically stimulated leg cycling (FES-LC) and arm ergometry (AE).

Study Week	Weeks 1-2	Weeks 3-6	Weeks 7-10	Weeks 11-16
Location	Exercise Physiology Laboratory and/ or Home	Home		
Duration FES-LC	10-20 minutes (in intervals as needed)	20-25 minutes	25-30 minutes	30-40 min as tolerated
Duration Arm Ergometry	20 minutes (in intervals as needed)	20-25 minutes	25-30 minutes	30-40 min as tolerated
Frequency FES-LC and AE	1-3 days/wk	3 days/wk	3 days/wk	4 days/wk as tolerated
Intensity FES-LC and AE	40-50% WRpeak RPE: (11-13)	50-60% WRPeak RPE: (12-14)	60-70% WRPeak RPE: (13-15)	70-80% WRpeak RPE: (11-16)
AE = arm ergometry; WRpeak = peak work rate; Frequency, duration, and intensity adjusted according to exercise tolerance. The frequency of training in the exercise laboratory will be determined by the Exercise Physiologist and the subject's knowledge of using an FES-LC machine				

Rationale for intervention duration. We weighed the advantages and disadvantages of shorter (up to 12 wks) and longer intervention duration (12 months). We selected a 4-month

duration because the effects of androgen, arm exercise, and FES-LC on aerobic capacity, muscle mass, strength, and insulin sensitivity become manifest within this period[18-20,40-42,46-50]. Longer durations are associated with higher attrition rates, reduced compliance, and higher costs. A 4-month intervention duration provides the best trade-off.

6.1.2 DOSING AND ADMINISTRATION

Testosterone undecanoate injections will be administered by the study personnel. The subjects will be observed for 30-minutes as recommended. The testosterone undecanoate dose for men (first dose of 750-mg on the day of randomization, second 750-mg dose during week 4 (Day 29+/- 7 days), and the third 750-mg dose during week 14 (day 98 +/- 7days) is based on the approved regimen and Endocrine Society guidelines. The dose used in women will be one fourth that used in men (first 180 mg dose on the day of randomization, second 180-mg dose during week 4, and the third 180-mg dose during week 14). A large body of published data have shown the safety and efficacy of testosterone in increasing lean mass and strength, and bone density. The participants randomized to the control group will receive an equal volume of placebo on Day 1, Day 29+/-7 days, and Day 98 +/- 7 days.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The study drug product supplies will be provided by ENDO Pharmaceuticals, the manufacturer of the drug in the USA and shipped to the Investigational Drug Services (IDS) at the Brigham and Women's Hospital, where it will be stored at 4C until its dispensing.

Investigational product supplies will be counted and reconciled by the Investigational Drug Services at the Brigham and Women's Hospital.

The investigator and the IDS will ensure that the investigational product is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of the investigational product, the investigator or designee will maintain records of all investigational product delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Receipt of investigational product, the unblinded pharmacist or designee will verify the contents of the shipments against the packing list. The unblinded verifier should ensure that the quantity is correct, the medication is in good condition, and no temperature excursions have occurred. If quantity and conditions are acceptable, the unblinded verifier will acknowledge the receipt of the shipment by signing bottom half of the packing list and faxing per instructions provided on the form. If there are any discrepancies between the packing list versus the actual product received, the Sponsor will be contacted to resolve the issue. The packing list will be filed in the investigator's essential document file.

The IDS will maintain 100% accountability for all investigational products received and dispensed during the conduct of the study.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The study medication (testosterone undecanoate, AVEED) will be purchased from ENDO Pharmaceuticals, the approved manufacturer in the USA. The drug will be stored in the Investigational Drug Services at the Brigham and Women's Hospital. The pharmacist will draw the medication in syringes, label them and mask the syringes to maintain blinding. Testosterone undecanoate is supplied at a concentration of as 250 mg/ mL.

6.2.3 PRODUCT STORAGE AND STABILITY

The study medication will be stored at room temperature at 25C; excursions permitted (15 to 30 C. The drug is stable until the expiration date on the label.

6.2.4 PREPARATION

Testosterone undecanoate is supplied at a concentration of as 250 mg/ mL. The appropriate dose of the active medication or placebo for each participant will be loaded by the IDS pharmacist and provided to the study personnel on the day of its use.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The participants will be randomly assigned to one of two intervention groups, using a computer-generated concealed block-randomization scheme with randomly varying blocks of 4 and 6, and stratification for sex (male, female), and age (19 to 44, 45 to 80 years), and AIS score (A, B, C, or D).

Subjects will be assigned to receive their treatment (active or placebo) according to the randomization schedule developed by the study Biostatistician. Subjects will be assigned a randomization number in the order in which they are enrolled.

This randomization number will be used by the clinical site to facilitate the pre-labeling of samples, and will be the only subject identifier used on all sample collections. It should also be contained on the transport vials shipped to the bioanalytical laboratories and will be used by the laboratory to report the subject data results. This 4-digit number will be used for all procedures to identify the subjects throughout the study.

The Study Biostatistician will generate the randomization schedule and will provide it to the site pharmacist prior to the start of this study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

INVESTIGATIONAL PRODUCT BLIND MAINTENANCE

The investigational product blind is maintained through a randomization schedule held by the dispensing pharmacist and the study biostatistician. The study is double-blind in that the study subjects and the study staff involved in outcomes assessments will be unaware of the intervention assignment. The randomization schedule will be masked from all study personnel except those specifically designated below.

The personnel who will have access to the intervention assignment include:

a. The study biostatistician who performs the randomization.

b. The staff of the Investigational Drug Pharmacy Services.

c. The DSMB, if requested.

6.4 STUDY INTERVENTION COMPLIANCE

Treatment adherence will be assessed as the proportion of scheduled injections actually administered and the number of home-based exercise sessions undertaken.
The trial embeds several strategies to enhance adherence: motivational interviewing-based approach to engage the participant and caregiver; video supervision of home-based exercise; frequent phone contact; and the offer of post-study open-label androgen therapy for participants in the control group; and assistance with transportation to enable subjects to keep scheduled appointments.

6.5 CONCOMITANT THERAPY

At each visit, the study staff will record any concomitant medications, its start date, reason for its use, and end date. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

6.5.1 RESCUE MEDICINE

Not applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

The following Termination Criteria will be used:

- An increase in hemoglobin level above 18.0 g/dL would warrant discontinuation of treatment.
- Myocardial infarction or stroke
- Diagnosis of prostate or breast cancer
- Serious hypersensitivity reaction to study drug administration

We recognize that other unexpected adverse events can occur. Therefore, we have instituted a comprehensive plan for structured monitoring to ensure early detection of adverse events. The Data Safety Monitoring Board will be empowered to discontinue treatment in one or more subjects, or halt the study, should the occurrence of adverse events so warrant.

Follow-Up of Patients Whose Hemoglobin Rises Above 180 g/L

If the hemoglobin level rises above 180 g/L, and this increase is confirmed by repeating the measurement, the intervention will be discontinued and the participant will be referred to his/her primary care provider for further management. If the participant has neuro-occlusive symptoms, a therapeutic phlebotomy may be performed. The hemoglobin level will continue to be followed on a weekly basis until hemoglobin level has fallen to a safe level (<165 g/L).

Follow-up of Patients with PSA Elevation

PSA levels may fluctuate simply because of inter-assay variability. An expert panel of the Endocrine Society suggested urological consultation for evaluation of confirmed PSA increments > 1.4 ng/ml after initiation of androgen therapy[25]. This recommendation is based on observations that increases in PSA levels after **testosterone therapy** in androgen-deficient

men in excess of 1.4 ng/ml over a 3- to 6-month period are unusual. The 90% confidence limit for the change in PSA levels between two tests performed 3 to 6 months apart in a study of men with benign prostatic hyperplasia was 1.4 ng/ml. In a systematic review, the average PSA increase after initiation of **testosterone therapy** was 0.3 ng/ml in young, hypogonadal men and 0.44 ng/ml in older men[25]. Therefore, if a PSA elevation above baseline exceeds 1.4 ng/mL and is confirmed, intervention will be discontinued and the participant will be referred to a Urologist for further evaluation.

Discontinuation from study intervention does not mean discontinuation from the study, and every effort will be made to complete the remaining study procedures as indicated by the study protocol.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for scheduled visits over a 4-week period and is unable to be contacted by the study site staff.

The following actions will be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

We have included both performance-based measures of exercise capacity and function, as well as patient-reported outcomes which will provide a comprehensive assessment of efficacy.

Peak Aerobic Capacity. Cardiopulmonary exercise tests (CPXT) will be used to ascertain peak aerobic capacity and other parameters of cardiopulmonary function separately for FES leg cycling (FES-LC) and arm ergometry, and concurrent FES-LC plus arm ergometry. Standardized procedures for CPXT will be used for all tests. Subjects will come to the exercise laboratory for equipment and procedure familiarization on a separate day prior to the three tests described above. The familiarization visit will include showing participants proper electrode placement, setting their stimulation parameters, how to navigate the RTI tablet, and adjusting the RT300 set-up for each participant.

FES-LC CPXT: Warm-up for the FES-LC will consist of 3-min of motor-assisted FES-LC with no resistance and no electrical stimulation at a pedal frequency of 35-30rpm [25]. FES-LC will be performed with sequential electrical stimulation, via surface electrodes, applied to quadriceps, hamstrings, and gluteii at a frequency of 35-45 Hz, pulse width of 300 to 400 μsec, intensity of 100-140 mA per channel adjusted to maintain a pedaling frequency of 35-40 rpm. Work rate will start at 0 watts then increase 0-3 watts per min to volitional fatigue as tolerated. Electrical stimulation will be discontinued when cadence drops below 30 rpm.

Arm Ergometry: The arm ergometer incremental test will be performed using a Monark 891E arm ergometer (Monark Exercise AB, Vansbro, Sweden) administered 30 minutes after completion of the FES-LC CPXT. Work rates will be incremented by 10-20 watts per min to volitional fatigue. Arm cranking frequency will be set at 50 RPM. No electrical stimulation will be applied during arm ergometer CPXT.

Concurrent FES-LC Plus Arm Ergometry Exercise CPXT: Subjects will undergo CPXT while performing concurrent FES-LC plus Arm Ergometry. The subjects will begin the CPXT test using the arm ergometer. FES-LC will begin after arm exercise has started so that both FES-LC and arm exercise end together.

Measurement of VO_2 peak: A fully automated metabolic measurement system (Cardio2, Medical Graphics Corporation, Minneapolis, MN) will be used to measure minute ventilation and expired O_2 and CO_2 breath-by-breath via a bidirectional pitot tube flow sensor and electronic gas analyzers, respectively. $\dot{V}O_2$ and CO_2 output will be calculated with computer algorithms. Peak aerobic capacity will be identified as the highest 15-sec $\dot{V}O_2$ achieved during the last minute of the test. The EKG will be continuously monitored. Ratings of perceived exertion (Borg RPE scale) will be assessed every2 minutes . Blood pressure will be assessed every 3 minutes.

Upper Body Strength and Fatigability. Muscle strength in the upper body will be measured with the seated chest press exercise using a pneumatic resistance (Keiser Corporation, Fresno, CA) and the 1-repetition maximum method (1-RM). Subjects will transfer to the seat on the chest press machine with assistance. A shoulder harness and seat belt will be applied to help stabilize the subject and the feet will be supported. Seat height, handle position, and full range of motion will be standardized. Subjects will be familiarized with the exercise, practice the technique, and complete a brief low resistance warm-up. The 1-RM procedure consists of a warmup set with 5 to 8 repetitions at a resistance set to about 50% of the participant's estimated 1-RM. The test progresses with increasing loads interspersed with standardized rest periods until the subject is able to perform only one full range-of-motion repetition in good form. Load increments are determined by subject perception of effort and the examiner's experience. The participants will be tested twice on nonconsecutive days with the better of the 2 trials reported as the 1-RM. Fatigability in the chest press exercise will be assessed on the same machine and subject positioning used for the 1-RM tests. Subjects will

perform as many full range of motion, continuous repetitions as possible using good form. The load for this test will be 80% of the individual 1-RM. This load typically yields about 8 repetitions.

Body Composition and Intra-Abdominal fat by MRI using the Dixon Method. Whole body and regional muscle and fat mass will be assessed using a 2-point Dixon technique with a 3D gradient echo sequence on a 3T scanner, enabling acquisition of high-resolution 3D volumes. Both in-phase, and out of -phase, fat and water images can be generated from a single acquisition. Head-to-toe acquisition will be facilitated by the use of body coils to image the torso, and peripheral coils to image the lower extremities. Different fat compartments will be quantified using non-linear segmentation, based on the Dixon method[165-168]. Ground truth will be performed by comparing manual segmented image slices versus auto-segmented slices in a subset. Reproducibility will be evaluated by repeat analysis in a subset of the population. Body composition and fat mass will also be measured by DEXA.

Total, trabecular and cortical volumetric bone density; trabecular and cortical microarchitecture, both measured using high resolution peripheral quantitative computed tomography (HR-pQCT) at the ultradistal tibia, proximal tibia, and ultradistal radius.

Estimated bone strength of the ultradistal tibia and radius, assessed using microfinite element analysis of the HR-pQCT data.

Areal bone mineral density of the hip and lumbar spine using dual-energy X-ray absorptiometry (DEXA) . (aBMD will be measured because DEXA is a clinically used and accepted measure of bone density, and aBMD is predictive of fracture risk.)

Serum bone turnover markers, including markers of bone formation (osteocalcin, bone specific alkaline phosphatase, PINP) and bone resorption (CTX).

Determination of Circulating Metabolic Profiles: Ten ml fasting blood will be stored for hemoglobin A1C, plasma lipids, apolipoproteins A, B and CIII, and lipoprotein particles; inflammation markers hsCRP and IL-6.

Patient-reported Outcomes: Validated patient-reported outcome scales will provide a comprehensive assessment of how the ***"…participant functions, feels, and lives"*,** which the FDA views as important aspects of intervention efficacy. The study staff will provide standardized instructions to participants on how to fill the questionnaires. As discussed earlier, SCI-FI AT will be used to measure mobility, fine motor function, ambulation, and wheelchair mobility. **Wellbeing** measures include mood (PHQ-9), pain (Modified Brief Pain Inventory (BPI), anxiety (GAD-7), the Three-Item Loneliness Scale and life satisfaction, as described earlier.

8.2 SAFETY AND OTHER ASSESSMENTS

The safety assessment will involve recording of Adverse Events (AEs) and Serious Adverse Events (SAEs). Events will be classified according to MedDRA and SOC coding system. Safety measures include complete blood counts, blood chemistries, PSA levels in men, EKG, and physical exams. All injuries will also be recorded. Prostate (in men) and breast exam and menstrual history (in women) will be recorded.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.
- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should

be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

A study physician will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

A study physician will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked.

Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious AE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Non-serious AEs of Grade 1, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol. Subjects who experience any AE of Grade 2 or higher must be followed until resolution or stabilization of the event.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date and time.
3. Severity.
4. Investigator's opinion of the causal relationship between the event and administration of study medication(s) (related or not related).
5. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
6. Action concerning study medication.
7. Outcome of event.
8. Seriousness.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

An SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s)
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

The study PI will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable

8.3.9 REPORTING OF PREGNANCY

Any pregnancies in the female participant should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active investigational product, eg, after Visit Day 1 or within 12 weeks of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form.

Should the pregnancy occur during or after administration of blinded investigational product, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Partner pregnancy of subjects randomized to placebo need not be followed.

All pregnancies in the female participant will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported. An evaluation after the birth of the child will also be conducted.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The unanticipated problems are those that involve risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The PI will report unanticipated problems (UPs) to the Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DSMB within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DSMB at the time of the DSMB meeting or during the annual review.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary hypothesis is that a Home-Based Multimodality Functional Recovery and Metabolic Health Enhancement Program that includes FES-LC plus arm ergometry and androgen (testosterone undecanoate) will be more efficacious than FES-LC plus arm ergometry plus placebo in improving aerobic capacity.

Secondary hypotheses are that a home-based multimodality intervention that includes FES-LC plus arm ergometry and testosterone undecanoate will be associated with greater improvements in muscle mass, muscle strength and fatigability, function, metabolism, and wellbeing compared to FES-LC plus arm ergometry plus placebo.

9.2 SAMPLE SIZE DETERMINATION

We plan to recruit 84 subjects, based on the following considerations:

1. type-I error probability 0.05;
2. randomization in a 1:1 ratio and stratification by sex (male, female), age (19-44, 45-80), and AIS level (A, B, C, or D);
3. a loss-to-follow-up rate of up to 20%. This assumption of 20% loss to follow up rate was based on experience from intervention trials conducted by co-Is Zafonte and Latham in SCI patients. We expect a higher adherence and lower loss-to-follow up rate because of the home-based intervention, the use of a visiting nurse, and other measures but have assumed at most 20% loss-to-follow-up rate to be conservative.

There are no published trials of the combined administration of an androgen and FES-LC plus arm ergometry in patients with SCI. Therefore, the sample size estimates were guided by data on the effects of exercise in patients with SCI, the effects of testosterone in hypogonadal men and in patients with SCI, and the effects of testosterone undecanoate in other populations. This study will be powered to detect clinically meaningful differences in within-subject change in the primary outcome – aerobic exercise capacity - attributable to randomization to multi-modality intervention vs. exercise. The gains in aerobic capacity have varied substantially across trials, but have averaged around 10 to 14%[15-18]. Based on previous studies, we hypothesize that the mean gain attributable to exercise will be ~12%; we anticipate that addition of testosterone undecanoate exercise will augment the treatment effect and that the mean gain in peak oxygen uptake attributable to multimodality intervention will be 20%. Thus, conservatively, the treatment effect will be 8% improvement in peak aerobic capacity (SD no greater than 11%). Under the assumed effects described above, simulation studies estimated that the proposed primary mixed-effects analysis will have ~ 90% power to detect an effect size f = 0.75 SD with conservative assumption of within subject autocorrelation, rho = 0.45; however, based on our previous trials, we expect substantially higher within subject correlation. These changes are clinically meaningful because gains in aerobic capacity of 6-10% have been associated with improvements in outcomes in patients with SCI[15-18] and COPD[34].

We anticipate that multimodality intervention will increase lean mass by an average 2.8 kg whereas the exercise alone will induce only an increase of 0.8 kg. Using assumptions similar to our primary outcome, a sample size of 84 has more than 90% power to detect the hypothesized difference of 2.0 kg (SD 2.6 kg) between arms. In our previous studies in young and older adults, an equivalent dose of testosterone alone induced lean body mass gains averaging 2.8 to 3.2 kg[33]; these effects of androgen will be augmented by exercise training. In another trial by Bauman[53] et al, the lean mass gain after testosterone replacement of SCI patients averaged 2.7 kg, while the control group experienced a loss of 1.4 kg.

There are no data on the effects of the proposed multimodality intervention on vBMD or bone strength in persons with spinal cord injury. Therefore, we used data on the effects of

testosterone and other bone anabolic interventions on vBMD and bone strength measures.

We assume that the treatment effect will be smaller than that reported in intervention trials of testosterone and other anabolic interventions of 1 year or longer duration because the intervention duration of this trial is shorter. Because the treatment effect is related negatively to the baseline vBMD; subjects with lower vBMD have greater treatment response to bone anabolic agents than subjects with higher baseline vBMD. Because persons with SCI typically are profoundly osteoporotic or osteopenic, the treatment response to multi-modality intervention would be expected to be greater.

In the TTrials, we found that testosterone treatment of older men with low testosterone levels was associated with a 6.8% (SD 2.0%) greater improvement in vBMD by pQCT than placebo (effect size f = 3.4 SD units) (32). Because of the shorter intervention duration, we conservatively assume that the effect size for vBMD in SCI subjects receiving multi-modality intervention would be only half as much (1.7 SD units). Under the assumed effects described above, simulation studies estimated that the proposed primary mixed-effects analysis with a sample size of 66 subjects (33 in each arm) will have ~ 90% power to detect an effect size >1 SD and >95% power to detect the hypothesized effect size of 1.7 SD units for the primary outcome with conservative assumption of within subject autocorrelation, rho = 0.45; however, based on our previous trials, we expect substantially higher within subject correlation. This sample size was inflated to account for 20% loss-to-follow-up rate.

We anticipate that multimodality intervention would improve insulin sensitivity by ~30%, and the exercise alone by ~ 10%. A subsample of 30 completers has at least 80% power to detect this difference of 20% between intervention arms (SD no more than 18%). These assumptions are reasonable because in previous studies, FES and cycle ergometry have been shown to improve HOMA by ~25%[22]. Also, testosterone administration to hypogonadal men has been associated with an average 20% improvement in HOMA index; conversely, sex-steroid withdrawal in men was associated with 25-30% decrease in insulin sensitivity[27]. Similarly, the trial has sufficient power to detect effect sizes of 0.75 SDs or larger associated with the administration of multimodality intervention relative to exercise for all secondary outcomes.

9.3 POPULATIONS FOR ANALYSES

Intention-to-Treat (ITT) Analysis Dataset (also referred to as the randomized set) will consist of all randomized subjects (subjects who passed screening and were allocated a randomization number). This analysis set will be used for summarizing disposition, demographics, and baseline characteristics and for primary efficacy analyses.

Safety Analysis Dataset: The safety analysis set will consist of all subjects who are enrolled and received the investigational product (testosterone undecanoate or placebo), including subjects who do not complete all scheduled study visits. Subjects in this analysis set will be used for safety, demographic, baseline characteristics and summaries.
Per-Protocol Analysis Dataset: defines a subset of the participants in the full analysis (ITT) set who complied with the study and who took at least 80% of study medication and participated in at least 80% of the scheduled training sessions.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

We will employ descriptive analysis to describe the cohort and inform development of statistical models of intervention effects on outcomes. We will then utilize analysis of covariance (ANCOVA) and linear mixed-effect regression models to formally estimate intervention effects and test specified hypotheses with statistical control for design effects (i.e. control for stratification factors)). Model-based point estimates of treatment effect will be

accompanied by 95% confidence intervals. Participants will be analyzed according to randomized assignment (intent-to-treat). Hypothesis tests will assume a type I error probability 0.05. For primary and pre-specified secondary hypotheses, no type 1 error adjustment will be made, as recommended by Pocock.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Specific Aim 1 is concerned with estimating the efficacy of multimodality intervention in improving aerobic capacity relative to the control group. We will use an ANCOVA model to assess between-group difference in maximal aerobic capacity at baseline and each follow-up time points (baseline, 8 weeks, and 16-18 weeks) simultaneously. treatment effect, baseline value and will control for stratification factors (age, sex, AIS score) Estimated changes from baseline and 95% CIs will be extracted from ANCOVA model.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Specific Aims 2 and 3 will assess intervention effects on secondary outcomes (SCI-FI AT scores; wellbeing measures; plasma lipids, apolipoproteins and lipoprotein particles; and inflammation markers). We will use an approach similar to that for Aim 1, using mixed effects linear regression model controlling for stratification factors and baseline values, accounting for repeated measures using a person-specific random intercept, and employing robust variance estimation. Lean and fat mass, muscle performance, and insulin sensitivity will be examined by ANCOVA model with an approach similar to that for Aim 1.

Sensitivity Analyses will determine if pre-specified covariates influence the effect estimates. We will use a dimensionality-reduction strategy, using propensity scoring as a global adjustment factor. The following variables will be considered: sex; age (19-45, >45); baseline function; and adherence. Additional covariates may be incorporated based on exploratory analyses. We will perform per-protocol analyses on completers. Also, per-protocol analysis of subjects, who complete the trial, adjusting for compliance will be performed.

Treatment Adherence will be assessed as the proportion of scheduled injections actually administered and the number of home-based exercise sessions undertaken. A sensitivity analysis will employ adjustment for adherence. In prior trials involving injectable testosterone, we have achieved high adherence rates; e.g., in OPTIMEN Trial, we had 98% adherence with injections even in subjects with limited mobility.

Analyses of Bone Substudy. We will utilize analysis of covariance (ANCOVA) and linear mixed-effect regression models to formally estimate intervention effects and test specified hypotheses with statistical control for design effects (i.e. control for stratification factors - age, sex, injury level). Model-based estimates of treatment effect will be accompanied by 95% confidence intervals. Participants will be analyzed according to randomized assignment (intent-to-treat). All subjects who have a baseline and a post-treatment assessment of vBMD will be included in the analyses. Hypothesis tests will assume a type I error probability 0.05. For primary and pre-specified secondary hypotheses, no type 1 error adjustment will be made, as recommended by Pocock. **Sensitivity Analyses** will determine if pre-specified covariates influence the effect estimates. We will use a dimensionality-reduction strategy, using propensity scoring as a global adjustment factor. The following variables will be considered: sex; age (19-40, >40); baseline vBMD; baseline testosterone and estradiol levels; and adherence. Additional covariates may be incorporated based on exploratory analyses. We will perform per-protocol analyses on completers. Also, per-protocol analysis of subjects, who complete the trial, adjusting for compliance will be performed.

Analyses will not be adjusted for multiple comparisons because the hypotheses being tested are pre-specified; furthermore, the bone outcomes are highly correlated, making such adjustments overly conservative.

9.4.4 SAFETY ANALYSES

The Safety Assessment will involve tabulation of Adverse Events (AEs) and Serious Adverse Events (SAEs), and assessment of differences in event rates as appropriate. Events will be classified according to MedDRA and SOC coding system and tabulated as absolute number of events and number and proportion of participants experiencing one or more event. Testing of differences between the proportions of individuals with one or more events across arms will use multiple regression analyses with control for design effects.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

We will assess the distributional characteristics of outcomes and covariates. Participant characteristics will be summarized using means, medians, standard deviations, skewness, kurtosis, interquartile intervals and ranges for continuous variables, and counts and proportions for discrete variables. Where appropriate, transformation of variables to combat skew, or other irregularities will be employed. Comparability of groups will be assessed using graphical methods.

9.4.6 PLANNED INTERIM ANALYSES

No interim analyses are planned. We will however monitor safety, accrual, adherence, attrition, data quality, and comparability of groups. Data quality tables will be developed for DSMB reporting.

9.4.7 SUB-GROUP ANALYSES

We will control for sex, age, and AIS score as they are stratification factors in the design. Additionally, primary analysis will be assessed for robustness to control for age, sex, baseline function, and comorbid conditions. We will also consider the potential for sex to modify the effect of intervention on outcomes using interaction terms. However, this proof-of-principle study does not have sufficient power to determine sex differences. Potential sex-specific adverse effects (e.g., hair growth or menstrual irregularity in women, and prostate-related adverse events in men) will be recorded.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be listed.

9.4.9 EXPLORATORY ANALYSES

No exploratory analyses are planned.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for

purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the subject and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the subject and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care. Consent form describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent will be required prior to starting intervention/administering study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator, nurse practitioner or designee will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided to study participants, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

The Investigator reserves the right to terminate the study in the interest of subject safety and welfare. The Sponsor reserves the right to terminate the study at any time for administrative reasons.

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor and IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, MHRA, PMDA), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 13.2)

Certificate of Confidentiality

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored by the trial's Data Coordinating Center and deposited with the clinicaltrials.gov as required by law. After the study is completed, the de-identified, archived data will be transmitted to and stored at the clinicaltrials.gov.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored in the PI's laboratory for future use.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Principal Investigator and the Medical Monitor.

Principal Investigator	**Medical Monitor**
Shalender Bhasin	*To be designated upon funding*
Brigham and Women's Hospital	
75 Francis Street, Boston, MA 02115	
617 525 9150	
sbhasin@bwh.harvard.edu	

10.1.6 SAFETY OVERSIGHT

Data Safety Monitoring Board

The DSMB will include three to five individuals with expertise in spinal cord injury, clinical trials, and biostatistical analysis of clinical trials data. These individuals will be appointed by the NIH program staff upon recommendation of the investigators and after review of their expertise and potential conflicts of interest by the NIH staff.

SAFETY REVIEW PROCEDURES:

1. The DSMB will meet to review the safety data every 6 months. This review will take place either in person or by teleconference. A majority must be present at the DSMB meeting to have a quorum.

2. **Risk categorization:** The categorization for this ongoing study is considered moderate risk. Based on the review of published and unpublished experience with testosterone undecanoate and exercise and FES-LC interventions, we feel that the overall risks to participants are in the moderate category. Therefore, six-monthly reviews by the DSMB are appropriate.
3. Generation of safety reports. The DCC and the study staff will generate the initial safety reports. This will be done in a blinded fashion. The unblinded biostatistician will add a code that will allow the DSMB to review the safety data by individual treatment groups, while keeping the study team blinded.
4. The unblended statistician will send the finished report directly to the various DSMB members. This will allow the DSMB to review the safety data by individual treatment groups, while keeping the study team blinded. In the event that the DSMB requests unblinding of the study, the code will be sent from the third party directly to the DSMB. Thus, the DSMB members can have access to the categorized data, while the investigating team remains blinded.
5. Review of all adverse events will be performed by treatment group (coded A or B).

   Each DSMB report will include the enrollment status, including the number of subjects recruited, screened, and randomized. In addition, it will incorporate the number of dropouts and the reason for the dropouts. The investigating team will comply with the NIH as well as institutional policies on reporting adverse events. The report will list all adverse events since the previous reporting period. In addition, a cumulative list of all adverse events will be provided to the DSMB members. The summary of all adverse events will allow for a comprehensive review of the events rates. All AE's will be evaluated for severity and attribution. In order to protect participant confidentiality, the data provided to the DSMB will be coded so that individual participants cannot be identified.

   Each DSMB meeting will be comprised of 2 portions. Research personnel will be present for the "open discussion" at the start of the DSMB meetings. The initial "open" portion of the meeting will have study personnel available to give an update on the enrollment status and safety data, and to respond to any questions that the DSMB may have. The second portion of the meetings will be "closed" to study personnel so that DSMB members may conduct independent deliberation. Provisions will be made for study personnel to be available to the DSMB committee during these deliberations, should their input be required.
6. In addition to these review procedures the DSMB will receive copies of all serious adverse events, with study group assignment (A or B) as they occur.
7. DSMB will meet twice each year.

Transmission of DSMB Recommendations to IRBs

A summary of the DSMB review and recommendations will be sent to the Principal Investigator and the NIH program staff after each DSMB meeting. The PI will then forward the DSMB report to the IRBs of the participating sites.

Summary of Closed Deliberations:

The NIH Program staff will receive a copy of the "closed" deliberations. This information will be kept in a secure file, accessible only to the NIH Program Staff.

10.1.7 CLINICAL MONITORING

An external monitor may be designated by the NIH or by the institution to perform site monitoring periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Regulatory Binder, investigational product, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare Products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency [PMDA] of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the Data Management System. The data system is FDA compliant and includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

The investigator agrees to keep the records as required by the institutional and federal regulations. These documents include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

10.1.10 PROTOCOL DEVIATIONS

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents and follow the IRB requirements for documenting and reporting of protocol deviations. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation eCRF should be completed by the site and signed/acknowledged by the sponsor or designee for any significant deviation from the protocol.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the <specify NIH Institute or Center (IC)> has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

This study will be conducted with the highest respect for the individual subjects (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator". The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

The Principal Investigator or designee will register the trial with ClinicalTrials.gov and will post the results of the applicable clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Policy/Standard, applicable laws and/or regulations.

10.3 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

11 REFERENCES

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