Title: **Improving Quality of Life of Prostate Cancer Survivors with Androgen Deficiency**

DFCI Protocol Number: **18-733**

WIRB Protocol Number: **20182169**

National Clinical Trial (NCT) Identified Number: NCT03716739

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Funded by: National Institutes on Aging

Version Number: 1.22

Date: **21 November 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:

Improving Quality of Life of Prostate Cancer Survivors with Androgen Deficiency

Study Description:

The overall objective is to conduct a proof-of-concept double-blind, placebo-controlled, parallel group, randomized trial to determine the efficacy and safety of testosterone replacement therapy (TRT) in improving the symptoms of androgen deficiency (sexual symptoms, low energy, and physical dysfunction) and overall health-related quality of life in men with prostate cancer who have undergone radical prostatectomy for organ-localized disease (pT2,N0,M0), Gleason score $\leq$7 (3+4), who have undetectable PSA ($\leq$0.1 ng/mL using a sensitive PSA assay) for > 2 years after radical prostatectomy, and who have androgen deficiency.

Objectives:

Primary Objective:

To determine the safety and efficacy of TRT in improving sexual function (sexual activity, sexual desire, erectile function, distress and sexual life quality) in men, who have undergone radical prostatectomy for organ-localized prostate cancer, have symptomatic androgen deficiency and low risk of disease recurrence. Safety will be assessed by adverse events recording, and monitoring of PSA, hematocrit, lipids, and physical examinations. Evaluation of major cardiovascular adverse events

will be performed using a structured instrument. An independent Data and Safety Monitoring Board will oversee progress and safety.

Secondary Objectives:

- To determine whether TRT improves fatigue, well-being, and disease-specific quality of life.
- To determine the efficacy of TRT in improving self-reported physical function and wellbeing (mood, anxiety, pain, and life satisfaction)
- To determine whether TRT improves muscle mass and strength, self-reported and performance-based measures of physical function, and aerobic capacity ($VO_{2\ peak}$).

Endpoints:

Primary Endpoint:

Our primary outcome is change in sexual activity, assessed by the Psychosexual Daily Questionnaire question 4 (PDQ-4)

Secondary endpoints:

Other measures of sexual function.

- **Erectile function** will be assessed by IIEF
- **Sexual desire** will be assessed by DeRogatis Inventory of Sexual Function (DISF-SD)

HRQOL using the hormonal and sexual domains of the Expanded Prostate Cancer Index Composite (EPIC).

Sexual distress will be measured using the erectile dysfunction "bother scale". Adapted from: WHO 1st International Consultation on Erectile Function, Paris, 1999.

Energy level will be assessed by the Hypogonadism Energy scale.

Mood and well-being will be assessed by PANAS.

Executive cognitive function will be assessed using the digit symbol substitution test (DSST) at the BWH site only.

- **Physical Function.** We will assess physical function by measuring stair climbing power with or without a standardized load, i.e., the "loaded stair climb" or the "unloaded stair climb" for subject who are unable to safely carry the standardized load. Walking speed will be measured by a 50m carrying task. The Dual-task walking performance ("walking while performing mental arithmetic) and voluntary stepping reaction time will only be conducted at the BWH site
- Remote gait monitoring for seven days

Self-reported physical function will be assessed using physical function domain of MOS SF-36 (PF10)

Maximal voluntary strength in the leg press exercise by the 1-RM method.

Lean body mass using dual energy X-ray absorptiometry (DXA)

VO_2 peak as a marker of aerobic capacity.

	Hormone Levels. Total testosterone, DHT and estradiol will be measured using LC-MS/MS in a CDC-certified laboratory, free testosterone by equilibrium dialysis.
Study Population:	We will enroll men with prostate cancer, 40 years or older, who have organ-localized disease with very low risk of recurrence, as indicated by Stage pT2, N0, M0 lesions, combined Gleason score of ≤7 (3+4), preoperative PSA<10 ng/mL (we will enroll participants with preoperative PSA 10.01 ng/mL to 20 ng/mL if all other inclusion criteria are met with except for the preoperative PSA level. In this case, participants will be considered for inclusion based on study physician assessment of prostate cancer recurrence risk after a thorough review of all available medical documentation specifically including operative pathology report, years free of recurrence after prostatectomy, current PSA and post-operative PSA history, and communication with subject's treating physician), and undetectable PSA for >2 years after surgery. The rationale for selecting men with these criteria is that this group of men has <0.5% disease recurrence rate over ten years. We will include men, 40 years or older, because prostate cancer is predominantly a disease of middle-aged and older men and is uncommon before age 40. The trial plans to randomize 134 eligible subjects at three trial sites.
Phase:	Phase 2
Description of Sites/Facilities Enrolling Participants:	This is a multi-site study. Subjects will be enrolled from the Brigham and Women's Hospital and St. Elizabeth's Medical Center in Boston, MA, and Johns Hopkins University School of Medicine in Baltimore, MD.
Description of Study Intervention:	Testosterone cypionate 100 mg IM weekly or placebo injection IM weekly
Study Duration:	Approximately 54 months
Participant Duration:	Approximately 6-8 months (3 months for screening and baseline studies, and 12 weeks of intervention, and 3 months follow-up).

Screening - Within 3 months of Day 0

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

- Obtain written informed consent
- Medical history including review of records to verify the diagnosis of prostate cancer, stage, and Gleason score
- Physical examination
- Vital signs, height and body weight
- EKG
- Concomitant medications
- Complete blood count, blood chemistry, PSA, HbA1c, urinalysis
- Total and free testosterone
- FACIT-Fatigue Questionnaire
- IIEF
- DISF-SD - DeRogatis Inventory of Sexual Function Sexual Desire Questionnaire
- Check conformity to eligibility criteria

Subject's eligibility will be determined based on the results of the medical history, review of medical records as needed, physical examination, questionnaires, and blood tests. 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 2 Weeks Prior to Day 0

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 2-week window prior to randomization. These studies may take 2 to 3 visits over the course of 2 weeks. The following baseline studies will be performed.

- Complete blood count, blood chemistry, PSA
- Record AE/ SAEs
- Serum lipids
- PDQ-4 psychosexual diary will be administered over 7 days
- IIEF
- DISF-SD
- Hormonal and sexual domains of EPIC
- PANAS
- Hypogonadism energy scale (HED)
- MOS SF-36 (PF10)
- IPSS
- Sexual Distress Questionnaire (Erectile dysfunction "bother scale")
- Whole body and appendicular lean tissue mass by DXA
- DSST (BWH site only)
- Maximal voluntary muscle strength using 1-RM in the leg press and chest press exercises
- EKG (if subjects are screened at St. Elizabeth's, this will be completed as a baseline procedure at the BWH site)
- Loaded or unloaded stair climbing speed and power
- Loaded carrying task

- 6-minute walk test
- Dual-task walking and choice stepping reaction time (BWH site only)
- Remote gait speed monitoring
- Hormone levels (total and free testosterone, DHT, LH, and estradiol)
- VO2 peak

Randomization - Day 0
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 cypionate or placebo) based on the randomization number. The study staff will administer the first injection of the blinded study medication under supervision in the Clinical Research Unit.

Weekly Blinded Injections of the Study Medication
The study staff will administer weekly intramuscular injections of the study medication in the clinical research unit. These injections will be given in the gluteal muscles, but in some circumstances, could be given in the muscles of the thighs. The prescribed dose of the study medication (testosterone cypionate or placebo) will be prepared by the IDS and dispensed to the study staff, who will administer the weekly injections of the study medication. During these weekly visits, the Study staff will also do Interim Status Checks and record AEs and SAEs. Weekly visits will have a +/- 3 day window to allow for flexibility in scheduling.

Study Assessments During Week 2

- Interim Status and Record AE/SAE
- Record concomitant medications
- PSA

Study Assessments During Week 4
The subject will arrive in a fasting state (fasting for at least 8 hours).

- Interim Status and Record AE/SAE
- Record concomitant medications
- Complete blood count
- PSA

Study Assessments During Week 6
The subject will arrive in a fasting state (fasting for at least 8 hours).

- Interim Status and Record AE/SAE
- Record concomitant medications
- Physical exam
- Vital signs and body weight
- Complete blood count, blood chemistries, urinalysis
- PSA
- Total and free testosterone, DHT, LH and estradiol
- IIEF
- DISF-SD

- Hormonal and sexual domains of EPIC
- PANAS
- Hypogonadism energy scale (HED)
- MOS SF-36 (PF10)
- IPSS
- Sexual Distress Questionnaire (Erectile dysfunction “bother scale”)
- PDQ for psychosexual diary, administered over 7 days

Study Assessments During Week 8

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

- Interim Status and Record AE/SAE
- Record concomitant medications
- Complete blood count
- PSA

End-of-Study Assessments During Week 12

The subject will arrive in a fasting state (fasting for at least 8 hours). These studies may need to be scheduled on 2 or 3 separate days.

- Interim Status and Record AE/SAE
- Record concomitant medications
- Physical exam
- Vital signs and body weight
- Complete blood count, blood chemistries, urinalysis
- PSA
- Hormone levels (total and free testosterone, DHT, LH and estradiol)
- Serum lipids
- PDQ psychosexual diary will be administered over 7 days
- IIEF
- DISF-SD
- Hormonal and sexual domains of EPIC
- PANAS
- Hypogonadism energy scale (HED)
- MOS SF-36 (PF10)
- DSST (BWH site only)
- IPSS
- Sexual Distress Questionnaire (Erectile dysfunction “bother scale”) Whole body and appendicular lean tissue mass by DXA
- Maximal voluntary muscle strength using 1-RM in the leg press and chest press exercises
- Loaded or unloaded stair climbing speed and power
- 6-minute walk test
- Loaded carrying task
- Dual-task walking and choice stepping reaction time (BWH site only)
- Remote gait speed monitoring
- VO2 peak

End-of-Study Assessments in Participants who are Discontinued from the Study Before Week 12

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:

- Interim Status and Record AE/SAEs
- Concomitant medication
- Physical exam
- Vital signs
- Complete blood count, blood chemistry, urinalysis, PSA.
- Total and free testosterone, DHT, LH and estradiol
- Serum lipids
- PDQ psychosexual diary will be administered over 7 days
- IIEF
- DISF-SD
- Hormonal and sexual domains of EPIC
- PANAS
- Hypogonadism energy scale (HED)
- MOS SF-36 (PF10)
- DSST (BWH site only)
- IPSS
- Sexual Distress Questionnaire (Erectile dysfunction “bother scale”)
- Whole body and appendicular lean tissue mass by DXA
- Maximal voluntary muscle strength using 1-RM in the leg press and chest press exercises
- Loaded or unloaded stair climbing speed and power
- 6-minute walk test
- Loaded carrying task
- Dual-task walking and choice stepping reaction time (BWH site only)
- Remote gait speed monitoring
- Hormone levels (total and free testosterone, DHT, LH, and estradiol)
- VO2 peak

3-Month Follow-up

This visit will take place 3 months (+/- 2 wks) after the last dose of the study drug.

- Interim Status and Record AE/SAE
- Record concomitant medications
- PSA

Some study procedures may be done remotely via phone or Enterprise Zoom (a Mass General Brigham approved tool) that will minimize the participants time in the clinic. The calls will not be recorded on Zoom and the chat feature in Zoom will not be used. Study staff can go over the consent form prior to the subject’s screening visit and answer any questions the subject may have during the Zoom or telephone call. Study staff will ask subjects to provide a medical history and medications list to minimize the time in the clinic. During the in-person screening visit, the subject will sign the consent form and will be screened using the eligibility criteria. Although approved to review the consent remotely with study staff, Subjects will strongly be encouraged to come to the clinic for an initial screening visit to establish rapport with study staff and have to any consent questions answered in real time by the physician obtaining consent.

If participants miss a scheduled blood draw due to illness or unexpected event, the missed safety lab will be conducted as an additional and out of window procedure during the following scheduled weekly visit.

Home Visits and additional treatment locations- BWH Site

For subjects who express interest in participating but are not willing to travel to Boston for weekly injections, a study clinician (RN, NP or MD) will visit the subject's house to conduct study procedures such as blood draws, weekly injections, and administering questionnaires. Some weekly injections will be conducted at an IRB approved MGB research location, such as the BWH Patriot Place Multi-Specialty Clinic in Foxborough, Massachusetts, to provide feasible travel options to participants. The goal of these off-site visits is to reduce subject burden of traveling to the Boston clinic on a weekly basis. The clinician conducting home or off-site visits will be fully trained by the Study PI and will complete study procedures per protocol.

The clinicians will not be doing any of the exercise assessments because it will be too difficult to perform the procedures without the proper equipment. Therefore, some screening procedure, Baseline procedures, Week 6, and Week 12/Early termination visit will need to occur in the clinic.

Note: Subjects will be paid for each visit they complete. Individual visit payments range from $25 to $85. Subjects who complete all study visits will receive a total of $570 in compensation.

1.2 SCHEDULE OF ACTIVITIES (SOA)

Table 3. Schedule of Events

	Screening	Baseline Studies	Intervention Period						Planned Follow-up
	Screen	Days -14 to -1	Day 0	Week 2	Week 4	Week 6	Week 8	Week 12	3 months +/- 2 wks
Consent	↑								
Medical history	↑								
Randomization			↑						
PSA	↑	↑		↑	↑	↑	↑	↑	↑
CBC	↑	↑			↑	↑	↑	↑	
Chem. Panel	↑	↑				↑		↑	
HbA1c	↑								
Urinalysis	↑					↑		↑	
Lipids		↑						↑	
Vitals	↑		↑			↑		↑	
Height and Weight (Height at Screening only)	↑					↑		↑	
EKG	↑	↑*							
Con Meds*	↑	↑	↑	↑	↑	↑	↑	↑	↑

Interim status[a]		↑	↑	↑	↑	↑	↑	↑	↑
AE recording[a]		↑	↑	↑	↑	↑	↑	↑	↑
Weekly Injections of study medication [a]			←	—	—	—	—	→	
Questionnaires [b] (Screening)	↑								
Questionnaires [c] (Outcomes)		↑				↑		↑	
DXA, Strength, physical function, aerobic capacity		↑						↑	
Hormone Levels^	↑	↑				↑		↑	
Physical Exam	↑					↑		↑	

a)Interim Status, Con Meds, and AE Recording will take place at the Week 3,5,7,9,10, and 11 injection visits. These visits are not shown on Schedule.
b) Questionnaires (screening) : FACIT, IIEF, DISF-SD
c) Questionnaires (outcomes); PDQ-4, IIEF, DISF-SD, EPIC, PANAS, HED, SF-36 (PH-10), DSST (BWH site only), IPSS, Erectile Dysfunction bother scale.
* ECG will be a screening procedure for subjects screening at the BWH site. Subjects that are screened at St. Elizabeth's Medical center will conduct their EKG during baseline procedure at the BWH site.

2 INTRODUCTION

2.1 STUDY RATIONALE

Prostate cancer (PCa) will affect 1 in 7 American men in their lifetime[1]. The majority of men diagnosed with PCa have low-grade, organ-confined prostate cancer and excellent prospects of long term survival[2-5]. Substantial improvement in survival in men with prostate cancer has focused attention on the high prevalence of sexual dysfunction, physical dysfunction, and low energy, which are important contributors to suboptimal health-related quality of life (HRQOL)[6-20]among survivors. The pathophysiology of these symptoms - sexual dysfunction, low energy, and physical dysfunction - after radical prostatectomy is multifactorial, but androgen deficiency is a frequent and important remediable contributor to these symptoms[18,21-33] that contributes to poor HRQOL[6-11]. Testosterone replacement therapy (TRT) improves these symptoms in healthy hypogonadal men, who do not have prostate cancer[34-37]. However, neither the safety nor the efficacy of TRT has been evaluated in a randomized trial in prostate cancer survivors.

Testosterone promotes the growth of metastatic prostate cancer and androgen deprivation causes regression of metastatic prostate cancer[38-40]. Therefore, many oncologists and urologists fear giving TRT to prostate cancer survivors. The relationship between testosterone and PCa is complex[24-28,41-49]. Epidemiologic studies have revealed no consistent relationship between testosterone levels and PCa risk[41-49]. Elegant studies have found little or no effect of testosterone administration on intraprostatic androgen concentrations or on androgen-dependent gene expression in the prostate[48,49]. Open-label trials of TRT have reported very low rates of disease recurrence in men with PCa who have undergone radical prostatectomy[18,24-33,50-52]. Thoughtful editorial commentaries have presented cogent arguments for TRT of men with PCa, who are deemed cured of cancer after radical prostatectomy and who are androgen deficient[18,24-26].

In spite of the absence of randomized trials data, the use of TRT to treat symptoms of androgen deficiency has continued to grow. The South West Oncology Group (SWOG) patient advocates indicated that this is a high priority question for prostate cancer survivors. The SWOG Survivorship Committee also recognized the imperative for a large RCT of TRT in correcting the symptoms of androgen deficiency among prostate cancer survivors and recommended that if efficacy can be demonstrated in an initial smaller RCT, a much larger safety and efficacy trial should follow (see support letters). This RCT is being proposed to implement this recommendation of the Survivorship Committee.

2.2 BACKGROUND

Androgen deficiency is common in men with prostate cancer, and an important contributor to distressing symptoms, poor health-related quality of life, and adverse health outcome. The prevalence of androgen deficiency is high in men with prostate cancer[18,24-27,54-57]. Testosterone levels decline with age[58-71] and men with prostate cancer are at risk of having low testosterone levels by virtue of their age. The men with prostate cancer, who have undergone prostatectomy, have even lower total and free testosterone levels than non-cancer age-matched controls[72].

Androgen deficiency in men with prostate cancer is associated with distressing symptoms and adverse health outcomes[18,24,72-87]. Low libido, erectile dysfunction (ED), hot flashes, mobility limitation, decreased physical function, and role limitations due to physical problems are major complaints of these men[6-16,19,20,24,25,72,73,87-95]. Fatigue and functional limitations are important contributors to the decline in HRQOL[6-12], have been associated with androgen deficiency, and would be expected to improve with TRT. Even with bilateral nerve-sparing procedure, more than 50% of men develop sexual dysfunction after surgery[72,73,88,91]. Although there is some recovery of sexual function with passage of time, 40-50% of men undergoing

radical prostatectomy find their sexual performance to be a moderate-to-large problem 18 months after surgery[6,72,73,92-94]. Sexual problems are a source of distress in men with localized prostate cancer[14,18,72,73]. Androgen deficiency in men with prostate cancer increases the risk of bone fractures, diabetes, anemia, and frailty[77-86].

A history of prostate cancer has traditionally been considered a contraindication for testosterone therapy[21]. This guidance is based on observations that testosterone promotes the growth of metastatic prostate cancer[38-40]. Metastatic prostate cancer generally regresses after orchidectomy[38]and androgen deprivation therapy[96-100]. PSA levels are lower in hypogonadal men and increase after testosterone therapy[101,102]. Prostate volume is lower in hypogonadal men and increases after testosterone therapy to levels seen in age-matched controls[101,102].

However, the role of testosterone in prostate cancer is complex. Epidemiological studies and meta-analyses have not revealed a consistent relationship between serum testosterone and prostate cancer[41-47]. Others have reported that low testosterone levels are associated with high grade cancers[54-57,103]. In a landmark randomized trial[48], testosterone therapy of older men with low testosterone did not affect intraprostatic androgen levels or the expression of androgen-dependent prostatic genes. The suppression of circulating testosterone levels by a GnRH antagonist also did not affect intraprostatic androgen concentrations[49].

Many open label trials and retrospective analyses of TRT in men with prostate cancer[18,24-33,52], who have undergone radical prostatectomy and have undetectable PSA levels after radical prostatectomy, have found very low rates of PSA recurrence. However, these trials were neither randomized nor blinded. Even in men with high grade prostatic intraepithelial neoplasia (HGPIN)– a group at high risk of developing prostate cancer– TRT for one year did not increase PSA or rates of prostate cancer[104]. In an analysis of men with untreated prostate cancer and androgen deficiency, there was no increase in PSA or disease progression after TRT for 1 to 8.1 years[105].

Using the Surveillance, Epidemiology, and End-Results-Medicare data, Kaplan *et al*[50,51] assessed overall mortality, cancer-specific mortality, and the use of salvage hormone therapy among 1,181 men who received testosterone treatment following their prostate cancer diagnosis. In this population-based observational study, TRT in men with a history of prostate cancer was not associated with increased overall or cancer-specific mortality. Hence, several thousand men with prostate cancer, who had undergone radical prostatectomy or radiation therapy, have been treated with testosterone with no apparent increase in disease recurrence rates.

A majority of men diagnosed with prostate cancer today has localized disease that can be potentially cured by radical prostatectomy[1-5,106]. The men with organ-confined prostate cancer (pT2, N0, M0), Gleason score $\leq$7 (3+4), are at a very low risk of disease recurrence after radical prostatectomy[5a.] with 0.5% biochemical recurrence rate and 0.2% local recurrence rate over 10 to 15 years[2-5]. Similarly, pre-operative PSA <10 ng/mL is associated with lower risk of disease recurrence than PSA > 10 ng/mL[107,108.] We will consider enrolling participants with preoperative PSA of 10.01 ng/mL to 20 ng/mL if all other inclusion criteria are met except for the preoperative PSA level. D'Amico et al[278] classified patients with prostate cancer into risk groups based on clinical and pathologic parameters to enable prediction of relapse risk before treatment; patients with pre-operative PSA ≥ 20 ng/mL had higher recurrence rates than those with pre-operative PSA < 20 ng/mL. An undetectable PSA after radical prostatectomy is a good indicator of biochemical recurrence-free survival at 5 years[5,53,107]. Therefore, men with organ-confined prostate cancer (pT2), Gleason score $\leq$7 (3+4), and a pre-operative PSA of <10 ng/mL (in addition to men with preoperative PSA of 10.01 ng/mL to 20 ng/mL who are thoroughly assessed for low prostate cancer recurrence risk), who have had undetectable PSA levels ($\leq$0.1 ng/mL) for $\geq$ 2 years after radical prostatectomy have very low risk of disease recurrence (<0.5% at 10 years) and are the most appropriate candidates for this trial.

TRT improves many domains of sexual function in androgen-deficient men[109-119], including sexual desire, sexual thoughts, sexual activity, spontaneous erections, and attentiveness to

erotic stimuli[34-36,109-119]. Young, androgen-deficient men have decreased frequency of sexual thoughts and lower overall sexual activity. Testosterone increases the frequency and duration of sleep-entrained, penile erections[117-119]. Testosterone's effects on mood and wellbeing also could indirectly affect sexual function. Testosterone also plays an important role in regulating erectile mechanisms at multiple levels[120-138].Testosterone regulates nitric oxide synthase activity in cavernosal tissue[129,132,134], sensitivity to α-adrenergic stimulation[131], and penile blood flow[123,130]. Some non-NO-dependent pathways are also androgen sensitive[126,133]. Testosterone exerts a trophic effect on bulbospongiosus and cavernosal smooth muscle[127], improves erectile response to central and peripheral stimulation[126], and is essential for achieving veno-occlusion[128,130]. Recent large RCTs have established that TRT improves sexual activity, libido, erections, and satisfaction with intercourse in men with testosterone level < 300 ng/dL and low libido[34-37].

Testosterone levels are correlated with mood indices in older men and in chronic illnesses[139-141]; however, the relationship of testosterone with depression has been inconsistent[142]. Low testosterone is associated more with subsyndromal depression than with major depression[141]. TRT in hypogonadal men improves positive aspects of mood and reduces negative aspects of mood[113,143]. Similar small improvements in mood have been reported in older men with low testosterone, HIV-infected men[144,145], and surgically menopausal women[146].

Fatigue has been widely recognized as a symptom of androgen deficiency[21,22,144]. Men with prostate cancer who receive ADT report more fatigue than those who do not[95]. Androgen therapy has been reported to reduce fatigue in HIV-infected men[144,145,147-154]. The effects of TRT on fatigue in older men have been inconsistent when FACIT-1 scale has been used[34]. However, a large RCT, which used a novel psychometrically robust instrument for assessing energy in hypogonadal men, reported improvements in energy following TRT[36]. Therefore, our study focuses on assessment of energy, mood, and positive and negative affect, that contribute to HRQOL, using psychometrically robust instruments which have been shown to be androgen-responsive.

Testosterone increases muscle mass and strength, VO2 peak, and stair climbing power[37,71,113,114,155-169]. A meta-analysis of RCTs in older men reported greater increments in lean mass, grip strength, and self-reported physical function[170,171] with TRT. The changes in gait speed have been small and less consistent[168,169,172].

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWNPOTENTIAL RISKS

The potential risks of the study include the risks of the administration of testosterone, blood drawing, dual energy X-ray absorptiometry, the assessment of self-reported sexual and physical function, mood, fatigue and health-related quality of life, and performance-based measures of muscle performance and physical function.

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.

Risks of Testosterone Administration in Prostate Cancer Survivors

Two types of potential risks of testosterone administration need to be considered in prostate cancer survivors: the risks the risks associated with testosterone replacement therapy in all hypogonadal men; and the risk of disease recurrence associated with administering testosterone to prostate cancer survivors.

Randomized and open-label trials in young hypogonadal men report a low frequency of serious adverse events with replacement doses of testosterone. Common drug-related adverse events include acne, oiliness of skin, and breast tenderness. The frequency of breast enlargement, sleep apnea, and prostate events has been low in testosterone trials of hypogonadal men. Erythrocytosis is the most frequent adverse event reported in RCTs of testosterone. The frequency of neuro-occlusive events in men enrolled in RCTs who developed erythrocytosis has been very low.

Testosterone therapy is associated with a small decrease in high-density lipoprotein cholesterol levels. There have been no RCTs that were large enough or long enough to determine the effects of testosterone replacement therapy on major adverse cardiovascular events (MACE). In addition, there is no conclusive evidence that testosterone supplementation is associated with increased cardiovascular risk in hypogonadal men.

The data relating cardiovascular disease and venous thromboembolism (VTE) risk with testosterone replacement in hypogonadal men are few and inconclusive. The relationship of endogenous testosterone levels and coronary artery disease in cross-sectional and prospective cohort studies has been inconsistent. The relationship between testosterone levels and cardiovascular events in prospective epidemiologic studies is also inconsistent. A small number of epidemiologic studies have reported a negative relationship between endogenous testosterone concentrations and measures of sub-clinical atherosclerosis, such as common carotid artery intima-media thickness.

The relationship of testosterone and mortality has been heterogeneous across studies. A meta-analysis by Araujo *et al.* associated lower testosterone levels with higher risk for all-cause mortality, especially cardiovascular mortality. It is possible that testosterone is a marker of health, and those who are at higher risk of dying have lower testosterone levels. Epidemiological studies can only show association but cannot prove causality, and reverse causality cannot be excluded. Other studies suggest that men with erectile dysfunction and low testosterone may have an increased risk of cardiovascular disease and all-cause mortality, but a causal association cannot be inferred.

There are no adequately powered RCTs on the effects of testosterone replacement on MACE. The few RCTs that have reported cardiovascular events were limited by their small size, short intervention durations, variable quality of adverse event reporting, and failure to pre-specify and adjudicate cardiovascular events. Retrospective analyses of data using electronic medical records have also been inconclusive and are similarly constrained by the lack of randomized allocation and prospective adjudication of cardiovascular events; confounding by indication; and heterogeneity of patient populations, testosterone doses, and intervention durations. A number of meta-analyses have examined the association between testosterone-replacement therapy and cardiovascular events, MACE, and death in RCTs. However, overall, most meta-analyses have not shown a statistically significant association between testosterone treatment and cardiovascular events, MACE, or deaths. The trials included in these meta-analyses suffered from various limitations, including heterogeneity of eligibility criteria, dosing, formulations, and intervention durations; variability in the quality of adverse event recording; lack of large trial cohorts; failure to pre-specify and adjudicate cardiovascular outcomes; and lack of a sufficient number of MACE. Thus, there are insufficient data to establish a causal link between testosterone therapy and cardiovascular events.

In response to a citizen petition to add a “black box” warning about the potential cardiovascular dangers of T, the FDA conducted an extensive review and concluded “the studies presented in the petition have significant limitations that weaken their evidentiary value for confirming a causal relationship between T and adverse cardiovascular outcomes”. Nevertheless, the FDA mandated pharmaceutical companies to add labeling information about a possible increased risk of cardiovascular events with the use of T. The European Medicines Agency concluded that there is no consistent evidence of an increased risk of coronary heart

disease associated with T therapy in hypogonadal men (21 November 2014; EMA/706140/2014).

There are too few testosterone-associated VTE events in RCTs to draw meaningful inferences. However, some case reports have suggested that the risk for VTE may be increased in the presence of thrombophilia even without a raised hematocrit, especially within the first 6 months after starting T therapy. Case-control and pharmaco-epidemiologic studies have not shown a consistent increase in the risk of VTE with T treatment. However, the FDA has required manufactures to include a warning about the risk of VTE for testosterone products.

The relationship between T administration and the risk of prostate cancer remains poorly understood. No RCT has been long enough or large enough to have adequate statistical power to determine whether T administration increases the risk of prostate cancer.

There is no strong evidence for the association between prostate cancer risk and testosterone levels or polymorphisms in genes that encode for proteins involved in androgen action or metabolism. Meta-analyses of prospective epidemiologic studies, reviewed in the Research Strategies section of this grant, found no significant association between endogenous testosterone levels and the risk of prostate cancer; although, there are some inconsistencies among studies. However, androgen receptor signaling plays a central role in the biology of prostate cancer, and testosterone administration promotes the growth of metastatic prostate cancer. Therefore, we recommend against testosterone supplementation in men with prostate cancer and advocate assessing prostate cancer risk prior to treatment initiation.

Many older men harbor small foci of subclinical cancer in their prostate; we do not know whether T replacement might cause these subclinical cancers to grow and become clinically overt.

Testosterone therapy increases the risk of detecting subclinical prostate cancer because of increased surveillance and testosterone-induced increase in PSA levels, which may lead to increased risk of prostate biopsy. Because of the high prevalence of subclinical prostate cancer in older men, an increased number of prostate biopsies in men receiving testosterone therapy would lead to the detection of a greater number of subclinical prostate cancers. In a meta-analysis of RCTs, a greater proportion of men randomized to testosterone had prostate biopsies than those assigned to placebo. Therefore, it is important to establish a standardized monitoring process and criteria for referring patients receiving testosterone treatment for possible prostate biopsies to minimize the risk of unnecessary testing.

Metastatic prostate cancer and breast cancer are hormone-dependent cancers that testosterone treatment may stimulate to grow. Testosterone should not be administered to men with metastatic prostate cancers.

There are no RCTs of testosterone replacement therapy in prostate cancer survivors. A large number of open label trials of testosterone have been conducted in men with localized cancer. These recent open-label studies have not shown evidence of an increased risk for de novo prostate cancer, progression of the disease, or biochemical recurrence in hypogonadal men with a history of low-grade, organ-confined prostate cancer treated with testosterone therapy. Using the Surveillance, Epidemiology, and End-Results-Medicare data, Kaplan *et al* assessed overall mortality, cancer-specific mortality, and the use of salvage hormone therapy among 1,181 men who received testosterone treatment following their prostate cancer diagnosis. In this population-based observational study, TRT in men with a history of prostate cancer was not associated with increased overall or cancer-specific mortality. Hence, several thousand men with prostate cancer, who had undergone radical prostatectomy or radiation therapy, have been treated with testosterone with no apparent increase in disease recurrence rates.

Potential Risks of DXA Scanning

The radiation exposure during a DXA scan is minimal (less than 25 mrems, less than a that from a chest X ray). While we do not know whether any dose of radiation is completely safe, this amount of radiation to which the subjects will be exposed during the course of the study is well within the limits considered "safe" by federal and state regulations.

Potential Risks of Physical Function and Muscle Performance Testing

There is a small risk of incurring injury during assessment of muscle performance and physical function. This risk will be minimized by properly instructing the participants, and by performing these tests under direct supervision of an experienced exercise technician. Gordon et al have reported on the safety of maximal strength testing in 6,653 males and females aged 20-69 years. Of this sample, 1112 subjects were over 50. Only one of the 6663 subjects experienced a clinically significant, non-fatal or fatal cardiovascular event in association with strength testing. The authors complemented these data with two additional data sets: 1) 1819 maximal strength assessments performed at the Cooper Clinic (Dallas, TX) and 2) approximately 4500 subjects who completed approximately 20,000 maximal strength tests at the University of Florida's Center for Exercise Science. These subjects were aged 18-93 years. Shaw and colleagues studied maximal strength testing in 83 elderly persons with a mean age of 66 $\pm$6 years using the same 1-RM methodology proposed for this study. Strength in five resistance training exercises was determined in these subjects. Eighty-one subjects completed the testing without injury, 48 complained of muscle soreness after testing, and 2 subjects (2.4%) sustained an injury. Bassey using the same equipment for testing leg power that we have proposed in this study, successfully tested 26 frail elderly male and female residents of a chronic care hospital. The average age of these subjects was 88.5 $\pm$ 6 years and the subjects had multiple chronic conditions. In addition to the leg power testing, all subjects completed a battery of four physical function tests, including a 4-step stair climb, a 6-meter walk, and repetitive rising from a chair. No injuries or adverse effects from the testing procedures were reported. Fiatarone et al measured maximal voluntary strength in nonagenarians without problems. Taken together, these data indicate that maximal strength and physical function testing can be performed safely in older men.

Our group has extensive experience in the application of the physical function and muscle performance tests from our studies in healthy older men, older men with COPD, and older men with mobility limitation (Please, see Drs. Bhasin and Storer's biosketches). We have conducted these tests in young and older men and women without incident for over 20 years. We attribute this remarkable safety record in part to the general safety of the tests as indicated above, the application of rigorously standardized testing procedures, and stringent medical 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 in older, frail individuals. This equipment has been used extensively in aging research and shown to be safe when used with elderly persons. The risks of physical function and muscle performance testing include muscle soreness and injury. These risks will be minimized by following careful procedures (standardized protocols) for warm-ups, progressive increase in workload, and careful supervision of the subjects during their testing by trained and experienced technicians. We will employ careful instruction and demonstration and provide practice sessions so that subjects may become familiar with the procedures.

Potential Risks of Questionnaires

The instruments used for the assessment of sexual function, mood, and health related quality of life 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 at all times by the use of systematic data processing methods.

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.

The SWOG patient advocates confirmed that this is a high priority question for prostate cancer survivors (see support letter). The SWOG Survivorship Committee, in consultation with the Genitourinary Cancer Committee, also has recognized the imperative for a large RCT of TRT in correcting the symptoms of androgen deficiency among prostate cancer survivors and recommended that if efficacy can be demonstrated in an initial smaller RCT, a much larger safety and efficacy trial should follow (see support letter). This RCT is being proposed to implement this recommendation of the Survivorship Committee.

As discussed in the body of the proposal, the studies have the potential of demonstrating the efficacy of a treatment for the distressing symptoms of androgen deficiency in men with prostate cancer, an area of considerable unmet need. As androgen deficiency in patients with prostate cancer is also associated with increased risk of osteoporosis, frailty, diabetes and cardiovascular disease, testosterone therapy may have additional beneficial effects on bone health, physical function, and cardiometabolic outcomes. The trial will address an important clinical issue that is of relevance to this large patient population. This issue is timely and has assumed greater importance because testosterone use in men who have undergone radical prostatectomy for localized prostate cancer has been growing, even though there are no RCT data on the safety or efficacy of androgen therapy in this population.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The intervention trial has moderate level of risk to the participants. The project addresses an important health problem among prostate cancer survivors. The SWOG The SWOG patient advocates confirmed that this is a high priority question for prostate cancer survivors. 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. All subjects will be monitored by frequent physical examinations, blood counts, chemistries and PSA levels. We will follow hematocrit and hemoglobin, plasma lipids, blood chemistries, PSA and record all adverse events reported by the subjects 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 exercise testing will be minimized by several safety measures. Subjects will be evaluated by the PI or Medical co-I to assess their fitness for participating in each of the physical function assessments. Some subjects may be excluded from certain assessments, based on investigator discretion. The subjects will be instructed in proper technique and the risks minimized by careful supervision. Patients will be screened with ECG stress testing to rule out cardiac ischemia and arrhythmias. This test will be done in the presence of an experienced physician. The likelihood of musculoskeletal injury from exercise testing will be minimized by providing a warm-up period proceeding each exercise session including warm-up stretching exercises. Further, an experienced exercise trainer will oversee all exercise testing sessions.

The risks of testosterone therapy will be minimized by institution of several safeguards:

- We will carefully enroll men with organ-confined, low grade (Gleason 7 (3+4) or lower) prostate cancer without any metastatic disease, who have undergone radical prostatectomy and in whom the PSA levels have been undetectable for 2 or more years after radical prostatectomy. This group of patients has an extremely low risk of disease recurrence.
- We will closely monitor all participants 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 on Androgen Deficiency Syndromes, ISSAM, and the American College of Physicians/American Society of Internal Medicine Disease Management Module for Male Hypogonadism for monitoring of men receiving an androgen. Although these guidelines were developed for testosterone therapy, they are appropriate for following men receiving any type of androgen therapy. We have incorporated in this trial several additional measures to minimize risk:

a. The inclusion and exclusion criteria will assure selection of subjects at very low risk of disease recurrence.

b. We have established rigorously defined criteria for biochemical recurrence and for progression from stage 1.

c. We have established *a priori* stopping rules based on PSA change.

d. We will perform frequent PSA measurements to ensure early detection of biochemical recurrence.

e. An independent DSMB, established in discussions with the NIH staff, will oversee the study after its initiation

Termination Criteria

The following **Termination Criteria** will be used:

- An increase in PSA to 0.2 ng/mL or higher, if confirmed by a repeated test, will result in treatment discontinuation and referral to a urologist.
- Any evidence of disease recurrence will lead to immediate treatment discontinuation.
- An increase in hemoglobin level above 18.0 g/dL would warrant discontinuation of treatment.
- Myocardial infarction or stroke

We recognize that other unexpected adverse events can occur. Therefore, we have instituted a comprehensive plan for 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.

3 OBJECTIVES AND ENDPOINTS

3.1.1 Primary Objective

- To determine the safety and efficacy of TRT in improving sexual activity in men, who have undergone radical prostatectomy for organ-localized PCa, have symptomatic androgen deficiency and low risk of disease recurrence, compared to placebo.

3.1.2 Secondary Objectives

- To determine whether TRT improves fatigue, well-being, and disease-specific quality of life, more than placebo.
- To determine whether TRT improves muscle mass and strength, self-reported and performance-based measures of physical function, and aerobic capacity ($VO_{2\ peak}$) more than placebo.
- To evaluate the safety of TRT in this population by assessing adverse events, and monitoring PSA, hematocrit, and lipids.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine whether TRT improves sexual activity more than placebo	Change in sexual activity, assessed using PDQ-4	Our primary outcome is change in sexual activity, assessed by the Psychosexual Daily Questionnaire question 4 (PDQ-4), because sexual dysfunction is the most prevalent symptom in men, who have undergone radical prostatectomy, and it affects HRQOL. This scale has been used widely in testosterone trials, and sexual activity, assessed by PDQ-4, is one of the most meaningful integrated measures of sexual function, and responsive to TRT.
Secondary		
• To determine whether TRT is more efficacious than placebo in Improving erectile function	• Erectile function domain of International Index of Erectile Function	• Erectile function will be assessed by **IIEF**, which has been validated and is responsive to TRT in older men with low testosterone levels. The IIEF is a 15-item questionnaire that evaluates 5 response domains, including erectile function, intercourse satisfaction, and overall satisfaction.
• To determine whether TRT is more efficacious than placebo in Improving sexual desire	• DeRogatis Inventory of Sexual Function Sexual Desire (DISF) and by libido-related questions in IIEF	• **Sexual desire** will be assessed by DeRogatis Inventory of Sexual Function Sexual Desire (DISF) and by libido-related questions in IIEF. DISF provides a more robust

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		assessment of libido than IIEF, has high degree of internal consistency, reliability, and has been shown to be responsive to TRT.
• To determine whether TRT improves disease-specific quality of life more than placebo	• Disease-specific HRQOL using the hormonal and sexual domains of the Expanded Prostate Cancer Index Composite (EPIC)	• We will use the hormonal and sexual domains of the Expanded Prostate Cancer Index Composite (EPIC). The EPIC is a 50-item, disease-specific HRQOL questionnaire designed to evaluate the impact of treatments on HRQOL in men with prostate cancer. We will use the sexual and hormonal domains, which are affected by androgen deficiency and expected to improve with TRT.
• To determine the efficacy of TRT in reducing sexual distress compared to placebo.	• Sexual distress	• Sexual distress will be assessed using Erectile dysfunction “bother scale”. Adapted from: WHO 1st International Consultation on Erectile Function, Paris, 1999.
• To determine whether TRT improves energy / vitality more than placebo	• Energy level using Hypogonadism Energy scale.	• Energy level will be assessed by the Hypogonadism Energy scale. This instrument has been well-validated and responsive to treatment.
• To determine whether TRT improves mood and wellbeing more than placebo	• Mood and wellbeing will be assessed by PANAS affectivity balance scale	• Mood and well-being will be assessed by PANAS affectivity balance scale, which includes 10 questions each for Positive Affect (e.g., joy) and Negative Affect (e.g., anxiety, depression).
• To determine whether TRT improves executive cognitive functioning more than placebo	• Executive cognitive performance will be assessed using the digit symbol substitution test (DSST).	• The DSST assesses psychomotor speed and working memory over a 2-minute period. The instrument is reliable, well-validated and responsive to interventions.
• To determine whether TRT increased lean body mass	• Lean body mass using dual energy X-ray absorptiometry	• Whole body and appendicular lean body

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
more than placebo		mass will be measured using DXA, calibrated using a soft tissue phantom.
• To determine whether TRT is efficacious in increasing maximal voluntary muscle strength more than placebo	• Maximal voluntary strength in the leg press and chest press exercises	• Maximal voluntary strength with be identified as the one-repetition maximum (1-RM) in the leg press and chest press exercises using the Keiser leg press and chest press machines.
• To determine whether TRT improves performance-based measures of physical function more than placebo	• Stair climbing power and speed, while carrying a standardized load or without a standardized load, dual task walking performance, voluntary stepping reaction time, 6-minute walking distance, and a loaded 50m carrying task	• We will assess physical function by measuring loaded or unloaded stair climbing power and speed, dual task walking performance, choice stepping reaction time,6-minute walking distance, and a loaded carrying task
• To determine whether TRT improves self-reported function more than placebo	• We will use physical component of the MOS SF-36 questionnaire (PF10) to assess self-reported function	• MOS SF-36 (PF10) is a validated and widely used instrument to assess self-reported physical function that has been shown to be responsive to TRT.
• To determine whether TRT improves aerobic capacity more than placebo.	• VO_2 peak	• We will assess aerobic capacity by measuring VO2 peak.
	• Safety Assessments. Adverse event recording; CBC, blood chemistries, lipids, PSA, urinalysis, physical exams, and IPSS questionnaire for lower urinary tract symptoms in men.	• structured adverse event recording, PSA levels, blood counts, blood chemistries, lipids, and physical examinations, and IPSS questionnaire.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Hypothesis: This phase 2 efficacy trial will test the hypothesis that TRT in men who have undergone radical prostatectomy for organ-confined, prostate cancer and have very low risk of recurrence, and who have symptomatic androgen deficiency will be safe and efficacious in improving sexual activity, sexual desire, erectile function, distress and sexual life quality, mood, energy, lean body mass, maximal voluntary strength, and function more than placebo.

This proof-of-concept trial will be a 12-week, randomized, placebo-controlled, double-blind parallel group trial in community dwelling men, 40 years or older, with PCa who have undergone radical prostatectomy for organ-localized disease (pT2, N0, M0), Gleason score ≤ 7 (3+4), who have undetectable PSA (≤0.1 ng/mL using a sensitive PSA assay) for > 2 years after radical prostatectomy, and who have androgen deficiency.

This phase 2 trial will be conducted at two trial sites. Subjects will be enrolled from a third clinical site, St. Elizabeth's Hospital.

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 and age (40 to 60, >60 years), and use of phosphodiesterase 5 inhibitors (PDEIs) (yes, no).

Group A: Testosterone cypionate 100 mg IM weekly

Group B: Placebo injection IM weekly

No interim analyses 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.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Rationale for the selection of Pca survivors at low risk of disease recurrence. We will enroll men with prostate cancer, who have organ-localized disease with very low risk of recurrence, as indicated by Stage pT2, N0, M0 lesions, combined Gleason score ≤7 (3+4), preoperative PSA<10 ng/mL (we will include participants with preoperative PSA 10.01 ng/mL to 20 ng/mL if all other inclusion criteria are met except for the preoperative PSA level. In this case participants will be considered for inclusion based on study physician assessment of prostate cancer recurrence risk after thorough review of all available medical documentation specifically including operative pathology report, years free of recurrence after prostatectomy, current PSA and post-operative PSA history, and communication with subject's treating physician), and undetectable PSA for >2 years after surgery. The rationale for selecting men with these criteria is that this group of men has <0.5% disease recurrence rate over ten years.

Rationale for age limits: We will include men, 40 years or older, because prostate cancer is predominantly a disease of middle-aged and older men and is uncommon before age 40.

Rationale for testosterone thresholds. We will recruit men, who have an average of two early morning, fasting, total testosterone levels, measured using LC-MS/MS, < 275 ng/dL. These thresholds are based on the results of the Testosterone Trials (The TTrials), which demonstrated that TRT of men with an average of two total fasting testosterone levels <275 ng/dL and low libido was associated with significant improvements in libido, erectile function, overall sexual activity, and satisfaction with erections. Similarly, in an efficacy trial of Testosterone Solution in hypogonadal men with total testosterone < 300 ng/dL, TRT was associated with significant improvements in sexual drive and erections in hypogonadal men with low libido, and significant improvements in energy level in men with low energy[36]. In contrast, in another RCT in men, 60 or older, TRT did not improve any domain of sexual function in men >60 years with mean testosterone > 300 ng/dL who did not have sexual symptoms. Furthermore, in the European Male Aging Study, total testosterone < 312 ng/dL was associated with a syndromic cluster of sexual symptoms. SHBG levels are higher in older men; therefore, some older men with total testosterone greater than the upper limit of normal

may have free testosterone below the lower limit of normal for healthy, young men. Thus, we will include men with free testosterone ≤70 pg/mL (lower limit in Framingham Heart Study <69 pg/mL).

Phosphodiesterase Inhibitors Use. Because PDE5Is may independently affect sexual function (and HRQOL), we will stratify randomization based on PDEI use, and include it as covariate in analyses.

Inclusion of Well Controlled Diabetics. Glycemic control improves during trials; this may affect body composition and physical function. However, excluding all diabetics will limit generalizability as >25% of older men will have diabetes. Therefore, we will include men with diabetes if they are in good control (A1C <7.5%).

As described in detail under Sample Size Estimation and Statistical Power, the trial plans to randomize 134 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 age (40-60, >60), and PDE5I use (yes, no); 3. a loss-to-follow-up rate of up to 12%; 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

100 mg of testosterone cypionate administered once a week is widely recognized as the replacement dose of testosterone that is used in clinical practice for the treatment of hypogonadal men.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he 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

The rationale for selecting men with the following criteria is that this group of men has less than 0.1% disease recurrence rate over ten years. Therefore, we will enroll men with prostate cancer, who have:

- Stage pT2, N0, M0 lesions (confined to the gland, if AJCC staging is not available in medical records, the investigators will infer the staging based on extensive review of the pathology report),
- Combined Gleason score of 7 (3+4) or less
- Preoperative PSA less than 10 ng/mL (if pre-operative PSA is not available in medical records, low-risk subjects with a Gleason score of 6 (3+3) and who are at least 5 years out of surgery will be considered for enrollment) or (If preoperative PSA is 10.1 ng/mL to 20 ng/mL, the study physicians will thoroughly review all available medical documentation specifically including operative pathology report, years free of recurrence after prostatectomy, current PSA and post-operative PSA history, and communication with subject's treating physician to fully asset risk of prostate cancer reoccurrence)

- Stable and undetectable PSA level (PSA less than ≤0.1 ng/mL using an assay that has a functional sensitivity of 0.1 ng/mL) for at least two years after radical prostatectomy

- Age: 40 years and older
- Presence of symptoms related to sexual dysfunction, or fatigue/low vitality, or physical dysfunction. We have selected these symptoms because they are commonly reported by men treated for prostate cancer and likely to respond to testosterone replacement. Sexual dysfunction will be operationalized as the presence of low libido and/ or erectile dysfunction. The diagnosis of erectile dysfunction will be established by using the International Index of Erectile Dysfunction (IIEF). Men with IIEF scores <25 will be selected. Low libido will be assessed using the DeRogatis Inventory of Sexual Function Sexual Desire domain score ≤20, as was done in the NIA-funded T (Testosterone) Trials. Fatigue/ low vitality will be defined as a score on the FACIT-Fatigue subscale of <30, which is one SD below the mean for men >65 years (FACIT Fatigue manual) and captures >75% of cancer patients with symptomatic anemia.
- An average of two fasting, early morning serum testosterone levels, measured by LC-MS/MS, less than 275 ng/dL(if the first total testosterone value in a subject is >500 ng/dl, that subject would not require a second total testosterone draw as it is unlikely for the average value to fall below 275 n/dl) and/or a single free testosterone by equilibrium dialysis ≤70 pg/mL (if the free testosterone concentrations are ≤70 pg/ml, then the subject will be considered qualified and a 2nd total testosterone measurement would not be required). These testosterone thresholds are based on the results of the TTrials, which demonstrated that testosterone replacement of men with total testosterone less than 275 ng/dL and low libido was associated with significant improvements in libido, erectile function, overall sexual activity, and satisfaction with erections. Similarly, in an efficacy trial of Testosterone Solution in hypogonadal men with baseline total testosterone less than 300 ng/dL, testosterone replacement therapy was associated with significantly greater improvements in sexual drive and erections in hypogonadal men with low libido, and significantly greater improvements in energy level in men with low energy. In contrast, testosterone administration did not significantly improve any domain of sexual function in middle-aged and older men with mean testosterone levels > 300 ng/dL.

  We recognize that SHBG levels are higher in older men; therefore, some older men with total testosterone levels greater than the upper limit of normal may have free testosterone levels that are below the lower limit of normal for healthy, young men. Thus, we would include men with free testosterone level below ≤70 pg/mL (lower limit of normal in FHS <69 pg/mL).
- Willingness to not make any major changes in dietary intake and to maintain current exercise activities and avoid any new exercise programs.
- Ability and willingness to provide informed consent

5.2 EXCLUSION CRITERIA

- Men who have undergone radiation therapy alone will be excluded because defining biochemical recurrence can be difficult in these men because of fluctuating PSA levels. Men who have received adjuvant radiation therapy after prostatectomy and men who have received salvage radiation therapy after prostatectomy would also be excluded.
- Men receiving androgen deprivation therapy will be excluded.
- Hemoglobin <10 g/dL or >17.1g/dL

- Severe untreated sleep apnea
- Uncontrolled heart failure
- Myocardial infarction, acute coronary syndrome, revascularization surgery, or stroke within 3 months
- Serum creatinine >2.5 mg/dL;
- ALT 3x upper limit of normal;
- Hemoglobin A1c >7.5% or diabetes requiring insulin therapy
- Body mass index (BMI) >40 kg/m^2
- Untreated depression. Subjects with depression who have been on stable anti-depressant medication or undergoing Cognitive Behavioral Therapy for more than three months are eligible.
- Men with uncontrolled axis I psychiatric disorder, such as schizophrenia, will be excluded.
- Subjects who have used the following medications within the past 6 months: testosterone, DHEA, estrogens, GnRH analogs, antiandrogens, spironolactone usage greater than 200 mg daily, ketoconazole, rhGH, megesterol acetate, prednisone 20 mg daily or equivalent doses of other glucocorticoids for more than two weeks

5.3 LIFESTYLE CONSIDERATIONS

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- BWH and SEMC. We will recruit potential participants from the Urology clinics at BWH, other Mass General Brigham (MGB) Hospitals, and St. Elizabeth's Medical Center (SEMC). Recruitment methods will include use of the RPDR registry, the CRISP database, direct advertising, the Mass General Brigham clinical trials research portalrally.massgeneralbrigham.org (RALLY), Research Match, Partners RSVP, Patient Gateway Research Invitation Letters, and the Men's Health Clinical Research Unit website (hosted by MGB Research Computing). In addition, we will use Study Protocol.io as a recruitment vendor, which will advertise the study through various ad campaigns and social media platforms such as Facebook. When participates show interest in the study, a research staff member will receive their contact information to phone screen all incoming requests. As part of the pre-screening procedure, interested subjects will receive an initial set SMS pre-screening questions to assess if they will fit the protocol demographic for history or prostate cancer. All responses will go to a study team member and participants will be contacted regardless of eligibility. We will advertise through the Mass Prostate Cancer Coalition (MPCC).

Advertising with MPCC includes presenting at an Online Annual Symposium Virtual Exhibit Booth, being featured on the MPCC website and in the MPCC Newsletters. Only IRB-approved text will be used for advertising in all recruitment methods.

Subjects recruited at the SEMC site will complete screening procedures at SEMC. Those deemed eligible will be referred to the BWH site where eligibility confirmation (by completing the eligibility checklist using data collected at SEMC), randomization, and all remaining study visits will take place.

The Urology Groups at Brigham and Women's Hospital and other Mass General Brigham (MGB) hospitals perform approximately 600 and 850 radical prostatectomies annually, respectively, and follow approximately 1500 men who have undergone radical prostatectomy. Co-investigators Drs. Adam Kibel and Basaria have specialized practices focused on patients with prostate cancer. Therefore, we do not anticipate difficulty in recruiting 84 to 90 men over five years.

The geographic proximity of three hospitals within the MGB Health Care System – the Brigham and Women's Hospital, and the Dana Farber Cancer Center, provides an outstanding opportunity to recruit potential subjects from some of the nation's largest prostate cancer clinical services. The Prostate Cancer Service at Dana-Farber/Brigham and Women's Cancer Center integrates one of the world's leading cancer institutes within one of the world's leading hospitals to create one clinical team – with a unique combination of resources to manage patients with prostate cancer. This service sees approximately 750 new prostate cancer patients each year.

The Research Patient Data Registry (RPDR) is a centralized clinical data registry, or data warehouse that gathers clinical information from various MGB hospital systems. An online Query Tool allows researchers to explore clinical data through a self-service system in order to assess clinical study feasibility, identify patients for clinical trials, provide patient data with approved IRB protocol, search clinical notes for specific text terms and phrases in order to identify patient cohorts who have notes/reports that contain the searched text, query for patients with specific laboratory data (e.g., PSA values).The RPDR ensures the security of patient information by controlling and auditing the distribution of patient data within the guidelines of the IRB and with the use of several built-in, automated security measures. The online search in real time results in a faster data turnaround with extensive specificity of patient criteria.

A systematic search of the electronic medical records at the MGB Health Care using RPDR revealed that RPDR repository has records of over 13,000 men who have undergone radical prostatectomy since the institution of the electronic medical record 17 years ago. These men will be made aware of the trial using an IRB-approved process and provide a large reservoir of potential participants.

The Prostate Cancer CRIS Database at Dana Farber Cancer Institute (DFCI) and Brigham and Women's Hospital. To facilitate subject enrollment in clinical research and improve patient care, an integrated Prostate Cancer Clinical Research Information System (Prostate *CRIS*) was developed as a research database to collect, store, and access clinical, treatment, and outcomes data coupled to legacy information systems for patients treated at the Dana-Farber Cancer Institute (DFCI) and Brigham and Women's Hospital (BWH). The *CRIS* system consists of data-entry software, a central data repository, collection of patient data including comprehensive follow-up of all patients, and tightly integrated security measures. Data are stored in an Oracle relational database (Oracle, Inc., Redwood Shores, CA). PowerBuilder (Sybase, Inc., Dublin, CA) was used to develop the database environment. *CaTissue* is a separate but integrated product designed to record collection and storage status

on research specimens. *CaTissue* is directly linked to *CRIS* and other institute systems through the reporting tool, *Business Objects* (Business Objects, Inc., San Jose, CA).

The current version of Prostate *CRIS* became available for prospective data entry in November 2001. The following data elements are captured: demographics, initial diagnosis date, symptoms, progressions, PSA values, key radiological studies, surgical procedures, pathology (>90% centrally reviewed), TNM staging, physical exam, all treatments received, disease and treatment category, family history, and enrollment in research protocols. Each category has been uniquely adapted for prostate cancer. Current staffing for the Prostate *CRIS* team includes a physician leader, a full-time medical director, full-time project manager, three full-time study coordinators, a half-time biostatistician and a half-time programmer. Medical oncologists, urologists, radiation oncologists, and nurse practitioners participate in data collection.

Most patients seen for care at DFCI and BWH with a diagnosis of prostate cancer are approached to participate. The consent rate for patients approached through August 2011 was 86% (7419 of 8587 patients). A study coordinator enters all outside medical record information into *CRIS*, then prints out a Patient Summary Report (PSR) which is provided to the clinician at the point of contact with the patient. Key data elements are reviewed and updated by the clinician. Once completed, the study coordinator enters new or corrected information into the *CRIS* database.

Patients may choose to consent to give 1) blood samples, 2) permission for researchers to have access to discarded tissue related to any surgery, 3) access to clinical information for research purposes, and/or 4) permission to re-contact them or their families regarding future research. Prior to their visit, patients receive an IRB-approved letter by mail summarizing the study and stating that they will be approached in the clinic by a study coordinator.

Patient confidentiality is protected throughout the data-collection and reporting process. *CRIS* was implemented after the institution of HIPAA regulations and thus has been in compliance since its inception. *CRIS*, *caTissue*, and *Business Objects* are password-protected applications, with access limited to specified programmers, database staff, and physicians.

Recruitment Plan – Johns Hopkins University School of Medicine:

At Johns Hopkins, we will recruit subjects from the urology and survivorship clinics. Subjects will also be identified using the prostatectomy database. Subject outreach may also include flyers, mailed recruitment letters, brochures, electronic letters sent through the institutions patient medical record charting system and Hopkins Clinical Trials website. Only IRB-approved text will be used for advertising in all recruitment methods.

Inclusion of Minority Participants

Persons of all racial groups will have an equal chance of participating in the project. There are no data to suggest that the response to testosterone administration is different among different ethnic groups. Therefore, the study does not have sufficient power to determine differences in response among individuals of different ethnic background. We will, however, record the race of all participants.

The challenges in the recruitment and retention of minority participants in clinical trials have been widely recognized. For instance, in spite of intensive effort for minority recruitment in the Prostate Cancer Prevention Trial, a randomized trial of finasteride versus placebo for preventing prostate cancer in healthy men age 55 years and older, randomized African American men comprised 4% of the total 18,882 randomized men compared to a goal of 8%.

Over the last 3 years, close to 186 prostate cancer patients have been accrued to therapeutic trials at USC, approximately 24% of which are enrolled at the Los Angeles County Medical Center. Twenty-five percent of the accrued patients were Hispanic, 9% African-American, and 10% Asian.

In the CRIS database at the Dana Farber Cancer Center and the Brigham and Women's Hospital, 88% of the participants are White and 12% minorities (4% African-Americans, 7% Hispanic and others, <1% unclassified), reflecting the ethnic and racial composition of the patients served by these institutions.

Subject Retention Plan

We will use several retention strategies based on extensive experience and published literature, including: 1. Employing enthusiastic staff that establishes a supportive rapport with subjects and family. 2. Maintaining regular contact with subjects by telephone; 3. Emphasizing the importance of research question to subjects and their families;4. Offering flexible scheduling; 4. Compensation commensurate with the time subjects will spend in the study in conformity with IRB guidelines; 5. Periodic analyses of factors that contribute to subject attrition during course of trial.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

We chose testosterone cypionate for this trial because of its high bioavailability, the ease of once weekly administration, and predictable pharmacokinetics. The transdermal gel is easy to apply and has low frequency of skin reactions, but there is substantial variation in on-treatment testosterone levels in hypogonadal men treated with the transdermal testosterone gel. Weekly IM administration of 100 mg testosterone cypionate will ensure compliance. In a recent RCT of high protein diet versus the RDA with and without testosterone, this regimen raised testosterone levels into the normal range; adherence with the regimen exceeded 99%.

Rationale for intervention duration. Effects of TRT on sexual function, muscle mass, strength, well-being and mood become apparent within 3 months; PSA rises within 3-4 weeks and reaches a plateau by 12-weeks. Thus, 3-months will be sufficient to detect meaningful changes in outcomes and PSA.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Testosterone cypionate will be purchased by Brigham and Women's Hospital's Investigational Drug Services (IDS)and by Johns Hopkins (the second site). Drug will be stored at 20-25^{o}C, USP Controlled Room Temperature" per manufacturer's drug labelling

At both sites, Investigational product supplies will be counted and reconciled by the Investigational Drug Services. 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. The IDS at both sites will maintain 100% accountability for all investigational products received and dispensed at their respective sites during the conduct of the study.

The BWH research clinician conducting home or off-site drug administration, at an IRB-approved MGB research location, will follow BWH Policy for handling hazardous material and controlled substances. The IDS chain of custody documentation will be followed, showing the controlled substance being picked up and delivered to an administering provider. Once in possession of a trained research provider, the drug will be stored in a travel sized locked box allowing for transportation between the MGB IRB-approved research locations (Boston and Foxborough) or to the provider's residential home. Only the administering provider will have access to the locked box at home or at the offsite location in Foxborough, MA. There are no conditions under which non- research or protocol trained staff should have access to the controlled substance. All signoffs will be conducted, confirming that the study drug was dispensed to the appropriate research participants. Any unused drug will be returned to the research unit, where we will follow BWH policy for destroying controlled substances.

Prior to dispensing study drug, the delegated research team member will guarantee that study drug supplies are adequate and within an appropriate expiration date. The PI is responsible for ensuring that study drug is appropriately dispensed and/or administered per protocol by delegated research team members. The delegated research team members will ensure that each time a study medication is dispensed, the Research Study Medication Dispensing Log is completed. Documentation on CRF's will include:

- Amount dispensed
- Lot number (if applicable)
- Name of individual dispensing study drug
- Subject's number
- Subject's initials
- Date (and time, if appropriate) of dispensing
- Date (and time, if appropriate) and amount of study drug returned/destroyed upon return to the clinic

If errors are made on the accountability form, there will be a single line through the error, with the initials of the person correcting the error and the date corrected. When recording the date, the month, day, and year will be recorded. For short stability agents, the preparation time and date as well as the dose time will be documented, if required by the sponsor. If study drug is wasted in error during preparation by the research team, this will be documented as a separate entry on the drug accountability form with reason for the error. The delegated research team members will ensure that the correct study drug is used from the appropriate study supply and documented on the appropriate study drug accountability form.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The study medication and the placebo will be prepared and loaded into syringe and labeled by the IDS staff. The label will mask the contents of the syringe. Testosterone cypionate is supplied at a concentration of as 200 mg/ mL in cottonseed oil. Normal Saline (NS) will serve as the placebo.

6.2.3 PRODUCT STORAGE AND STABILITY

A braded FDA-approved product - testosterone cypionate in cottonseed oil will be purchased by the IDS. The product will be used before the expiration date on the product label.

6.2.4 PREPARATION

Testosterone cypionate is supplied at a concentration of either 100 mg/ml or 200 mg/mL in cottonseed oil. The appropriate dose of the active medication or placebo (NS) for each participant will be loaded by the IDS pharmacist into a syringe. The syringes will be labeled to mask the content and provided to the study staff 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 site, age (40 to 60, >60 years), and PDE5I use (yes, no).

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.

INVESTIGATIONALPRODUCT BLINDMAINTENANCE

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 INTERVENTIONCOMPLIANCE

Treatment adherence will be assessed as the proportion of scheduled injections actually administered.

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 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/dL

If the hemoglobin level rises above 18.0 g/dL, 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>0.2 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 0.2 ng/mL over a 3 to6-month period are unusual. The 90% confidence limit for the change in PSA levels between two tests performed3 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 oldermen[25]. Therefore, if a PSA elevation above baseline exceeds 0.2 ng/mL and is confirmed, intervention will discontinue 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.

Dosing Holds/Dose modifications

No dose holds, or modifications are allowed. Based on previous studies and the fact that 100 mg of testosterone cypionate administered once a week is widely used as the replacement dose of testosterone for the treatment of hypogonadal men, we anticipate very low frequency of DLT. Furthermore, the study is blinded; dose adjustment would require unblinding.

Criteria and Process for Unblinding

In both urgent and non-urgent situations: Only the trial's Data and Safety Monitoring Board is authorized to request unblinding of participant-level intervention assignment in one or more subjects in non-urgent situations should a safety concern warrant it. In urgent situations, the Principal Investigator may direct the study physician to unblind the intervention assignment should this information be deemed necessary by the patient's primary care provider or emergency department clinician to manage an urgent medical condition.

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:

- 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

Primary Outcome. Our primary outcome is change in sexual activity, assessed by the Psychosexual Daily Questionnaire question 4 (PDQ-4), because sexual dysfunction is the most prevalent symptom in men, who have undergone radical prostatectomy, and it affects HRQOL. This scale has been used widely in testosterone trials, and sexual activity, assessed by PDQ-4, is one of the most meaningful integrated measures of sexual function, and responsive to TRT. The scale covers 3domains: 1) sexual desire and enjoyment;2) sexual activity; and 3) mood.

Secondary outcomes

Other measures of sexual function. Erectile function will be assessed by IIEF, which has been validated in many trials of ED therapies, and shown to be responsive to TRT in older men with low testosterone levels and low libido. The IIEF is a 15-item questionnaire that evaluates 5 response domains, including erectile function, intercourse satisfaction, and overall satisfaction. It has high degree of specificity and sensitivity, reliability, internal consistency, and construct validity.

Sexual desire will be assessed by DeRogatis Inventory of Sexual Function Sexual Desire (DISF) and by libido-related questions in IIEF. DISF provides a more robust assessment of libido than IIEF, has high degree of internal consistency, reliability, and has been shown to be responsive to TRT.

We will measure the impact of TRT on HRQOL using the hormonal and sexual domains of the Expanded Prostate Cancer Index Composite (EPIC). The EPIC is a 50-item, disease-specific HRQOL questionnaire designed to evaluate the impact of treatments on HRQOL in men with prostate cancer. We will use the sexual and hormonal domains, which are affected by androgen deficiency and expected to improve with TRT, and which are not weighed appropriately in generic HRQOL instruments. This instrument has been used in numerous prostate cancer trials and has high Cronbach alpha coefficient. construct validity, and excellent sensitivity to change in response to hormonal treatment. Sexual distress will be assessed using Erectile dysfunction "bother scale". Adapted from: WHO 1st International Consultation on Erectile Function, Paris, 1999.

Energy level will be assessed by the Hypogonadism Energy scale. This instrument has been well-validated and responsive to treatment. SF-36 Vitality scale has also been used to assess vitality, but the HED scale is specific to hypogonadal men, and has been shown to be responsive to TRT in contrast to the FACIT-1 or the SF-36 Vitality scales which have not been shown to sensitive to change with TRT.

Mood and well-being will be assessed by PANAS affectivity balance scale, which includes 10 questions each for Positive Affect (e.g., joy) and Negative Affect (e.g., anxiety, depression). Many behavioral scientists consider affectivity balance as the best window on wellbeing. TRT has been reported to improve mood and affect in hypogonadal men. The scale has high Cronbach's alpha and test-retest reliability. The instrument can detect changes in well-being related to chronic illnesses and cancer.

Executive cognitive function will be measured using the DSST. Participants are given a series of numbered symbols and then asked to draw the appropriate symbols below a list of random numbers. The score is the number of correctly made matches in a 2-minute period[275].

The DSST is reliable, well- validated and responsive to interventions[276].

Hormone Levels. Total testosterone, DHT and estradiol will be measured using LC-MS/MS in a CDC-certified laboratory, free testosterone by equilibrium dialysis, and LH by an IFMA. These methods have been used in PI's lab for 30 yrs.

Evaluation of Physical Function, Muscle Strength, and Aerobic Exercise Capacity.

Methods for the measurement of physical performance have been published extensively by our group. We will measure physical function using 6 min walk test, the 12-step stair climbing power test, dual-task walking performance and choice stepping reaction time and a load carrying task that represents commons activities of daily living. For the 6-min walk test, the subject will walk at self-selected pace in a long corridor for 6 min. Walking speed is predictive of disability, hospitalization, and mortality. 6-min walk test is a reliable and valid measure of mobility. The 12-Step Stair Climbing Test requires subjects to walk up a staircase as fast as possible without running while carrying a load standardized to 20% body mass; this is known as the "loaded stair climb". Time is recorded by activation of electronic switch mats at the base of the stairs and on the 12th step. Participants who are unable to safely carry the standardized load will alternatively perform this procedure unloaded. Ascent time is measured with an electronic timer. Power (watts) is calculated as the product of (body mass (kg) plus load carried), total rise of the 12 steps (m) and acceleration of gravity all divided by time (s). Test-retest reliability is 0.85 and CV <5% over 5 weeks of testing. Stair climbing power is responsive to androgen treatment. The load carrying task requires the carrying of a load equivalent to 20% of body weight over 50 m. This task represents activities such as carrying groceries or objects. The test is reliable (test-retest = 0.88) and has a higher ceiling than chair stand and get up and go. We will measure maximal voluntary strength by the 1-RM method in the leg press and chest press exercises, using Keiser pneumatic machines. Subjects will undergo whole body warm up, followed by progressive warm-up lifts leading up to 1-RM. 1-RM strength is a safe and reliable measure of maximal voluntary strength and responsive to androgen treatment. During the dual-task assessment, subjects will first be asked to walk on an even surface for 10 meters at their self-selected usual preferred walking speed. Subjects will be then asked to repeat the walk in their usual pace at the same time as subtracting 3 from 50 and keep subtracting until the 10 meters walk is completed. Subjects' dual task walking speed will be timed with a stopwatch and each subtraction will be recorded. During these laboratory-based walking tests, subjects will be asked to wear a wristwatch for seven days to collect their total step count and distance walked throughout that time-period. Subjects will continue their usual daily activities and will remove the device at night before going to sleep. An instructional handout with an activity log to track wear time will be provided at each baseline and follow-up assessment. The Exercise Physiologist will use the Withings Healthmate application through a coded and HIPPA compliant account to access data from the Pulse™ Ox wristwatch. The Exercise Physiologist, study staff and study investigators are the only individuals who will have access to the data from the Withings Healthmate application.

The Choice Stepping Reaction Time test is a functional measure that evaluates the integration of sensory acuity, reaction time, and reactive mobility[277]. Subjects will stand on a nonslip black platform that contains four rectangular panels (32 cm x 13 cm), one in front of each foot and one to the side of each foot. The panels will be illuminated in a random order. Subjects will be instructed to step onto the illuminated panel as quickly as possible. Each panel contained a pressure switch to determine the time of foot contact. Subjects will have between four and eight practice trials involving the four possible responses and twenty trials will be then conducted with five trials for each of the four stepping responses.

Physical function and muscle strength assessments testing will be optional for the Hopkins participants in the case an exercise physiologist is not available to conduct the procedures.

When possible, Johns Hopkins participants will only conduct the physical function and muscle strength assessments mentioned above (Loaded or unloaded stair climb, Leg press, chest press, 6 minute walk test, and the loaded 50m carrying task). Hopkins subjects will not conduct the DSST, Dual-task walking, and choice stepping reaction time, Licensed exercise physiologist from the University of Maryland will oversee and conduct the exercise assessment at an approved Hopkins research location.

Aerobic performance ($\dot{V}O_2$peak) lactate threshold, and endurance time will be assessed during incremental (IXT) and constant work rate (CWR) exercise on a cycle ergometer (Viasys Sprint, VyAire, Yorba Linda, CA). An automated metabolic measurement (Cardio2 Ultima, Medical Graphic vs Corp, Minneapolis, MN) system will continuously monitor respiratory gas exchange breath-by-breath along with the electrocardiogram (ECG). Blood pressure will be measured at rest, every three minutes during exercise and recovery; ratings of perceived exertion will be obtained every 3 minutes during exercise. The IXT will include 3 min of rest, followed by 3 min of unloaded cycling warm-up. Thereafter the work rate will increase by 10-20 watts per minute in ramp fashion depending on estimates of individual $\dot{V}O_2$ peak ([272274]) to volitional fatigue. $\dot{V}O_2$ peak will be taken as the highest oxygen uptake ($\dot{V}O_2$) averaged over 15 sec. The lactate threshold will be estimated from gas exchange and identified as the $\dot{V}O_2$ at which carbon dioxide output ($\dot{V}CO_2$) increases out of proportion to $\dot{V}O_2$. All IXT will be conducted using standard guidelines for test administration and supervision

Endurance time will be assessed using a constant work test (CWR) at the treadmill speed and grade corresponding to 85% of peak work rate. Subjects will continue cycling until volitional fatigue or to a maximum of 15 min. The ECG and HR will be monitored.

We will use physical component of the MOS SF-36 questionnaire (PF10) to assess self-reported physical function. MOS SF-36 (PF10) is a validated and widely used instrument to assess self-reported physical function that has been shown to be responsive to TRT.

Whole Body and Appendicular Skeletal Muscle Mass by DXA. We will use Hologic 4500 DXA to measure whole body and appendicular lean and fat mass because of the precision, reproducibility, and ease. using a multi-component model. Scanner will be calibrated using a soft tissue phantom. Lean mass estimates by DXA have inter-scan variability of 2-3%.

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, and physical exams. All injuries will also 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 concurrent 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 concurrent 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.

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** 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 TRT will improve overall sexual activity when compared to placebo.

Secondary hypotheses are that TRT will improve erectile function, sexual desire, mood, energy, health-related quality of life, muscle mass, maximal voluntary strength, and performance-based as well as self-reported measures of physical function compared to placebo.

Sample Size Determination

We estimate that 134 men will be needed to test the primary hypothesis based on assumptions of two-sided type I error rate of 0.05, 90% power, and 12% loss-to-follow-up. Our primary outcome is change in sexual activity derived from Psychosexual Daily Questionnaire- question 4(PDQ-Q4)[217]. In the TTrials, the effect size of TRT relative to placebo was 0.6 units[34,35]. Other TRT trials have shown greater increases in sexual activity scores[37,113,114]. To be conservative, here we assume that the difference of interest in the change in sexual activity between the testosterone and placebo arms over 3 months is 0.6 units (SD 1.3) [34-35, 189]. This change is clinically meaningful and patient-important because our analyses of the TTrials data show that the minimal clinically important difference (MCID) for sexual activity using PDQ-4 is 0.5 units. Our experience from the TTrials suggests <5% cumulative loss to follow-up over 12 months, and even smaller amounts of missing data over that time. To be conservative, we assume up to 12% total loss of information due to attrition and other causes. We further assume that power under multiple imputation (see analytic plan) will be similar to that on analyses on complete-case data, as is consistent with prior experience. Under these assumptions, evaluable data on 63 participants per arm will be sufficient to obtain 90% power to detect a between-group mean difference of 0.6 units in PDQ-Q4 at 12 weeks provided the Pearson correlation between baseline and 12 week PDQ-Q4 measures is at least 0.67[271], which is less than the correlation observed in the T Trials over a one year period. To account for missingness, we will enroll 63/0.88 = 71 participants per arm. Even if the effect size is as small as 0.5 points, this sample size will provide 80% power to detect smaller differences as small as 0.5 points on PDQ-Q4.

Statistical Power for secondary endpoints. We hypothesize that the mean between-group difference in change in sexual desire is 2.5 (SD 5). This assumption is reasonable because in the TTrials, the mean difference in sexual desire was 2.93 units. With conservative assumption of 0.5 Pearson correlation coefficient between baseline and 12-weeks measures, the proposed sample size has 90% power to detect this difference. Similarly, we will obtain 90% power to detect between group difference of 2.5 points in change in erectile function (EF) using IIEF (assumed SD 5 points), a threshold deemed clinically significant[210,211,218,219]. In the TTrials, the mean between-group difference in EF score was 2.6 (P<0.001), which is similar to that observed in meta-analysis of TRT trials in hypogonadal men. The men enrolled in the TTrials had severe ED at baseline (mean baseline EF score 8); therefore, our assumption of treatment effect is reasonable and conservative.

Assuming mean (SD) LBM changes of 1.8 kg in the testosterone arm and 0.3 kg in the placebo arm, and SD 2.5 kg; effect size (f, 1.5/2.5, 0.60) simulation results indicate that this design achieves >90% power to demonstrate a treatment effect when the type 1 error is set at the 0.05 level with correlation between time points equal to 0.5 and 12% loss to follow-up. In a testosterone trial in HIV-infected men, a difference of 2.9 kg in fat-free mass was observed between testosterone and placebo groups[157]. Testosterone trials in older men that used smaller doses of testosterone observed an increase of ~1.5 kg[167].

We anticipate that the between-group difference in leg press strength will be 12 kg (SD 18 kg). This assumption is based on testosterone trials in older men[158, 179], HIV-infected men[157], and in COPD[166]. A 12 kg increase in leg press strength is clinically significant because a 10 kg increase was associated with improvements in walking speed[237]. Muscle performance tests will be optional at JHMI site. We expect that ~30 participants will be recruited at that hospital.

Assuming conservatively that no one at JHMI will choose optional muscle performance tests, 66 subjects per group will still provide ~90% statistical power to detect the effect size of 0.67..

For physical function domain of MOS-SF36, the difference of interest between 5 mg and placebo group is 4 points (SD 7 points). In randomized trials in older men with low testosterone, the difference in change in physical function domain score between testosterone and placebo groups was 4 points[167]. Ware et al[238] have determined that a 4-point change in the physical function domain of the MOS SF36 score is clinically meaningful. A sample size of 63 men in each arm will provide 96% power to detect this effect size.

To accommodate attrition of up to 12%, we will enroll 67 men per arm for a total of 134 men. Assumption of 12% attrition rate is conservative; the loss of information in the recent multicenter TTrials in older men was <5%[34-35]. Even if the dropout rate were 15%, we will have 86% power to detect the expected treatment effect for the primary and most of the secondary outcomes. The incorporation of 6-week measurement in the mixed effects model and the use of multiple imputation will provide even higher power than that claimed here.

9.2 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 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.

9.3 STATISTICAL ANALYSES

9.3.1 GENERAL APPROACH

Descriptive Analyses. Descriptive measures for each outcome and potential covariate will be computed. Graphical and tabular displays will be used to assess the distributional properties of outcomes and assess need for transformation. Preliminary assessments of association between covariates and outcomes will be obtained using semiparametric penalized likelihood approach implemented in generalized additive models[239]. We will use summary statistics and graphical techniques to compare baseline characteristics of groups.

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.

Compliance Analysis. Subject's compliance will be assessed in terms of the number of doses used, based on drug-use logs, expressed as a percent of the total number of doses that should have been used.

9.3.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Specific Aim 1 is concerned with change in sexual activity, measured by the PDQ-4. Six- and 12-week data will be analyzed simultaneously using mixed effects linear regression controlling for baseline and design effects (site, age group and PDEI use), with participants nested within

sites and treated as random effects. The primary analysis will be supplemented by comparisons of 12-week change in function, estimated via treatment contrast with statistical significance evaluated via likelihood ratio test. We will also compare the proportion of men achieving increase of >0.5 point on PDQ question 4 (sexual activity score, deemed to be the minimal clinically important difference) using generalized estimating equations via the modified Poisson regression approach, which can accommodate repeated measurements and are preferable to odds ratio in prospective designs. If the rate of improvement is very low, a zero-inflated alternative will be considered. Other domains of sexual function – sexual desire, erectile function, and distress – will be analyzed similarly using mixed effects regression model.

9.3.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Specific Aim 2 is concerned with estimation of the effects of TRT relative to placebo on well-being, affectivity balance, fatigue and HRQOL. These will be obtained at randomization and at 6 and 12 weeks. We will follow an analytic plan parallel to that described for Aim 1. **Aim 3** is concerned with the effects of TRT on measures of muscle mass, strength and physical function. As in Aims 1 and 2 we will utilize mixed effects regression to analyze endpoints with more than one post-randomization assessment. Analyses of executive cognitive function, dual-task walking performance ("walking while performing mental arithmetic) and voluntary stepping reaction time will be performed using analysis-of-covariance adjusted to site, age group and PDEI use.

Missing data. All subjects who are randomized will be included in the analyses (intention-to-treat) regardless of compliance. We will utilize multiple imputation by chained equations to generate plausible values for both missing outcomes and covariates simultaneously. This method allows for plausible association between covariates of binomial or multinomial distributions for discrete variables – and can accommodate the clustering of measurements. At least 50 replicates of the analysis will be generated. Assurance of convergence will be obtained using graphical methods. As an additional check against bias, we will employ multiple other methods to challenge these assumptions of missingness at random, including multiple sensitivity analyses; list-wise complete analyses; and pattern mixture models of outcomes.

Safety Analyses. Absent intervention, the clinical PSA recurrence rate in this group of men should be <0.5% over 10 years[2-5], so that few, if any clinical recurrences, are expected in the placebo arm over the three-month trial duration. We likewise anticipate few if any recurrences among subjects randomized to testosterone. To ensure that analyses are sensitive to even limited evidence of safety concerns, we will conduct a **one-sided** comparison of the proportion of subjects experiencing events in each arm using a Fisher's exact test with type-I error probability set at 0.20, as recommended by some FDA panels. Assuming recurrence risk on placebo is 1%, this comparison will have 85% power to detect an increased risk of 10% in the testosterone arm.

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.

Statistical Computing. Analyses will be on SAS 9.3 or later or R software version 3.3.1 or later

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: age (40-60, >60); 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.

9.3.4 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.

Absent intervention, the clinical PSA recurrence rate in this group of men should be <0.5% over 10 years[2-5], so that few, if any clinical recurrences, are expected in the placebo arm over the three-month trial duration. We likewise anticipate few if any recurrences among subjects randomized to testosterone. To ensure that analyses are sensitive to even limited evidence of safety concerns, we will conduct a **one-sided** comparison of the proportion of subjects experiencing events in each arm using a Fisher's exact test with type-I error probability set at 0.20, as recommended by some FDA panels. Assuming recurrence risk on placebo is 1%, this comparison will have 85% power to detect an increased risk of 10% in the testosterone arm.

9.3.5 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.

9.3.6 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.

9.3.7 SUB-GROUP ANALYSES

We will control forage, site, and PDE5I use as they are stratification factors in the design. Additionally, primary analysis will be assessed for robustness to control for age and baseline function.

9.3.8 TABULATION OF INDIVIDUAL PARTICIPANTDATA

Individual participant data will not be listed.

9.3.9 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 anytime 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 anytime without giving are as on 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 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 (ex. FDA, MHRA, PMDA), the sponsor's designated auditors, and the appropriate IRB store view 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, data and results will be reported to the clinicaltrials.gov.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples and data 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	*DSMB*
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 individuals with expertise in prostate cancer, clinical trials, andrology, 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 replacement therapy, 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 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 unblinded biostatistician directly to the DSMB. Thus, the DSMB members can have access to the categorized data, while the investigating team remains blinded.
4. 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.
5. 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.
6. 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 (ex. the Food and Drug Administration [FDA]. 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 FDA compliant Data Management System. The data system 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) E6Section4.9.5requirestheinvestigator to retain essential documents specified in ICHE 6 (Section8) 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, ICHE6 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 NIH (NIA) 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

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

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4. Stokes SH. Comparison of biochemical disease-free survival of patients with localized carcinoma of the prostate undergoing radical prostatectomy, transperineal ultrasound-guided radioactive seed implantation, or definitive external beam irradiation. *Int J Radiat Oncol Biol Phys.* 2000;47(1):129-136.
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