Testosterone replacement in prostate cancer survivors with testosterone deficiency: study protocol of a randomized controlled trial

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Short title: Testosterone treatment of prostate cancer survivors

Keywords: Testosterone treatment, prostate cancer, prostatectomy, hypogonadism

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/andr.13299.

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ABSTRACT

Background. Most men diagnosed with prostate cancer today have organ-confined disease and low risk of disease recurrence after radical prostatectomy. Testosterone deficiency in prostate cancer survivors contributes to impaired health-related quality of life but testosterone treatment is viewed as a contraindication in this population.

Objectives. We describe the design of the first randomized trial to determine the safety and efficacy of testosterone treatment in men who have undergone prostatectomy for non-aggressive prostate cancer and have symptomatic testosterone deficiency.

Methods. Surviving Prostate cancer while Improving quality of life through Rehabilitation with Testosterone Trial (The SPIRIT Trial) is a randomized, placebo-controlled, double-blind, parallel group trial in 142 men, ≥40 years, who have undergone radical prostatectomy for organ-confined prostate cancer, Gleason score ≤7 (3+4), Stage pT2, N0, M0 lesions and have symptomatic testosterone deficiency and undetectable PSA for >2 years after surgery. Eligible participants are randomized to weekly intramuscular injections of 100-mg testosterone cypionate or placebo for 12 weeks and followed for another 12 weeks. Primary endpoint is change from baseline in sexual activity. Secondary outcomes include change in sexual desire, erectile function, energy, lean and fat mass, physical and cognitive performance. Safety is assessed by monitoring PSA, lower urinary tract symptoms, hemoglobin, and adverse events.

Results. The trial is being conducted at 2 trial sites in Boston, MA and Baltimore, MD. As of July 30, 2022, 42 participants have been randomized. No PSA or clinical recurrence has been noted to-date.

Discussion. Recruitment was slowed by COVID-19-related closures, slow subsequent ramp-up of research activities, and patient concerns about safety of testosterone treatment. Despite these challenges, participant retention has been high.

Conclusion. The SPIRIT Trial, a placebo-controlled, randomized trial, will determine whether testosterone replacement therapy is safe and efficacious in correcting symptoms of testosterone deficiency in prostate cancer survivors, and potentially inform clinical practice.

INTRODUCTION

Prostate cancer (PCa) is the most prevalent cancer in men worldwide [1]. Most men diagnosed today with prostate cancer have a non-aggressive, organ-confined PCa and radical prostatectomy is associated with excellent long-term disease-free survival [2-6]. Excellent long-term survivorship of men with low grade organ-localized PCa has focused attention on the high prevalence of sexual dysfunction, physical dysfunction, and chronic fatigue in this group, which contribute to impaired health-related quality of life (HRQOL) [7-12]. The pathophysiology of these symptoms after radical prostatectomy is multifactorial, but androgen deficiency is a frequent and important remediable contributor [7-11,13-17].

Androgen deficiency is common in men with prostate cancer who have undergone radical prostatectomy [11,14,15,18-21]. Low libido, erectile dysfunction (ED), hot flashes, mobility limitation, decreased physical function, fatigue, and role limitations due to physical problems are major complaints of these men [7,8,22-27]. Even with a bilateral nerve-sparing procedure, more than 50% develop sexual dysfunction after surgery [22,24,28,29].

Testosterone replacement therapy (TRT) improves corresponding symptoms in hypogonadal men without prostatic disease [30-34]. Several large RCTs have established that TRT in older men with testosterone deficiency improves sexual activity, libido, erections, and satisfaction with intercourse [30-33]. TRT reduces fatigue in HIV-infected men and a large 2016 randomized controlled trial reported improvements in energy following TRT [35,36] although some other trials did not find improvements in fatigue[30]. In young and middle-aged hypogonadal men, TRT has a positive impact on mood [34,37]. Similar improvements in mood have been reported in older, hypogonadal, HIV-infected men [35,36]. TRT also increases muscle mass and strength, aerobic capacity, and stair-climbing power [33,34,38-43]. In older men, a meta-analysis of RCTs with TRT reported greater increments in lean mass, self-reported physical

function, and stair climbing power[44] while the reported improvement in gait speed has been small and less consistent [45-47].

A history of PCa has been usually considered a contraindication for testosterone therapy [13]. This guidance is based on observations that testosterone promotes the growth of metastatic prostate cancer, and that androgen deprivation therapy causes regression of metastatic PCa [48-50]. Therefore, many clinicians have reservations about administering TRT to PCa survivors.

However, the relationship between testosterone and PCa is complex [14-17]. Epidemiologic studies have not revealed a consistent relationship between testosterone levels and PCa risk[51-53]. Open-label trials and retrospective analyses have reported very low rates of disease recurrence in men treated with TRT after prostatectomy[11,14-16]. Even in men with high-grade prostatic intraepithelial neoplasia (HGPIN) – a group at potentially increased risk of developing PCa – TRT for one year did not increase PSA or rates of PCa[54]. However, these trials were neither randomised nor blinded. Men with Klinefelter Syndrome have lower mortality due to prostate cancer than the general population[55]. In Mendelian randomization studies, higher genetically-determined testosterone level has been associated with increased life time risk of prostate cancer [56]. Despite the absence of randomised trial data, the use of TRT to treat symptoms of androgen deficiency has continued to grow. Whether TRT is safe and efficacious in improving symptoms of testosterone deficiency in PCa survivors at low risk of recurrence is a high priority question for these men and motivated this randomised clinical trial.

The primary objective of this trial is to determine whether TRT is safe and more efficacious in improving overall sexual activity than placebo in men who have undergone radical prostatectomy for organ-confined PCa, and have a low risk of recurrence and symptomatic androgen deficiency. Secondary objectives are to determine whether TRT is

more efficacious than placebo in improving sexual desire, erectile function, distress associated with sexual dysfunction, sexual life quality, mood, energy, lean and fat mass, maximal voluntary strength, and physical function. Our primary hypothesis is that TRT will be safe and associated with greater improvements in overall sexual activity when compared to placebo. Our secondary hypothesis is that TRT will be associated with greater improvements in sexual desire, erectile function, distress associated with sexual dysfunction, sexual life quality, mood, energy, lean and fat mass, maximal voluntary strength, and performance-based as well as self-reported measures of physical function compared to placebo.

METHODS

The study has been approved by the Central WCG Institutional Review Board (IRB), Dana Farber Cancer Center IRB, and the Johns Hopkins Medical Institutions IRB. All study participants provided written, informed consent. The trial is registered with the clinicaltrials.gov [National Clinical Trial (NCT) Identified Number: NCT03716739].

Overall study design

This investigator-initiated proof-of-concept trial is a 12-week, randomised, placebo-controlled, double-blind parallel group trial in 142 community dwelling men, 40 years or older, with PCa who have undergone radical prostatectomy for organ-localised disease who have undetectable PSA for > 2 years after radical prostatectomy, and who have androgen deficiency and one or more symptoms of testosterone deficiency. The study is being conducted at the Brigham and Women's Hospital (BWH) in Boston, USA, and the Johns Hopkins Medical Institutions in Baltimore, USA. The eligible participants are randomly assigned to receive testosterone cypionate 100 mg weekly or placebo injection weekly, stratified for age and use of phosphodiesterase 5 inhibitors (PDEIs). Efficacy outcomes are assessed at 6 and 12 weeks and include measures of sexual, physical, cognitive, and mood functions. Adverse event recording and safety laboratory tests, including PSA levels are performed every 2 weeks during the study drug administration period. The length of the intervention was set to 12 weeks because the 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[57]. Thus, 3-month intervention duration is sufficient to detect meaningful changes in efficacy outcomes and PSA. The participants are followed for 3-months after the completion of the intervention period.

Eligibility criteria

The trial is enrolling 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 6 or 7 (3+4) (Gleason Grade Group 1 and 2), preoperative PSA<20 ng/ml, undetectable PSA for >2 years after surgery, and one or more of the following: low libido, erectile dysfunction, fatigue (**Table 1**). Those with preoperative PSA between 10 to 20 ng/mL, who meet all other criteria are considered for inclusion by study physician after assesment of cancer recurrence risk based on 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. The rationale for selecting men with these criteria is that this group of men has <0.5% disease recurrence rate over ten years. We 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 men are required to have an average of two early morning, fasting, total testosterone levels, measured using LC-MS/MS, < 275 mg/dL. SHBG levels are higher in older men, which may lead to falsely elevated total testosterone levels. Thus, we will include men with free testosterone ≤70 pg/mL, the lower limit of the normal range in the Framingham Heart Study [58]. This threshold for total testosterone level is based on the results of the Testosterone Trials (The TTrials), in which 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 a 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 [32]. 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 [59]. Furthermore, in the European Male Aging Study, total testosterone < 312 ng/dL was associated with a syndromic cluster of sexual symptoms [60].

Participant Recruitment

Potential participants are being recruited from the Brigham and Women's Hospital, Boston, USA, and from the Brady Urological Institute, Johns Hopkins Medical Institutions, Baltimore, USA. Recruitment methods include the use of a prostate cancer registry and electronic health records research database together with direct advertising through websites and social media platforms. Participants are also recruited directly from the urology and survivorship clinics at the two trial sites. The Institutional Review Board (IRB)-approved texts are used for advertising in all recruitment methods.

Potential participations are pre-screened for major eligibility criteria using a structured telephone interview by a staff member; those who qualify during pre-screening are invited to an in-person screening visit where the person's eligibility is determined based on the results of the medical history, review of medical records including Pathology report, physical examination, questionnaires, Short Physical Performance Battery (SPPB), and blood tests.

Prospective Allocation of Study Participant

The eligible participants are 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). The randomization is stratified based on age, PDEI use, and trial site because these factors may independently affect sexual function and HRQOL.

Blinding

The participants and the study staff are blinded to the study medication. Treatment assignment is known only to the Data Coordinating Center and the Investigational Drug Pharmacy.

Study Intervention

We chose testosterone cypionate for this trial because of its high bioavailability, the ease of once-weekly administration, and predictable pharmacokinetics. All injections are administered by the study staff in the clinical research unit which ensures adherence. In a recent RCT of a high protein diet versus the recommended dietary allowances (RDA) with and without testosterone, this regimen of 100 mg testosterone cypionate weekly raised testosterone levels into the normal male range, and adherence with the regimen exceeded 99%. The control group receives weekly IM placebo injections.

Study Outcomes

Study outcomes are listed in Table 2. Our primary outcome is change in sexual activity assessed using the well validated Psychosexual Daily Questionnaire, question 4 (PDQ-4) [61]. The PDQ-Q4 asks participants to list how many of 12 specified activities (sexual daydreams, anticipation of sex, sexual interactions with partner, flirting by you, flirting toward you, orgasm, ejaculation, intercourse, masturbation, night spontaneous erection, day spontaneous erection, and erection in response to sexual activity) they engaged in each day of the week, and the daily count is averaged over 7 days for a total score ranging from 0–12. Overall sexual activity, assessed by PDQ-4, is a meaningful integrated measure of sexual function, and has been found to be androgen responsive in prior studies[30].

Secondary outcomes include other measures of sexual function. Erectile function is assessed by International Index of Erectile Function (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 is assessed by DeRogatis Inventory of Sexual Function - Sexual Desire (DISF). 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.

The impact of TRT on HRQOL is assessed 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[62,63]. We use the sexual and hormonal domains, which are affected by androgen deficiency and expected to improve with TRT. Energy level is assessed by the Hypogonadism Energy scale. This instrument has been well-validated, is specific to hypogonadal men, and has been shown to be responsive to TRT. Mood and wellbeing is assessed by PANAS affectivity balance scale, which includes 10 questions each for Positive Affect (e.g., joy) and Negative Affect (e.g., anxiety, depression)[64]. Many behavioral scientists consider affectivity balance to be the best window on wellbeing. Other secondary outcomes are measures of aerobic capacity and aerobic endurance, upper and lower extremity maxiamal voluntary muscle strength using the 1-RM method, cognitive performance, reaction time, and physical function. Performance-based measures of physical function consist of loaded stair climbing power, 6-minute walking distance and speed, dual-task walking and the loaded 50 m walk test. Self-reported physical function is assessed using the MOS SF-36 physical function domain (PF10) [12]. These measures have been shown to be androgen-responsive [33,34,38-42,65-67]. Stair climbing power which is related to leg press power is more responsive to TRT than the 6-minute walk test. Whole body and appendicular skeletal muscle mass is

measured by dual-energy X-ray absorptiometry (DXA) using Hologic 4500 DXA machine a multi-component model because of its precision, reproducibility, and ease. The DXA scanner is calibrated using a soft tissue phantom. Lean mass estimates by DXA have inter-scan variability of 2-3%.

Safety Assessment

We have incorporated several measures to minimize risk. The eligibility criteria are designed to insure the selection of subjects at low risk of disease recurrence. The participants are monitored closely with structured adverse event recording, PSA levels, blood counts, blood chemistries, and lipids. Serum PSA levels are measured at screening, baseline and during weeks 2, 4, 8, 12, 24 and hemoglobin and hematocrit at screening, baseline, and during weeks 6 and 12. We have established rigorously defined criteria for biochemical recurrence and stopping rules. We have incorporated the procedures recommended by the Expert Panel of the Endocrine Society on Androgen Deficiency Syndromes, and the ISSAM, for monitoring of men receiving TRT. An NIA-appointed Data and Safety Monitoring Board (DSMB) reviews safety data and study progress every 6 months.

Defining Biochemical Recurrence. An Expert Panel of American Urological Association defined biochemical recurrence in men who have undergone radical prostatectomy an "*an initial PSA of ≥0.2 ng/mL with a second confirmatory level of PSA ≥0.2 ng/ml*[68]." We use this definition, which represents the consensus view of an expert panel. Patients who develop PSA recurrence will have the intervention stopped and referred to their urologist.

STATISTICAL CONSIDERATIONS

Sample Size Determination

In the TTrials, the effect size of TRT relative to placebo in the PDQ-Q4 was 0.6 units [30,31]. Other TRT trials have shown greater increases in sexual activity scores [33,34,38]. To be conservative, here we assume that the difference in the change of interest in sexual activity between the testosterone and placebo arms over 3 months is 0.6 units (SD 1.3) [30,31]. This change is clinically meaningful and patient-important because post-hoc analyses of the TTrials data showed that the minimal clinically important difference (MCID) for sexual activity using PDQ-4 is 0.5 units [30]. 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. 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 [69], which is less than the correlation observed in the TTrials over a one-year period. To account for missingness, we will enroll 63/0.88 = 71 participants per arm = 142 in total. Even if the effect size is as small as 0.5 points, this sample size will provide 80% power to detect differences as small as 0.5 points on PDQ-Q4.

DATA ANALYSIS

Intention-to-Treat (ITT) Analysis Dataset will consist of all randomised participants. This analysis set will be used for summarising disposition, demographics, and baseline characteristics and for primary efficacy analyses. The safety analysis set will consist of all randomised participants who received at least one dose of the investigational

product (testosterone or placebo). Per-Protocol Analysis Dataset defines a subset of the participants in the ITT set who complied with the study protocol and who took at least 80% of the study medication.

Descriptive analyses: Graphical and tabular displays will be used to assess the distributional properties of outcomes and assess the need for transformation. Preliminary assessments of associations between covariates and outcomes will be obtained using semiparametric penalised likelihood approach implemented in generalised additive models[70]. We will use summary statistics and graphical techniques to compare baseline characteristics of groups. Participant characteristics will be summarised 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. The participant's adherence 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.

Analysis of the efficacy endpoints: Hypothesis tests will assume two-sided type I error probability of 0.05. No interim analyses are planned. We will however monitor safety, accrual, adherence, attrition, and data quality.

For the primary endpoint of change in sexual activity, 6 and 12-week data will be analysed 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 an increase of >0.5 points on PDQ question 4 (sexual activity score, deemed to be the minimal clinically important difference) using generalised 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. Model-based point estimates of treatment effect will be accompanied by 95% confidence intervals. Other domains of sexual function – sexual desire, erectile function, and distress – will be analysed similarly using mixed effects regression model.

Sensitivity analyses will determine if pre-specified covariates modify the treatment effect. Also, per-protocol analysis of participants, who complete the trial, adjusting for adherence will be performed.

Safety Analyses: Adverse events will be classified according to Medical Dictionary for Regulatory Activities (MedDRA) and System Organ Class (SOC) coding system.

Absent intervention, the clinical PSA recurrence rate in this group of men should be <0.5% over 10 years[4-6], 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 clinical recurrences among participants randomised 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 participants experiencing events in each arm using the Fisher's exact test.

CURRENT STATUS

As of July 14, 2022, the trial had screened 1,562 persons on the telephone and 100 participants in-person. Of these 52 met the eligibility criteria and 43 were randomized. The first participant was randomized on May 13, 2019 and 30 participants have completed study procedures.

DISCUSSION

The SPIRIT Trial is the first placebo-controlled randomized trial of the efficacy and safety of TRT in prostate cancer survivors with symptoms of androgen deficiency and unequivocally low testosterone levels. Although a few open-label trials of TRT have been published, none was either randomized or placebo-controlled. The proposed RCT has many attributes of good trial design: concealed block randomization, inclusion of a placebo control, parallel group design, attention to effect size and statistical power, and blinding. Testosterone thresholds for inclusion in previous open-label trials have varied across trials and many trials included men with normal or low normal testosterone levels, who would not be expected to improve with TRT. We will include men with unequivocally low testosterone levels and symptoms, consistent with Endocrine Society's guideline and the Institute of Medicine report. Recent large RCTs have shown that hypogonadal men, with symptoms and testosterone levels below these thresholds are the most likely to respond to TRT. Because sexual symptoms are the most prevalent and important contributors to distress and impaired quality of life among men who have undergone radical prostatectomy and are at low cancer recurrence risk, we have included several validated measures of sexual function. Our primary outcome is overall sexual activity assessed using a validated psychosexual diary maintained over 7 consecutive days, but we have also included measures of sexual desire, erectile function, and distress due to sexual dysfunction. We have included self-reported measures of energy and function as well as performance-based measures of muscle performance and physical function that will be assessed by expert exercise physiologists using standardized procedures in the setting of a research laboratory. Additionally, we have included validated instruments for evaluation of sexual function and energy that have been responsive to TRT in randomized trials of young and older hypogonadal men.

We have incorporated several measures to minimize risk, including the selection of men at low risk of disease recurrence, rigorous structured safety monitoring, pre-specified criteria for biochemical recurrence and stopping rules, and oversight by an independent DSMB.

The participant enrollment, a challenge in all clinical research studies, has been even more challenging due to several factors some of which are unique to this study population. Testosterone treatment has been deemed a contraindication in men with history of prostate cancer in the guidelines of most professional societies. Unsurprisingly, many men with prostate cancer are hesitant to participate in a blinded clinical trial of testosterone treatment; many primary care providers share these concerns and are hesitant to refer their patients for the trial. The study enrollment in the trial started in March 2019. Due to the global COVID-19 Pandemic, all clinical research activities were halted in the US in March 2020. After a 7-month complete shutdown of non-Covid-related research, there was a gradual return to limited study activities until the reactivation of in-person study activities in early 2021. The participant recruitment in 2021 remained low due to the reluctance of middle-aged and older adults to come to the medical centers for research visits due to the fear of contracting the infection. Nevertheless, we have retained 89% of randomized participants in the study and 97% of subjects who started the intervention have adhered to all study procedures.

The trial's design should be viewed in the context of some limitations. There may be considerable heterogeneity in the baseline sexual function of the participants due to the type of prostatectomy they have received and this could also affect their response to the study intervention. We anticipate that randomization should result in balancing the distribution of baseline sexual function in the study arms. Some of the subjects with longstanding sexual dysfunction may not be sexually active and this may attenuate their response to study intervention. The inclusion criteria did not consider drug assisted IIEF score. However, the

randomization is stratified by PDE5I use and furthermore, the primary endpoint of change in sexual activity will be analysed using mixed effects linear regression controlling for baseline and design effects including PDE5I use.

The trial is neither large enough nor long enough to determine the risk of clinical cancer recurrence. Therefore, if the SPIRIT trial shows efficacy and short-term safety, that would provide the rationale for conducting larger, trials to establish long-term safety of testosterone replacement therapy in this patient population.

Authors' contributions

SB obtained the grant funding; SB, KMP, ASK, and TWS designed the trial; RV and MH wrote the first draft of the manuscript. All authors participated in the trial's implementation, and in manuscript review and revisions.

Funding

The SPIRIT Trial is supported by National Institutes on Aging grant number 1RO1AG06539-01. This research is partially supported by the infrastructural resources provided by the Boston Claude D. Pepper Older Americans Independence Center at Brigham and Women's Hospital (P30AG013679) and Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award UL1 TR001102) and financial contributions from Harvard University and its affiliated academic healthcare centers.

Competing Interests

Dr. Bhasin reports receiving research grants from the National Institute on Aging, the National Institute of Nursing Research, National Center for Medical Rehabilitation Research of the National Institute of Child Health and Human Development, Patient Centered Outcomes Research Institute, AbbVie, and Metro International Biotech, and consulting fees from OPKO and Aditum Bio. These grants are managed by the Brigham and Women's Hospital and overseen by the Office of Industry Interaction of the Mass General Brigham.

Acknowledgements

We thank Amy Larson for her stalwart regulatory and institutional support. We thank Drs. Adrian Dobbs, Walter Ambrosius and Rahul Aggarwal for serving as the Data and Safety Monitoring Board members.

REFERENCES

1. Bray F, Ren JS, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. *International journal of cancer.* 2013;132(5):1133-1145.
2. Rebecca L, Siegel M, Kimberly D, Miller M, Ahmedin Jemal D. Cancer statistics. *Ca Cancer J Clin.* 2017;67(27):7-30.
3. Siegel R, Ward E, Brawley O, Jemal A. The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *Ca-a Cancer Journal for Clinicians.* 2011;61(4):212-236.
4. Hernandez DJ, Nielsen ME, Han M, et al. Natural history of pathologically organ-confined (pT2), Gleason score 6 or less, prostate cancer after radical prostatectomy. *Urology.* 2008;72(1):172-176.
5. 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. *International Journal of Radiation Oncology* Biology* Physics.* 2000;47(1):129-136.
6. Potosky AL, Davis WW, Hoffman RM, et al. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. *Journal of the National Cancer Institute.* 2004;96(18):1358-1367.
7. Litwin MS, Flanders SC, Pasta DJ, Stoddard ML, Lubeck DP, Henning JM. Sexual function and bother after radical prostatectomy or radiation for prostate cancer: multivariate quality-of-life analysis from CaPSURE. *Urology.* 1999;54(3):503-508.
8. Litwin MS, Gore JL, Kwan L, et al. Quality of life after surgery, external beam irradiation, or brachytherapy for early-stage prostate cancer. *Cancer.* 2007;109(11):2239-2247.
9. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *New England Journal of Medicine.* 2008;358(12):1250-1261.
10. Penson DF, Latini DM, Lubeck DP, Wallace K, Henning JM, Lue T. Is quality if life different for Men with erectile dysfunction and prostate cancer compared to Men with erectile dysfunction due to other causes? results from the ExCEED data base. *The Journal of urology.* 2003;169(4):1458-1461.
11. Khera M. Androgens and erectile function: a case for early androgen use in postprostatectomy hypogonadal men. *The journal of sexual medicine.* 2009;6:234-238.
12. Ficarra V, Novara G, Galfano A, et al. Twelve-month self-reported quality of life after retropubic radical prostatectomy: a prospective study with Rand 36-Item Health Survey (Short Form-36). *BJU international.* 2006;97(2):274-278.
13. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism.* 2010;95(6):2536-2559.
14. Morgentaler A. Testosterone therapy in men with prostate cancer: scientific and ethical considerations. *The Journal of urology.* 2009;181(3):972-979.
15. Morgentaler A. Guilt by association: a historical perspective on Huggins, testosterone therapy, and prostate cancer. *The journal of sexual medicine.* 2008;5(8):1834-1840.
16. Khera M, Grober ED, Najari B, et al. Testosterone replacement therapy following radical prostatectomy. *The journal of sexual medicine.* 2009;6(4):1165-1170.
17. Khera M, Lipshultz LI. The role of testosterone replacement therapy following radical prostatectomy. *Urologic Clinics of North America.* 2007;34(4):549-553.
18. Schatzl G, Madersbacher S, Thurridl T, et al. High-grade prostate cancer is associated with low serum testosterone levels. *The Prostate.* 2001;47(1):52-58.

19. Severi G, Morris HA, MacInnis RJ, et al. Circulating steroid hormones and the risk of prostate cancer. *Cancer Epidemiology and Prevention Biomarkers.* 2006;15(1):86-91.
20. Morgentaler A, Bruning CO, DeWolf WC. Occult prostate cancer in men with low serum testosterone levels. *Jama.* 1996;276(23):1904-1906.
21. Ahluwalia B, Jackson M, Jones G, Williams A, Rao MS, Rajguru S. Blood hormone profiles in prostate cancer patients in high-risk and low-risk populations. *Cancer.* 1981;48(10):2267-2273.
22. Glickman L, Godoy G, Lepor H. Changes in continence and erectile function between 2 and 4 years after radical prostatectomy. *The Journal of urology.* 2009;181(2):731-735.
23. Masterson TA, Wedmid A, Sandhu JS, Eastham JA. Outcomes after radical prostatectomy in men receiving prior pelvic radiation for non-prostate malignancies. *BJU international.* 2009;104(4):482.
24. Mulhall JP. Defining and reporting erectile function outcomes after radical prostatectomy: challenges and misconceptions. *The Journal of urology.* 2009;181(2):462-471.
25. Penson DF, McLERRAN D, Feng Z, et al. 5-year urinary and sexual outcomes after radical prostatectomy: results from the prostate cancer outcomes study. *The Journal of urology.* 2005;173(5):1701-1705.
26. Talcott JA, Rieker P, Clark JA, et al. Patient-reported symptoms after primary therapy for early prostate cancer: results of a prospective cohort study. *Journal of Clinical Oncology.* 1998;16(1):275-283.
27. Talcott JA, Rieker P, Propert KJ, et al. Patient-reported impotence and incontinence after nerve-sparing radical prostatectomy. *Journal of the National Cancer Institute.* 1997;89(15):1117-1123.
28. Burnett AL. Erectile dysfunction following radical prostatectomy. *Jama.* 2005;293(21):2648-2653.
29. Hyun JS. Prostate cancer and sexual function. *The world journal of men's health.* 2012;30(2):99-107.
30. Snyder PJ, Bhasin S, Cunningham GR, et al. Effects of testosterone treatment in older men. *New England Journal of Medicine.* 2016;374(7):611-624.
31. Cunningham GR, Stephens-Shields AJ, Rosen RC, et al. Testosterone treatment and sexual function in older men with low testosterone levels. *The Journal of Clinical Endocrinology & Metabolism.* 2016;101(8):3096-3104.
32. Brock G, Heiselman D, Maggi M, et al. Effect of testosterone solution 2% on testosterone concentration, sex drive and energy in hypogonadal men: results of a placebo controlled study. *The Journal of Urology.* 2016;195(3):699-705.
33. Steidle C, Schwartz S, Jacoby K, et al. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. *The Journal of Clinical Endocrinology & Metabolism.* 2003;88(6):2673-2681.
34. Wang C, Cunningham G, Dobs A, et al. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. *The Journal of Clinical Endocrinology & Metabolism.* 2004;89(5):2085-2098.
35. Wagner GJ, Rabkin JG, Rabkin R. Testosterone as a treatment for fatigue in HIV+ men. *General hospital psychiatry.* 1998;20(4):209-213.
36. Rabkin JG, Wagner GJ, Rabkin R. A double-blind, placebo-controlled trial of testosterone therapy for HIV-positive men with hypogonadal symptoms. *Archives of general psychiatry.* 2000;57(2):141-147.
37. Wang C, Alexander G, Berman N, et al. Testosterone replacement therapy improves mood in hypogonadal men--a clinical research center study. *The Journal of Clinical Endocrinology & Metabolism.* 1996;81(10):3578-3583.

38. Wang C, Swerdloff RS, Iranmanesh A, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. *The Journal of Clinical Endocrinology & Metabolism.* 2000;85(8):2839-2853.
39. Bhasin S, Storer TW, Berman N, et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *New England Journal of Medicine.* 1996;335(1):1-7.
40. Bhasin S, Storer T. Anabolic applications of androgens for functional limitations associated with aging and chronic illness. *Advances in the Management of Testosterone Deficiency.* 2009;37:163-182.
41. Bhasin S, Woodhouse L, Casaburi R, et al. Testosterone dose-response relationships in healthy young men. *American Journal of Physiology-Endocrinology And Metabolism.* 2001.
42. Bhasin S, Storer TW, Berman N, et al. Testosterone replacement increases fat-free mass and muscle size in hypogonadal men. *The Journal of Clinical Endocrinology & Metabolism.* 1997;82(2):407-413.
43. Bhasin S, Woodhouse L, Casaburi R, et al. Older men are as responsive as young men to the anabolic effects of graded doses of testosterone on the skeletal muscle. *The Journal of Clinical Endocrinology & Metabolism.* 2005;90(2):678-688.
44. Corona G, Giagulli VA, Maseroli E, et al. Testosterone supplementation and body composition: results from a meta-analysis study. *Eur J Endocrinol.* 2016;174(3):R99-R116.
45. Bhasin S, Calof OM, Storer TW, et al. Drug insight: testosterone and selective androgen receptor modulators as anabolic therapies for chronic illness and aging. *Nature clinical practice Endocrinology & metabolism.* 2006;2(3):146-159.
46. Page ST, Amory JK, Bowman FD, et al. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. *The Journal of Clinical Endocrinology & Metabolism.* 2005;90(3):1502-1510.
47. Dalton JT, Barnette KG, Bohl CE, et al. The selective androgen receptor modulator GTx-024 (enobosarm) improves lean body mass and physical function in healthy elderly men and postmenopausal women: results of a double-blind, placebo-controlled phase II trial. *Journal of cachexia, sarcopenia and muscle.* 2011;2(3):153-161.
48. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer research.* 1941;1(4):293-297.
49. Fowler Jr JE, Whitmore Jr WF. The response of metastatic adenocarcinoma of the prostate to exogenous testosterone. *The Journal of urology.* 1981;126(3):372-375.
50. Prout Jr GR, Brewer WR. Response of men with advanced prostatic carcinoma to exogenous administration of testosterone. *Cancer.* 1967;20(11):1871-1878.
51. Hormones E, Group PCC. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. *JNCI: Journal of the National Cancer Institute.* 2008;100(3):170-183.
52. Shaneyfelt T, Husein R, Bubley G, Mantzoros CS. Hormonal predictors of prostate cancer: a meta-analysis. *Journal of Clinical Oncology.* 2000;18(4):847-847.
53. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. *JNCI: Journal of the National Cancer Institute.* 1996;88(16):1118-1126.
54. Rhoden EL, Morgentaler A. Testosterone replacement therapy in hypogonadal men at high risk for prostate cancer: results of 1 year of treatment in men with prostatic intraepithelial neoplasia. *The Journal of urology.* 2003;170(6):2348-2351.

55. Swerdlow AJ, Schoemaker MJ, Higgins CD, Wright AF, Jacobs PA. Cancer incidence and mortality in men with Klinefelter syndrome: a cohort study. *Journal of the National Cancer Institute.* 2005;97(16):1204-1210.
56. Ruth KS, Day FR, Tyrrell J, et al. Using human genetics to understand the disease impacts of testosterone in men and women. *Nature medicine.* 2020;26(2):252-258.
57. Tenover JS. Effects of testosterone supplementation in the aging male. *The Journal of Clinical Endocrinology & Metabolism.* 1992;75(4):1092-1098.
58. Bhasin S, Pencina M, Jasuja GK, et al. Reference ranges for testosterone in men generated using liquid chromatography tandem mass spectrometry in a community-based sample of healthy nonobese young men in the Framingham Heart Study and applied to three geographically distinct cohorts. *The Journal of Clinical Endocrinology & Metabolism.* 2011;96(8):2430-2439.
59. Basaria S, Harman SM, Travison TG, et al. Effects of testosterone administration for 3 years on subclinical atherosclerosis progression in older men with low or low-normal testosterone levels: a randomized clinical trial. *Jama.* 2015;314(6):570-581.
60. Wu FC, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. *New England Journal of Medicine.* 2010;363(2):123-135.
61. Lee KK, Berman N, Alexander GM, Hull L, Swerdloff RS, Wang C. A simple self-report diary for assessing psychosexual function in hypogonadal men. *Journal of andrology.* 2003;24(5):688-698.
62. Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. *Urology.* 2000;56(6):899-905.
63. Szymanski KM, Wei JT, Dunn RL, Sanda MG. Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. *Urology.* 2010;76(5):1245-1250.
64. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of personality and social psychology.* 1988;54(6):1063.
65. Bhasin S, Storer TW, Javanbakht M, et al. Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. *Jama.* 2000;283(6):763-770.
66. Storer TW, Magliano L, Woodhouse L, et al. Testosterone dose-dependently increases maximal voluntary strength and leg power, but does not affect fatigability or specific tension. *The Journal of Clinical Endocrinology & Metabolism.* 2003;88(4):1478-1485.
67. Storer TW, Woodhouse LJ, Sattler F, et al. A randomized, placebo-controlled trial of nandrolone decanoate in human immunodeficiency virus-infected men with mild to moderate weight loss with recombinant human growth hormone as active reference treatment. *The Journal of Clinical Endocrinology & Metabolism.* 2005;90(8):4474-4482.
68. Cookson MS, Aus G, Burnett AL, et al. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. *The Journal of urology.* 2007;177(2):540-545.
69. Borm GF, Fransen J, Lemmens WA. A simple sample size formula for analysis of covariance in randomized clinical trials. *Journal of clinical epidemiology.* 2007;60(12):1234-1238.
70. Wood SN. *Generalized additive models: an introduction with R.* chapman and hall/CRC; 2006.

Table 1. The Inclusion and Exclusion Criteria

Inclusion Criteria

1. Men 40 years and older
2. A history of prostate cancer stage pT2, N0, M0 lesions, and prostatectomy treatment.
3. Combined Gleason score of 7 (3+4) or less.
4. Preoperative PSA < 10 ng/ml. Participants with preoperative PSA 10 ng/mL to 20 ng/mL will be considered for inclusion if all other criteria are met, subject to study physician assessment of cancer recurrence risk.
5. Stable PSA levels ≤0.1 ng/mL for at least two years after radical prostatectomy.
6. International Index of Erectile Function (IIEF) score <25 and/or DeRogatis Inventory of Sexual Function (DISF) Sexual Desire domain score ≤20 and/or Functional Assessment of Chronic Illness Therapy (FACIT) fatigue subscale score <30.
7. An average of two fasting, early morning serum testosterone levels, less than 275 ng/dL (9.5 nmol/L), and/or a single free testosterone ≤70 pg/mL.
8. Willingness to not make any major changes in dietary intake or exercise activities.
9. Ability and willingness to provide informed consent.

Exclusion Criteria

1. Previous prostate cancer treated with radiation as primary therapy, as adjuvant therapy or as salvage therapy.
2. Ongoing androgen deprivation therapy.
3. Hemoglobin <10 g/dL or >17.1 g/dL.
4. Severe untreated sleep apnea.
5. Uncontrolled heart failure.
6. Myocardial infarction, acute coronary syndrome, revascularization surgery, or stroke within the last 3 months.
7. Serum creatinine>2.5 mg/dL.
8. Serum Alanine transaminase 3x upper limit of normal.
9. Hemoglobin A1c >7.5% or a diagnosis of diabetes requiring insulin therapy.
10. Body mass index (BMI) >40 $kg/m^{2.}$
11. Untreated depression.
12. Axis I psychiatric disorder, such as schizophrenia.
13. Use of medications such as testosterone, DHEA, estrogens, GnRH analogs, antiandrogens, spironolactone, ketoconazole, rhGH, megesterol acetate, prednisone 20 mg daily or equivalent doses of other glucocorticoids for more than two weeks within the past 6 months

Table 2. Study Outcomes and Assessments

Primary/ Secondary/ Tertiary or Exploratory	Study question	Endpoint	Measure/ Study Assessment
Primary	Does TRT improve sexual activity more than placebo?	Change from baseline in sexual activity score	Psychosexual Daily Questionnaire question 4 (PDQ-4)
Secondary	Does TRT improve erectile function more than placebo	Change from baseline in erectile function, sexual distress.	International Index of Erectile Function, Erectile dysfunction
Secondary	Does TRT improve sexual desire more than placebo	Change from baseline in sexual desire score	DeRogatis Inventory of Sexual Function - Sexual Desire
Secondary	Does TRT improve distress associated with sexual symptoms more than placebo	Change from baseline in distress associated with sexual symptoms	Sexual distress will be assessed using Erectile dysfunction "bother scale". Adapted from: WHO 1st International Consultation on Erectile Function, Paris, 1999.
Secondary	Does TRT improve disease-specific quality of life more than placebo?	Change from baseline in Disease-specific Health Related Quality of Life	Expanded Prostate Cancer Index Composite (EPIC).
Secondary	Does TRT improve mood and wellbeing?	Change from baseline in mood and wellbeing	Positive and Negative Affect Scale (PANAS),
Secondary	Does TRT improve energy more than placebo?	Change from baseline in energy score	Hypogonadism Energy scale
Secondary	Does TRT improve executive function more than placebo?	Change from baseline in executive function	Digit symbol substitution test.
Secondary	Does TRT improve lean body mass more than placebo?	Change from baseline in whole body and appendicular lean mass	Dual energy x-ray absorptiometry
Secondary	Does TRT reduce whole body and	Change from baseline in whole body and intra-	Dual energy x-ray absorptiometry

	intra-abdominal fat mass more than placebo?	abdominal fat mass	
Secondary	Does TRT increasing maximal voluntary muscle strength more than placebo?	Change from baseline in maximal voluntary strength in the leg press and chest press exercises.	One-repetition maximum (1-RM) in the leg press and chest press exercises measured using Keiser pneumatic resistance machines
Secondary	Does TRT improve performance-based measures of physical function compared to placebo?	Change from baseline in stair-climbing power and speed, walking speed and distance in the 6-minute walk test, dual-task walking performance and choice stepping reaction time	Loaded stair climbing power and speed, and 6-minute walking distance dual task walking performance, choice stepping reaction time
Secondary	Does TRT improve self-reported function more than placebo?	Physical component of the 36-Item Short Form Health Survey questionnaire (SF-36) .	Physical component of the SF-36 questionnaire (PF-10).
Secondary	Does TRT improve aerobic capacity more than placebo?	VO_2 peak during a cardiopulmonary exercise test; time to fatigue during a constant work rate test	Cardiopulmonary Exercise Testing (CPXT) on a Metabolic cart
Safety	Is TRT safe?	Adverse event recording; PSA, hematocrit, and blood chemistries.	All adverse events; PSA, CBC, blood chemistries, and periodic health assessments

TRT: Testosterone Replacement Therapy

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	↑	↑			↑	↑	↑	↑	
Chemistry Panel	↑	↑				↑		↑	
HbA1c	↑								
Urinalysis	↑					↑		↑	
Lipids		↑						↑	
Vital signs	↑		↑			↑		↑	
Height and weight (Height at screening only)	↑					↑		↑	
EKG	↑	↑							
Con Meds*	↑	↑	↑	↑	↑	↑	↑	↑	↑
Interim health		↑	↑	↑	↑	↑	↑	↑	↑

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

a) Interim Status, concomitant medications, 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 (PF10), DSST, IPSS, Erectile Dysfunction bother scale.

Con meds, concomitant medications; IIEF, International Index of Erectile Function; PANAS, Positive and Negative Affect Scale; IPSS, International Prostate Symptom Score; HED, Hypogonadism Energy Scale; DISF-SD, DeRogatis Inventory of Sexual Function - Sexual Desire; SF-36 (PF10), Medical Outcomes Study Short Form - 36 (Physical Component); EPIC,

Extended Prostate Cancer Index Composite

PSA, prostate specific antigen; CBC, complete blood count; HbA1c, hemoglobin A1c; EKG, electrocardiogram; DXA, dual-Energy X-ray absorptiometry