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TITLE: A Selective Androgen Receptor Modulator for Symptom Management in Prostate Cancer
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NCI-Supplied Agent(s): N/A
Other Agent(s): N/A

Below, please describe the IND Status of this study by choosing IND #/Sponsor OR Exemption from IND requirements, making sure to delete the inapplicable field(s).

IND#: 126806. We have now received final approval from the FDA on our IND.
IND Sponsor: Shalender Bhasin, the PI of the study is the IND holder.

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1. OBJECTIVES

Androgen deficiency is common and associated with bothersome symptoms of sexual dysfunction, physical dysfunction, and fatigue in men with organ-localized prostate cancer who have undergone radical prostatectomy and have undetectable PSA levels for 2 or more years after their surgery. LY2452473 (LY SARM), a highly selective SARM, is particularly attractive for the treatment of symptoms of androgen deficiency in these patients because it displays agonist activities on sexual function and muscle but antagonist activity in the prostate in preclinical models and in human trials of up to 6 months duration. Our **overall objective** is to conduct a double-blind, placebo-controlled, parallel group, randomized dose ranging trial to determine the **efficacy** and **safety** of a SARM in improving the symptoms of androgen deficiency (sexual symptoms, fatigue/low vitality, and physical dysfunction) in men with prostate cancer who have undergone radical prostatectomy for organ-localized prostate cancer (pT2,N0,M0), Gleason score $\leq$ 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. In addition to demonstrating its safety, our **first aim** is to compare 0, 1,5 or 15 mg of LY SARM in men, who have undergone radical prostatectomy for organ-localized prostate cancer, have symptomatic androgen deficiency and very low risk of disease recurrence, with regard to sexual function (sexual activity score, sexual desire, erectile function, distress and sexual life quality). The **second aim** is to compare the effects of 0, 1, 5 or 15 mg of SARM on fatigue, well-being and affectivity balance, and disease-specific quality of life. Our **third aim** is to determine whether SARM administration improves muscle mass and strength, and self-reported and performance-based measures of physical function, and aerobic capacity (VO_{2max} , $VO_{2\ peak,\ and}$ lactate threshold)more than placebo.

1.1 Study Design

This will be a staged phase IIA randomized, placebo-controlled, parallel group, double blind trial in men, 19 years of age or older, who have undergone radical prostatectomy for organ-localized prostate cancer, have low testosterone levels and associated symptoms, and are deemed to be at low risk of recurrence. At the end, 114 subjects will have been randomized to placebo (n=36), 1 mg (n=28), 5 mg (n=36), and 15 mg (n=14) doses. A target sample size of 114participants from three trial sites will have 90% power to test the primary hypothesis.

1.2 Primary Objectives

Our **overall objective** is to conduct a double-blind, placebo-controlled, parallel group, randomized dose ranging trial to determine the **efficacy** and **safety** of a SARM in improving the symptoms of androgen deficiency (sexual symptoms, fatigue/low vitality, and physical dysfunction) in men with prostate cancer who have undergone radical prostatectomy for organ-localized prostate cancer (pT2,N0,M0), Gleason score $\leq$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. In addition to demonstrating its safety, our **first aim** is to compare 0, 1, 5 or 15 mg of LY SARM in men, who have undergone radical prostatectomy for organ-localized prostate cancer, have symptomatic androgen deficiency and very low risk of disease recurrence, with regard to sexual function (sexual activity score, sexual desire, erectile function, distress and sexual life quality).

1.3 Secondary Objectives

- To compare the effects of 0, 1, 5 or 15 mg of SARM on fatigue, well-being and affectivity balance, and disease-specific quality of life.

- To determine whether SARM administration improves muscle mass and strength, and self-reported and performance-based measures of physical function, and aerobic capacity (VO_{2max} , $VO_{2\ peak,\ and}$ lactate threshold)more than placebo.

2. BACKGROUND

2.1 Study Disease(s)

Prostate cancer is the most common malignancy in American men, accounting for 29% of all diagnosed cancers and approximately 13% of all cancer deaths; its incidence is on the rise, partly due to increased screening with PSA[52]. In 2010, approximately 217,730 new cases of prostate cancer were diagnosed in the United States, and there were 32,050 deaths related to prostate cancer[53]. The majority of these men have low-grade, organ-confined prostate cancer and excellent prospects of long term survival[54-57]. Substantial improvement in survival in men with prostate cancer has focused attention on the high prevalence of sexual dysfunction, physical dysfunction, and low vitality in these men[11-25, 58-61], which are important contributors to poor quality of life among these patients[11-18, 23]. The pathophysiology of these symptoms - sexual dysfunction, fatigue/low vitality, and depressed mood - after radical prostatectomy is multifactorial, but androgen deficiency is an important remediable contributor to these symptoms.

2.2 IND Agent

Preclinical and Phase I and II Experience with LY SARM

LY SARM, an oral, tissue-specific SARM, displays agonist effects on sexual function, anabolic effects on the muscle and bone, with antagonist effect on the prostate. Because of its AR antagonist properties on the prostate, its application is also being explored for the treatment of benign prostatic hypertrophy and prostate cancer.

There were no potentially serious or life threatening toxicities for LY SARM in preclinical toxicology studies. LY SARM-induced pharmacological effects consistent with androgen receptor agonism in repeat dose toxicological studies. The primary adverse effects in rats and dogs involved changes in reproductive organs consistent with the expected effects of an androgen receptor agonist. Safety pharmacology studies of up to 6-month duration indicate a high safety margin for the drug. In toxicological studies, LY SARM demonstrated no drug-related effects at doses up to 1000 mg/kg in gastrointestinal (GI), renal, pulmonary, and cardiovascular function studies.

In gonadectomized rodent model, LY SARM demonstrated anabolic effects on muscle and osteoanabolic properties on bone mass and biomechanical strength at doses that had no significant effect on prostate and seminal vesicles. Its nearly complete selectivity for AR has been demonstrated in preclinical models, and in phase I and II human trials. LY SARM has demonstrated agonistic activity on sexual function (stimulated mating behavior, sexual arousal, NOS, and PDE5 expression).

LY SARM has shown high degree of tissue selectivity. In a canine model, the administration of LY SARM was associated with a 40% reduction of prostate volume, consistent with its AR antagonist properties in the prostate. In mice bearing explants of AR+ prostate cancer, LY SARM suppressed the growth of explants.

LY SARM has undergone testing in multiple phase I and II trials, which have established its safety in doses of up to 75 mg daily in humans. Clinical trials of up to 6-month duration have been conducted. In phase I dose ranging studies of 21 day duration (figure 1), LY SARM increased muscle volume by pQCT (figure 1, left panel) and suppressed PSA levels (figure 1, right panel), and exhibited no grade 2 or 3 toxicity. LY SARM shares with other oral androgens the property of lowering HDL cholesterol as well as total cholesterol modestly. These data demonstrate LY SARM's safety and tissue selectivity; it is an agonist on the skeletal muscle and an antagonist on the prostate. Consequently, unlike testosterone or other androgens, LY SARM would not be expected to promote the growth of prostate cancer. This is analogous to the use of tamoxifen, a selective estrogen receptor modulator (SERM), which acts as an agonist on the uterus and bone but as an antagonist in the breast tissue.

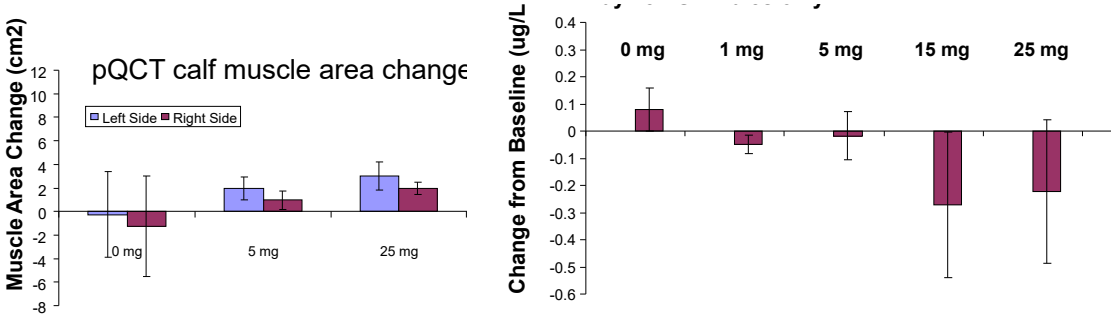


Figure 1. Dose ranging study of LY2452473 in healthy volunteers demonstrates dose-dependent gains in muscle cross-sectional area measured by quantitative CT scan of thigh muscles (left panel) and a dose-related lowering of PSA levels (right panel). These data demonstrate LY SARM's tissue selectivity; it is an agonist on the skeletal muscle and an antagonist on the prostate.

In phase II efficacy trials of 12 week duration, 5 mg LY SARM daily was demonstrated to be safe and increased lean body mass by ~1.5 kg and muscle volume (by CT) by 4-6%, and significantly reduced fat mass in line with other SARMs and replacement doses of testosterone. There was an expected decrease in total cholesterol and HDL cholesterol. No grade 2 or 3 toxicity was recorded.

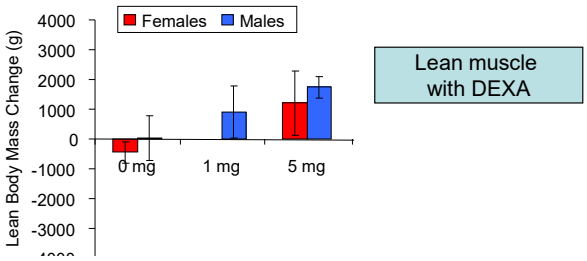


Figure 2. In a phase II trial, healthy men and women were treated with 0, 1 or 5 mg SARM daily for 6 months. Dose-dependent gains in LBM, measured by DXA are shown.

Several other SARM molecules have undergone phase I and II trials and one has undergone a phase III trial in patients with cancer cachexia. These trials have shown these SARM molecules to be generally safe. The class effects include a modest reversible decrease in total and HDL cholesterol, and mild transaminase elevations in a small fraction of subjects.

2.3 Rationale

Androgen deficiency in men who have undergone prostatectomy for organ-localized prostate cancer is common[1-12] and often associated with bothersome symptoms[13-17] and other adverse health effects that contribute to poor health-related quality of life (HRQOL)[18-23]. Improved survival of men with prostate cancer has focused attention on strategies to treat symptoms and improve the overall HRQOL[18-23].

Androgen signaling plays an important role in prostate cancer growth[24-31]. Testosterone therapy promotes the growth of metastatic prostate cancer and androgen deprivation causes regression of metastatic prostate cancer[32-34]. Not surprisingly, the expert guidelines of many professional societies list prostate cancer as a contraindication for androgen supplementation[24-25]. This proscriptive guidance does not fully reflect our new understanding of the complex relationship between testosterone and prostate cancer[1-5, 34-42]. Epidemiologic studies have revealed no consistent relationship between testosterone levels and prostate cancer risk[34-40].

Several elegant studies have found little or no effect of testosterone administration on intraprostatic androgen concentrations or on androgen-dependent gene expression in the prostate[41-42]. Several open-label trials of testosterone have reported very low rates of disease recurrence in men with prostate cancer who have undergone radical prostatectomy[1-11,43-44]. Consequently, testosterone use among men who have undergone radical prostatectomy has been increasing, even though neither the safety nor the efficacy of testosterone therapy in improving outcomes has been established in these patients. A confluence of historical factors – improved survival of men with prostate cancer, a growing recognition of the importance of symptom control in the lives of cancer survivors, increasing off-label use of testosterone in patients who have undergone radical prostatectomy, and accumulation of clinical experience from nonrandomized trials - has highlighted the need for randomized trials of androgen therapy in men with a history of prostate cancer, particularly for those, who experience symptoms of androgen deficiency – sexual dysfunction, fatigue, and physical dysfunction.

Selective androgen receptor modulators (SARMs) are a new class of ligands that displays tissue-selective anabolic activity in the muscle, anti-resorptive and anabolic activity in bone, androgenic activity in maintaining sexual behavior, and robust selectivity for muscle versus prostate[45-51]. LY2452473 (LY SARM), a highly selective SARM, is particularly attractive in men with prostate cancer because it displays agonist activity on sexual function and muscle but antagonist activity in the prostate in preclinical models and in human trials of up to 6-month duration. Unlike testosterone, LY SARM induces prostate atrophy in dogs and lowers PSA in men. Consequently, the administration of Lilly SARM would not be expected to increase the risk of disease recurrence; it is, in fact, possible that it may reduce prostate cancer recurrence risk. This is analogous to the use of tamoxifen in women with breast cancer; tamoxifen, a selective estrogen receptor modulator (SERM), is an estrogen antagonist in the breast but an agonist on the endometrium and bone. Thus, we believe that the clinical application of such a selective, prostate sparing SARM would be a very major scientific breakthrough.

2.4 Correlative Studies Background

Not applicable

3. PARTICIPANT SELECTION

This will be a phase IIA randomized, placebo-controlled, parallel group, double blind trial in men, 19 years of age or older, who have undergone radical prostatectomy for organ-localized prostate cancer, have low testosterone levels and associated symptoms, and are deemed to be at low risk of recurrence. At the end, a total of 135 subjects will have been randomized; 36, 28, 26 and 14 men to placebo, 1 mg, 5 mg and 15 mg doses, respectively.

3.1 Eligibility Criteria

3.1.1 Age 19 years or older.
3.1.2 Prostate cancer, with organ-localized disease with very low risk of disease recurrence, as indicated by Stage pT2, N0, M0 lesions(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, and preoperative PSA<10 ng/ml.The rationale for selecting men with these criteria is that this group of men has <0.5% disease recurrence rate over ten years [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].
3.1.3 Stable and undetectable PSA level (PSA<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
3.1.4 Serum testosterone, measured by LC-MS/MS, <300 ng/dL and/or calculated free testosterone ≤70 pg/mL.
3.1.5 Self-reported sexual dysfunction (DISF-M-II score ≤20 in the sexual desire domain), and/or fatigue (FACIT-F score<30), or physical dysfunction (self-reported difficulty in walking a 1/4 mile or climbing two flights of stairs, **and** short physical performance battery score (SPPB) between 4 to 9).
3.1.6 Ability to understand and willingness to sign a written informed consent document.
3.1.7 Agreeing to use adequate contraception prior to receiving the study drug, for the duration of study participation, and 4 months after completion of LY SARM administration. The effects of LY2452473 (LY SARM) on the developing human fetus are unknown. For this reason and because *SARM* agents are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, or abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while her partner is participating in this study, she should inform her treating physician immediately.

3.2 Exclusion Criteria

3.2.1 Men who have undergone radiation therapy alone will be excluded because defining biochemical recurrence can be difficult in these men due to fluctuating PSA levels.
3.2.2 Prior or current androgen deprivation therapy
3.2.3 Hematocrit > 50%
3.2.4 Severe untreated sleep apnea (treatment is defined as therapy with CPAP, BiPAP, ASV, or other positive air pressure device)
3.2.5 Uncontrolled heart failure as defined by New York Heart Association(NYHA)class 3 or 4
3.2.6 History of HIV (protease inhibitors can have interaction with the SARM)
3.2.7 Myocardial infarction, acute coronary syndrome, revascularization surgery, or stroke within 3 months
3.2.8 Serum creatinine >2.5 mg/dL; ALT or AST outside normal limits for the lab being used
3.2.9 Hemoglobin A1c >7.5% or diabetes requiring insulin therapy
3.2.10 Body mass index (BMI) >40 kg/m^2
3.2.11 Major psychiatric disorder, such as schizophrenia, bipolar disorder, or untreated depression (treatment for depression is defined as current therapy with antidepressant medication or cognitive behavioral therapy (CBT)).

3.2.12 Use of any of the following medications within the past 6 months: 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

3.2.13 Use of any of the following medications within the past 6 months: Clarithromycin, telithromycin, chloramphenicol, itraconazole, nefazodone, cobicistat.

3.2.14 Use of the following treatments for erectile dysfunction (ED): penile implants, vacuum pump devices, intracavernosal injections

3.3 Screening, Recruitment, and Enrollment

Participant Screening

Participants identified through institutional urology groups will be prescreened using medical records to determine if they are potentially eligible. The potentially eligible subjects will be contacted for further screening. If participants are interested, verbal consent will be obtained via an IRB approved script prior to administering a telephone screening with a standardized script and questionnaire.

At the Brigham and Women's Hospital site (BWH), use of EPIC and at the Beth Israel Deaconess Medical Center (BIDMC) subject referring site, use of the PIMS will be utilized to identify potential study subjects.

After obtaining consent, to determine eligibility, a directed medical history will be obtained and blood count, chemistries, total and free testosterone, and PSA will be measured. The pathological stage and pretreatment PSA level will be obtained from medical records. Subjects meeting eligibility criteria will be scheduled for baseline studies.

Participant Recruitment and Enrollment

Participants will be enrolled from the urology clinics at BWH and BIDMC (subject referring site only), from the oncology clinics at Dana Farber Cancer Center at the Boston site, from the Brady Urological Research Institute at the Johns Hopkins Medical Institute at the Baltimore site, and from the urology clinics and from the general community at the UFL site. At BWH we also will employ direct mailings to patients with prostate cancer identified through the institutional urology groups and medical records, institutional portals such as the Research Patient Data Registry (RPDR) and Research Study Volunteer Program (RSVP), whose use for subject recruitment has been IRB-approved.

RPDR is a centralized clinical data registry, or data warehouse. The RPDR gathers data from various hospital legacy systems and stores it in one place. The RPDR has two related but separate functions. First, an online Query Tool provides users with aggregate numbers of patients with user-defined characteristics such as diagnoses, procedures and/or laboratory results. Patient identifiers are not available at this function level. Secondly, the RPDR Data Acquisition Engine (DAE) allows the user to receive more detailed medical record information about the queried patients.

Research Study Volunteer Program (RSVP for Health) is a database that allows researchers to search by disease area, age, race, gender, and ethnicity. Once the researcher identifies the population they'd like to contact, RSVP for Health sends potential volunteers an email containing the IRB-approved study announcement and prepares letters for those who wish to be contacted through US mail. The identity of potential volunteers is maintained until they choose to contact the research team.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Office of Data Quality (ODQ) central registration system. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the (ODQ) protocol-specific eligibility checklist.

Patients are randomized at the time of registration, and treatment assignment will be communicated to each respective site investigational pharmacy so that the proper treatment assignment can be allocated to each patient. The biostatistician will provide the (ODQ) Registrars with the treatment assignment list prior to study activation. At the time of registration, the confirmation of registration would be sent to the study team, while the treatment assignment would be sent directly to pharmacy.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). Notify the (ODQ) Registrar of registration cancellations as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The (ODQ) registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin protocol therapy during off-hours or holidays, call the (ODQ) registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

- Obtain written informed consent from the participant prior to the performance of any protocol specific procedures or assessments.

- Complete the (ODQ) protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. **To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.**

- Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for a treatment protocol. Registration to both treatment and ancillary protocols will not be completed if eligibility requirements are not met for all studies.

- Fax the eligibility checklist(s) and all pages of the consent form(s) to the (ODQ) at 617-632-2295. For Phase I protocols, attach participant dose level assignment confirmation from the sponsor.

- The (ODQ) Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant when applicable.

- An email confirmation of the registration will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration. Treatment assignment will be sent directly to pharmacy via fax.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered in to the study centrally at the Brigham and Women's Hospital by the Study Coordinator.

Following registration, participants should begin protocol therapy within 5 days. Issues that would cause treatment delays should be discussed with the Overall PI. The Study Coordinator should be notified of cancellations as soon as possible.

Research activities for participants originating from Beth Israel Deaconess Medical Center will occur at Brigham and Women's Hospital and will be registered by the Brigham and Women's Hospital study coordinator. Participants referred from BIDMC will continue their routine clinical care outside of the research protocol.

4.4 Registration Process for Other Investigative Sites

The registration process for other investigative sites is located in the DSMP in section 15.7.1.

5. TREATMENT AND/OR IMAGING PLAN

5.1 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 so warrants. 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.

5.2 Treatment Regimen

LY SARM or Placebo will be administered daily for a period of 12 weeks. LY SARM or Placebo will be dispensed to the subject in pill form in four week supplies. The drug or placebo will be dispensed at baseline (Visit 2b), week 4, and week8. Reported adverse events and potential risks are described in Section 7. No investigational or prohibited therapies other than those described below may be administered during the course of this study.

The study medication should be taken daily in the morning on an empty stomach at about the same time each day. The medication should be swallowed whole with water. The bottle containing the medication should be stored at room temperature. The medication does not need refrigeration. If the subject vomits after taking the dose and sees the study drug capsule in the emesis, he should wait for an hour and then retake a new capsule of the medication. If the subject does not see the study drug capsule in the emesis, he should not take another dose. If the subject forgets to take the drug in the morning and remembers it later during the day including bedtime, he should go ahead and take the drug for that day as soon as it is

remembered. The medication is best taken in the morning on a fasting stomach at least 30 minutes before any meal, although if the participant forgets to take a dose but remembers later in the day, he should take the medication at that time. It may not be practical for many individuals, who are employed, to fast during the day. Breakfast can be eaten 30 minutes or later after taking the study medication. There are no prohibited foods. The drug is supplied in capsules. At one time, subjects will be provided sufficient medicine for a period of 4 weeks. At the end of the 4 week period, they should return any unused medication to the study staff along with the filled–in drug diary.

We will measure compliance using medication logs and pill counts, which provide the best trade-off between accuracy and cost[283-284]. The participant will be requested to maintain a medication diary of each dose of medication that will be provided to them by the study staff. The medication diary will be returned to clinic staff at the end of each cycle. Furthermore, pill counts will be done to measure compliance. Medication logs will be collected and unused pills will be counted. Adherence will be assessed as number of pills used divided by number of days.

1. LY2452473 is supplied as an oral capsule drug product in size 2 opaque white gelatin capsules. Each capsule contains 1 mg, 5 mg or 15 mg of LY2452473 and the inactive ingredients pregelatinized starch and dimethicone. LY2452473 is intended to be supplied for the proposed clinical trial as capsules packaged in 30 count white, induction sealed high density polyethylene (HDPE) bottles with child-resistant closures.
2. The drug product will be packaged and supplied to the IDS by Catalent Pharma Solutions, Kansas City, Missouri, USA.
3. The drug product will be stored at room temperature (25°C) with allowable excursions between 15 - 30°C.
4. The drug will be dispensed by the IDS in an amount sufficient for 30 days.
5. The IDS will release the study medication to an authorized study staff upon receipt of a prescription written and signed by a study clinician. The study staff will dispense the study medication to the participant in accordance with the study protocol along with a set of written instructions on how to take the medication.
6. The study staff will retrieve the unused medication from the participant for the purpose of assessing adherence.

Subject Intervention
The study intervention includes placebo and three doses of LY SARM (1, 5 and 15 mg daily). Subjects who meet the eligibility criteria, will be randomized, to either placebo, 1 mg SARM, 5 mg SARM or 15 mg SARM daily. The subject assignment will be based on the randomization tables, using permuted blocks with varying blocks sizes. Subjects will be stratified by age (19-50 and >50) and use of phosphodiesterase 5 inhibitors (PDEIs); PDEIs may influence sexual function (and mood and HRQOL) independently[228-231]. Stratification variables will be included as covariates in analyses.

SARM Doses and Regimen
The participants will be randomly assigned to receive either placebo, 1 mg LY SARM, 5 mg LY SARM, or 15 mg LY SARM daily for 12 weeks. In phase II trials of up to 6-month duration, these doses were safe and effective in increasing lean body mass. 5 mg dose increased fat-free mass by an average 1.5 kg in men.

Intervention Duration
The effects of SARM as well as testosterone on sexual function, muscle mass, strength, well being and mood become apparent within 3 months[48, 171-177]; PSA levels rise within 3-4 weeks and reach a plateau by 12-weeks[109-110]. Thus, 3-month duration will be sufficient to detect meaningful changes in outcomes and PSA.

Phosphodiesterase Inhibitors Use
PDEIs may independently affect sexual function (and HRQOL)[226-231]. To minimize confounding due to PDEI use, we will stratify randomization based on PDEI use. PDEI use will be used as a covariate in analyses.

5.3 Pre-Treatment Criteria

Prior to subject's enrollment, the study coordinators will explain the purpose of the study, the study procedures, and potential risks and benefits of participation in this trial, and answer any questions. The subjects will be asked to sign the IRB-approved consent form. To determine eligibility, a directed medical history will be obtained, and blood count, chemistries, total and free testosterone, and PSA will be measured. The pathological stage and pretreatment PSA level will be obtained from medical records. Subjects meeting eligibility criteria will be scheduled for baseline studies. Subjects, who meet the eligibility criteria will undergo baseline studies, which include baseline complete blood count, blood chemistries, and baseline assessment of physical function, sexual function, fatigue, as described in the protocol. The subjects who are eligible and have completed the baseline assessments will be randomized.

5.4 Agent Administration

Administration –The dose will be 0 mg (placebo), 1 mg, 5 mg, or 15 mg of LY SARM depending upon which study group that the subject is randomly assigned to. LY SARM or Placebo will be taken orally, once per day. The intervention period is twelve weeks. Subjects will be given the drug in four week supplies at baseline (Visit 2b), week 4 and week 8. Their compliance will be measured by pill counts at week 4, week 8 and week 12. In addition, medication logs will be given to subjects.

Protocol specific procedures –A study physician will obtain consent. The safety laboratory results will be reviewed by one of the study physicians. During each visit, a research coordinator will ask the participants about any adverse events. A study clinician will perform a physical examination at screening and during weeks 6 and 12.A study physician will be available if an issue arises at the study visits with the research coordinator.

The research staff will take interim status during baseline, weeks 2, 4, 6, 8, and 12. During interim status, the subject will be asked questions about any changes in health or medication. Blood tests will be done at screening, baseline, as well as during weeks 2, 4, 6, and 12. DXA and strength assessments will be performed at baseline and during week 12.

Infusion Reactions – Subjects will be monitored for PSA level, hematocrit, hemoglobin, HDL level, and liver enzymes.

Sometimes due to scheduling issues, staff availability, inclement weather or subject availability, we may ask the subject to return to our research clinic in order to complete a visit or a specific procedure at a different time or day. This may affect some of the procedures at any visit. In case of such an event, if the subject

parks in our valet parking area, their parking will be validated.

The investigators may omit any strength assessments (muscle performance or physical function procedures) for safety purposes. In such instances, the investigators will determine which procedures will be omitted and this will be documented in the subject's study file.

Caregiver Precautions -
Nurse's/ Study Staff's Instructions to Patients

1. The medication should not be dispensed by a woman who is pregnant or may become pregnant. Women who are pregnant or may become pregnant must use caution when cleaning up vomited matter.
2. Please, take your study medication daily in the morning on an empty stomach at about the same time each day.
3. The medication should be swallowed whole with water.
4. The bottle containing the medication should be stored at room temperature. The medication does not need refrigeration.
5. If you vomit after taking the dose, please wait for an hour and then retake the medication.
6. If you forget to take your medication in the morning and remember it later during the day including bedtime, please go ahead and take your medication for that day as soon as you remember it. If you forget to take your dose in the morning after an overnight fast, please do not eat or drink anything (other than water) for two hours prior to taking the drug. Once you have taken the drug, please do not eat or drink anything other than water for 30 minutes. After that, you may resume your regular diet.
7. The medication is best taken in the morning on a fasting stomach and continue fasting for at least 30 minutes before any meal.
8. You can eat your breakfast 30 minutes or later after taking the study medication.
9. There are no prohibited foods.
10. Please record the medication in the drug diary as soon as you take the medication. The drug diary will be provided to you by the study staff.
11. The drug is supplied in capsules. At one time, you will be provided sufficient medicine for a period of 4 weeks. At the end of the 4 week period, please return any unused medication to the study staff along with the filled–in drug diary.

5.4.1 IND agent
The IND agent is discussed in detail in Section 8.

5.4.2 Other Agent(s)
N/A

5.4.3 Other Modality(ies) or Procedures
N/A

5.4.4 Investigational Imaging Agent Administration
N/A

5.5 General Concomitant Medication and Supportive Care Guidelines

The case report form will be developed to capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.

- The use of the following medications if not allowed during the course of the study: testosterone, DHEA, estrogens, GnRH analogs, antiandrogens, spironolactone, ketoconazole, rhGH, megesterol acetate, prednisone 20 mg daily or equivalent doses of other glucocorticoids

5.6 Criteria for Taking a Participant Off Protocol Therapy

Treatment will continue for 12 weeks or until one of the following criteria applies:

- 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. An increase in PSA will be confirmed by a repeat test which may result in removal from the study. The study team will contact the participant within a week after test result becomes available for scheduling the repeat test if the first test revealed an increase in PSA. If the repeat test confirms the elevation, the intervention will be stopped and the participant will continue to be followed in the study per intent-treat analytical design. The study medication will continue until the results of the repeated test become available. The participant will also be referred to a urologist, medical oncologist, or a primary care provider depending on the nature of the problem. If the repeat test does not confirm the elevation, the participant will continue in the study and have the next set of lab tests per study protocol.

- Any other sign of disease recurrence (e.g., evidence of bone metastasis detected by the subject's oncologist)

- Myocardial infarction or stroke

- Unacceptable adverse event(s)

- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements

- Participant decides to withdraw from the protocol therapy

- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

- Other DLTs include hematocrit increase above 54% and transaminase elevation above 1.25 times the upper limit of normal, confirmed by repeating these tests. An increase in hematocrit and transaminase will be confirmed by a repeat test which may result in removal from the study. The study team will contact the participant within a week after test result becomes available for scheduling the repeat test if the first test revealed an increase in hematocrit or transaminases. If the repeat test confirms the elevation, the intervention will be stopped and the participant will continue to be followed in the study per intent-treat analytical design. The study medication will continue until the results of the repeated test become available. The participant will also be referred to a urologist, medical oncologist, or a primary care provider depending on the nature of the problem. If the repeat test does not confirm the

elevation, the participant will continue in the study and have the next set of lab tests per study protocol. Any abnormal liver function test, defined by a value that is greater than 1.25 times the upper limit of normal, will also require a repeat blood test within 3-7 days, to confirm the result and observe the trend. If the participant's levels do not exceed 1.25 times the upper limit of normal, they will continue on the study medication and transaminases will be monitored.

Note that for an abnormal lab value to meet the DLT definition, the lab test must be repeated and the repeat test must confirm the elevation.

If the participants experience a grade 4 non-hematological toxicity, the study medication will be stopped and the participant will be referred to his medical oncologist, urologist, or the primary care provider depending on the nature of the toxicity. However, study assessments will continue per study's intent-to-treat design.

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, will be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

A ODQ Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the ODQ website or obtained from the ODQ registration staff. The QACT Treatment Ended/Off Study Form will be completed by each site and then sent the Coordinating Center for all study participants.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Shalender Bhasin, MD at 617-525-9040.

5.7 Duration of Follow Up

The subjects who come off the study medication for disease recurrence or adverse events will be referred to their urologist or medical oncologist or primary care provider for further evaluation and treatment, depending on the nature of the problem. Because of the intent-to-treat analytical design, they will continue to be followed in the study for further study assessments per protocol.

5.8 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent
- Death

Consistent with the intent-to-treat primary analytical strategy, we will encourage all participants, including those in whom the study medication is discontinued because of the reasons listed above, to continue with their follow-up study assessments.

The reason for taking a participant off study, and the date the participant was removed, will be documented in the case report form (CRF).

A ODQ Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

The ODQ Treatment Ended/Off Study Form will be completed by each site and then sent to the Coordinating Center for all study participants.

5.9 Study Stopping Rules

In light of the phase I and II trials data, we anticipate very low rates of grade II or III toxicity. The main reason for trial's early termination would be unexpectedly high rates of PSA recurrence. By virtue of the eligibility criteria, this population should have very low recurrence rates (<0.5% over 5 years).

Among the first 50 enrolled subjects, we assume that we should have about 16 in placebo and about 34 or so in the two SARM arms.

In the control group, we expect a recurrence rate of <0.5% over 5 years (for the purpose of this calculation, we assumed a recurrence rate of 0.5% over 5 years). We will accept a difference of no more than 3 between the placebo and the SARM arms in aggregate after 50 subjects have been randomized. If the PSA recurrence occurs in 3 or more cases in the two SARM arms in aggregate or 3 or more cases in any one SARM arm, the DSMB may stop the trial. The probability of a single recurrence is 0.005 (probability of 'not recurrent' is 0.995 at 5 years). Thus, if the bar is set at 3 recurrences, the probability of making an error and stopping early when in fact there is no extra risk conferred by SARM is only 1 in 1250.

At 4 or more recurrences, the chance of erroneous early stoppage is 1 in 25000, which seems large. Therefore, we submit that a difference of 3 recurrences between the placebo arm and the 2 SARM arms in aggregate is reasonable as a stopping rule that DSMB will consider in its decision. The DSMB has the discretion of stopping the trial for other reasons.

6. DOSING DELAYS/DOSE MODIFICATIONS

No dose modifications are allowed. Dose modification is not planned in the context of this double blind phase II randomized trial for several reasons. One aim of the trial is to assess the dose response relationship of dose with the study's outcomes, which could be compromised if the dose adjustment were to occur. The study is blinded; dose adjustment may unblind the study. Also, the drug will be manufactured in either 1 mg, 5 mg or 15 mg capsules. Therefore, we do not have any mechanism for administering intermediate doses. Furthermore, based on the preclinical animal data, and phase I and II previous human studies, we anticipate very low frequency of DLT. Also, we do not have any previous data to guide rational dose adjustment.

If the subject forgets to take one or more doses, he will be asked to record the missed doses in the medication log and re-initiate the usual daily dosing. Study staff will encourage all participants to take all the pills as specified in the protocol. We will also perform pill counts and use drug logs to monitor compliance. However, because of the intent-to-treat analytical plan, the participants will continue in the study for their assessments per protocol.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of

reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Adverse Event List(s) for LY SARM

In previous phase I and II studies of LY SARM, the drug was well tolerated and no drug-related grade II or III toxicities were recorded. A modest decrease in total cholesterol and HDL cholesterol was noted, which is a class effect of oral androgens. There were no clinically significant changes in liver function. No significant changes in hemoglobin and hematocrit were noted. In phase I studies, a decrease in PSA was noted. The class effects of oral androgens and SARMs include a decrease in total and HDL cholesterol, increase in hematocrit (not observed with this SARM), and mild increases in AST and ALT. There may also be a risk of disease recurrence although that risk would be very small because of LY SARM's selectivity.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section(Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.2 For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

7.3.3 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC and DF/PCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report SAEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form will be forwarded to the Overall PI within the timeframes detailed in the table below.

Attribution	DF/HCC Reportable AEs				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 24 business hours of learning of the event.					

The Overall PI will submit SAE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.3.4 Protocol-Specific Expedited Adverse Event Reporting Exclusions

N/A

7.4 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.5 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.6 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

7.7 Adverse Event Reporting to Sponsor

A summary report of adverse events that the DCC will prepare for the DSMB report will be sent to Transition Therapeutics.

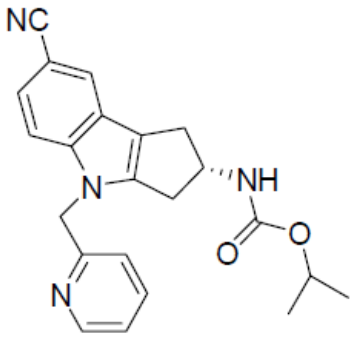
8. PHARMACEUTICALINFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 LY SARM

8.1.1 Description

LY2452473 is a white to practically white solid. The chemical name is: carbamic acid, N-[(2S)-7-cyano-1,2,3,4-tetrahydro-4-(2-pyridinylmethyl)cyclopent[b]indol-2-yl]-,1-methylester. The alternate chemical name is: (S)-(7-cyano-4-pyridin-2-ylmethyl-1,2,3,4-tetrahydro-cyclopenta[b]-carbamic acid isopropyl ester. The molecular formula is $C_{22}H_{22}N_4O_2$ and the molecular weight is 374.45 $gmol^{-1}$. LY2452473 is practically insoluble in water, has a pKa of 3.17, pH of 9.2 and is stable when stored at room temperature. The chemical structure of LY2452473 is presented below:



The plasma concentration-time profiles for LY2452473 after single dose up to 1000 mg showed measurable concentrations from 1 hour postdose, with maximum observed drug concentrations C_{max} 4 to 5 hours following dosing. The LY2452473 concentrations appeared to decline in a biexponential fashion characterized by a short distribution phase and a long terminal phase, with median terminal half-lives ($t_{1/2}$) ranging between 26.6 and 55.1 hours across doses. Mean apparent oral clearance was low to moderate, ranging from 10.9 to 41.5 L/h across dose levels. The mean apparent volume of distribution at steady state (Vss/F) ranged from 388 to 2290 L across doses. Multiple dosing at 1 mg and 5 mg of LY2452473, also showed decline in a biexponential fashion characterized by a short distribution phase and a long terminal phase, with median terminal $t_{½}$ ranging between 23.3 and 44.4 hours across doses The variability of C_{max} at steady state ($C_{max,ss}$) ranged from 14% to 84% across dose levels. The variability of AUC over the dosing interval at steady state ($AUC_{[\tau,ss]}$) ranged from 9% to 70% across dose levels. The pharmacokinetic characteristics observed supported once daily (QD) dosing.

8.1.2 Form

LY2452473 is supplied for clinical use as an oral capsule drug product in size 2 opaque white gelatin capsules. Each capsule contains 1 mg, 5 mg or 15 mg of LY2452473 and the inactive ingredients pregelatinized starch and dimethicone. LY2452473 is intended to be supplied for the proposed clinical trial as capsules packaged in 30 count white, induction sealed high density polyethylene (HDPE) bottles with child-resistant closures.

Our contractual agreement is with Transition Therapeutics. The drug product will be packaged and

distributed by Catalent Pharma Solutions, Kansas City, Missouri, USA.

8.1.3 **Storage and Stability**

The drug product will be stored at room temperature (25°C) with allowable excursions between 15 - 30°C. The drug product, previously packaged in blister packages (2 mil Aclar, 10 count), was shown to be stable for 2 years under long-term storage conditions and for 6 months under accelerated storage conditions. Stability of the drug product in the current packaging configuration (HDPE bottle with child resistant closure) will be monitored under both long-term and accelerated conditions to ensure that the product meets stability specifications over the duration of the proposed clinical trial.

8.1.4 **Compatibility**

Not applicable, as no adjunctive therapies will be used.

8.1.5 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

Since the drug product is supplied as an oral capsule, no special precautions or safety equipment are required for dispensing of the drug. The drug product must be stored at room temperature (25°C).

8.1.6 **Availability**

Collaborative Agreement – Not available

The drug product will be packaged and distributed by Catalent Pharma Solutions, Kansas City, Missouri, USA.

8.1.7 **Preparation**

Not Applicable. The drug will be supplied as an oral capsule (size 2 opaque white gelatin) packaged in 30 count white, induction sealed high density polyethylene (HDPE) bottles with child-resistant closures.

8.1.8 **Administration**

The study medication will be taken orally, daily for 12-weeks.

8.1.9 **Ordering**

The investigational drug will be ordered through Transition Therapeutics via the Data Coordinating Center. The drug product will then be shipped directly to each site's pharmacy.

8.1.10 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures

for Drug Accountability and Storage.)

The site study staff, designated by the investigator, will maintain a record of the inventory and disposition of the drug using the drug accountability form. The BWH Investigational Drug Services will also maintain a record of the study medication received from the manufacturer, the amount of study drug dispensed, and the amount returned or destroyed.

8.1.11 Destruction and Return

The unused supplies of the study drug will be returned by the study staff to BWH Investigational Drug Services, recorded, and destroyed by the BWH IDS.

8.2 Placebo

The capsules containing the placebo and the LY SARM will be identical and they will be packaged in identical bottles and the label will not indicate whether the bottle contains active medication or placebo. Each capsule contains inactive ingredients pregelatinized starch and dimethicone similar in amount to that in active drug-containing capsules.

The manufacturer will provide bulk supplies of placebo and active LY SARM 1 mg, 5 mg and 15 mg capsules. Although the placebo and LY SARM capsules will be identical in appearance and will have identical packaging, the pharmacy will have information on which bottles contain placebo and which contain active drug. The BWH Investigational Drug Service utilizes the Investigational Drug Service Informatics System (IDSIS) to dispense placebo and investigational products in numerous clinical trials. The Investigational Drug Service Informatics System (IDSIS) employs bar scanning technology to verify the investigational medications dispensed against the subject's treatment assignment in the clinical trials.

9. STUDY CALENDAR

Table 3. Schedule of Events

	Pre-screening	Screening	Baseline		Intervention Period						Off Treatment
Day or Week		Day -42 to Randomization			Week 2	Week 4	Week 6	Week 8	Week 12		30 Days Post Last Dose
Visit Number		1	2A	2B	3	4	5	6	7A	7B	
Study Procedure											
Phone Prescreening	X										
Informed Consent		X									
Demographics		X									
Review of Eligibility Criteria		X									
Medical History		X									
Concomitant Medications		X									
Short Physical Performance Battery (SPPB)		X									
Average Weekly Alcohol Consumption	X	X	X		X	X	X	X	X		
Questionnaires		X	X				X		X		
- FACIT-F, DISF		X					X		X		
- Harbor-UCLA 7-Day Diary, EPIC, MSHQ, PANAS, SF-36, IPSS, IIEF, HED, SAID			X				X		X		
Vital Signs		X	X				X		X		
Blood Draw*		X	X		X	X	X		X		
- HbA1c		X									
- CBC, CMP with eGFR§, lipid panel		X	X				X		X		
- PSA		X			X	X	X		X		
- Total testosterone, calculated free testosterone, SHBG		X	X				X		X		
- DHT, LH, estradiol			X				X		X		
Physical Exam		X					X		X		
EKG		X									
Whole Body DXA			X						X		
Muscle Performance, Physical Function, and Aerobic Capacity Tests**			X						X		
Randomization			X								
Drug Dispensing			X			X		X			
Adverse Events Monitoring			X		X	X	X	X	X		X
Interim Status			X		X	X	X	X	X		X
Medication Compliance Check						X		X	X		
Planned Follow-Up Phone Call											X
Additional Blood Draw for Substudy*** - Bone markers (osteocalcin, C-telopeptide, P1NP, bone specific alkaline phosphatase), Apolipoproteins (A1 and B, lipoprotein particles), Inflammatory markers (CRP, IL-6, C1 esterase inhibitor), HDL efflux, (TC) Insulin, (TC) HbA1c			X				X		X		

Note: Intervention visits window is +/- 3 days. Screening procedures may take place over the course of two visits if necessary. Baseline and Week 12 procedures will take place over the course of two visits.

*All blood draws are fasting and will be completed at or before 11:00.
**Aerobic capacity testing and muscle strength and physical function testing will take place on separate days.

***Optional substudy participants only
§ eGFR will be calculated retrospectively.

10. MEASUREMENT OF EFFECT

10.1 Primary Outcome

Our primary outcome is change in sexual activity score, assessed by the Harbor-UCLA 7-day Sexual Function Questionnaire, because sexual dysfunction is one of the most prevalent symptoms in men, who have undergone radical prostatectomy, and it affects HRQOL. This scale has been used widely in testosterone trials, and sexual activity scores, assessed by this instrument, are responsive to therapy. The scale covers 3domains: 1) sexual desire and enjoyment;2) sexual activity; and 3) mood.

10.2 Secondary outcomes

Other measures of sexual function. Erectile function will be assessed by **IIEF, SAID, and DISF-M-II**.

The IIEF which has been validated in many trials of ED therapies, and shown to be responsive to androgen therapy in men with ED and low testosterone. The IIEF is a 15-item questionnaire that evaluates 5 response domains, including erectile function, intercourse satisfaction, and overall satisfaction. It has been shown to have high degree of specificity and sensitivity, reliability, internal consistency, and construct validity.

The DISF-M-IIis a 25-item questionnaire that provides an estimate of perceived quality of sexual activities in 5 response domains: sexual desire/drive, sexual arousal, sexual activity, orgasm, and sexual satisfaction/partner relationship. It comprehensively evaluates sexual desire and has been shown to have androgen-treatment sensitivity. The DISF-M was the main sexual function questionnaire in the NIA-funded The Testosterone Trial which is a trial of 800 men evaluating the role of androgens on sexual function.

The SAID is an 8-item questionnaire that evaluates 3 response domains, including sexual thinking, sexual arousal, and sexual activity. This questionnaire was validated using separate qualitative studies and provides an assessment of items associated with hypogonadism[291, 292].

Sexual desire will be assessed by Men's Sexual Health Questionnaire (MSHQ) and by libido-related questions in IIEF, SAID, and DISF-M-II. MSHQ, a25-item questionnaire, provides a more robust assessment of libido than IIEF, especially in men with urogenital symptoms[240], has high degree of internal consistency, reliability, and ability to discriminate between men with and without lower urinary tract symptoms (LUTS) and sexual dysfunction.

We will measure the impact of androgen deficiency and sexual dysfunction 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. Of its four domains, we will utilize the sexual and hormonal domains, which are affected by androgen deficiency and expected to improve with SARM therapy, and which are important to men with prostate cancer but are not weighed appropriately in generic HRQOL instruments. This instrument has been used in numerous prostate cancer trials, and shown to have high Cronbach alpha coefficient, construct validity, and excellent sensitivity to change in response to hormonal treatment.

Fatigue will be assessed by the 13-item Functional Assessment of Chronic Illness Therapy fatigue scale(FACIT-F) and by the 4-item Hypogonadism Energy Diary (HED).

The FACIT-F has been well-validated and responsive to treatment. SF-36 Vitality scale has also been used to assess vitality, but the FACIT-F is more sensitive to change in those with low vitality/high fatigue than SF36. Another reason for selecting FACIT-F is its inclusion as "legacy instrument" for the NIH Roadmap PROMIS Fatigue item bank. This will ensure comparability to PROMIS.

The HED has been validated using separate qualitative studies and provides an assessment of low energy related to hypogonadism[291, 292].

Mood and well-being will be assessed by PANAS affectivity balance scale, which includes 10 questions each for Positive Affect and Negative Affect. Many behavioral scientists consider affectivity balance as the cleanest window on an individual's wellbeing. The affectivity balance incorporates negative affects (e.g., anxiety, depression) as well

as positive affects (e.g., joy).Testosterone has been reported to improve mood and affect in hypogonadal men. Alphas for negative and positive affect scales are 0.85 and 0.88, respectively; one-week test-retest reliabilities are 0.81 and 0.79. The instrument can detect changes in well being related to chronic illnesses and cancer.

Muscle Performance and Physical Function. We will assess physical function by measuring walking speed in the 6-min walk, stair climbing power, and load carrying time, self-reported physical function by the PF10 (physical function domain of MOS SF-36), maximal voluntary strength in the leg press exercise by the 1-RM method, and skeletal muscle mass by dual energy X-ray absorptiometry (DXA). We have used these measures in many previous trials and they have been shown to be androgen-responsive**.**

Hormone Levels. Total testosterone, DHT and estradiol will be measured by LC-MS/MS, free testosterone by equilibrium dialysis, and LH by an IFMA. These methods have been used in PI's lab for >25 yrs.

Safety measures: We will measure PSA, complete blood counts, plasma lipids, AST, ALT, bilirubin and alkaline phosphatase levels for safety monitoring. A structured evaluation of cardiovascular adverse events will be performed using a form, developed for NIA-funded T trials.

Physiologic measures. We will measure lean body mass using dual energy X-ray absorptiometry (DXA), and maximal voluntary strength as mediators of improvements in physical function. VO_{2max} and to a lesser extent VO_2 peak are markers of a person's aerobic capacity. The lactate threshold is a marker of one's capacity for prolonged, submaximal work without lactate accumulation and fatigue. We recognize that relationships of these physiologic mechanisms for aerobic energy production to fatigue are complex because in addition to these physiologic mechanisms, psychological factors, such as depressive symptoms, mood and wellbeing affect an individual's perception of fatigue; accordingly, we will also assess mood and depressive symptoms. We propose to split the assessments for muscle performance and physical function into two non-consecutive days of testing in order to reduce subject burden and ensure more accurate data.

At baseline, we propose to perform the cardiopulmonary exercise test (CPXT) alone on the first day of baseline testing. It is a longer test requiring progressively increasing subject effort to volitional fatigue and requires about 60 minutes to administer. It also provides valuable safety data that may be used prior to other physical function assessments. The remainder of the tests (the 6-minute walk test, the stair climb power tests, the 50-m walk tests, and the leg press strength test)will be administered on the second day of baseline testing with appropriate and standardized rest periods between tests.

At baseline, we propose to perform the cardiopulmonary exercise test (CPXT) alone on the first day of testing. It is a longer test requiring progressively increasing subject effort to volitional fatigue and requires about 60 minutes to administer. It also provides valuable safety data that may be used prior to other physical function assessments. The remainder of the tests (the 6-minute walk test, the stair climb power tests, the 50-m walk tests, and the leg press strength test)will be administered on the second day of baseline testing with appropriate and standardized rest periods between tests.

For the Week-12 (end of study) assessments, efforts will be made to repeat the test procedures in the same sequence and time of day; however, they could be altered to accommodate subject convenience and scheduling.

11. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

11.1 Data Reporting

11.1.1 Method

The ODQ will manage and coordinate quality checks on the data for this study.

11.1.2 Responsibility for Data Submission

All investigative sites are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ.

11.2 Data Safety Monitoring

In accordance with the National Institute of Nursing Research (NINR) requirements, an independent Data and Safety Monitoring Board will review and monitor study progress, toxicity, safety and other data from this study. The components of this committee and their safety review procedures are described in the NINR Data and Safety Monitoring Plan, located in Appendix B."

11.3 Transmission of DSMB Recommendations and Summary Reports of Adverse Events to IRBs

The transmission of DSMB Recommendations and Summary Reports of Adverse Events to IRBs for this trial is described in Appendix B.

11.4 Transmission of Summary of Closed Deliberations to the NINR Staff

This is described in Appendix B.

11.5 Protecting the Confidentiality of Participant Data

This is described in Appendix B.

11.6 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix A.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

11.7 Collaborative Agreements Language

N/A

12. STATISTICAL CONSIDERATIONS

STATISTICAL ANALYSIS

12.1 Descriptive Analyses

Descriptive measures for each outcome and potential covariate will be computed. Graphical and tabular displays will be used to establish 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[256]. We will use summary statistics and graphical techniques to compare baseline characteristics of groups.

12.2 Compliance Analysis

Subject's compliance will be assessed in terms of the number of doses used, based on pill counts, expressed as a percent of the total number of doses that should have been used.

12.3 Analytic plan

Following appropriate variable transformations, the primary analysis will utilize mixed effects regression controlling for baseline values, randomization, and stratification. Primary inferential targets of interest will be difference in outcomes measures between the 4 arms, estimated using treatment contrasts. Secondary analyses will incorporate control for additional factors based on the results of exploratory analyses mentioned above. We will consider the possibility of potential bias due to three stages of enrollment by performing sensitivity analyses with stage effect adjustment[293,294].Missing data will be accommodated using multiple imputation, with imputed values generated in accordance with the mixed effects model as implemented in the **mice** library in R[257-259]. Point estimates will be accompanied by 95% confidence intervals, and type-I error probability for hypothesis testing set at 0.05. Statistical analyses will be conducted using SAS version 9.3 or higher and R version 2.15.0.
Specific Aim 1 is concerned with change in sexual function as measured by the Harbor-UCLA 7-day Sexual Function Questionnaire (SFQ) and other outcomes measured at baseline and during weeks 6 and 12. Six and 12 week data will be analyzed simultaneously using mixed effects linear regression controlling for baseline measures as well as stratification factors (age and PDEI use), with site and subject 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 >1 point on sexual function score (thought to approximate the minimal clinically important difference on the SFQ) using generalized estimating equations[256] and modified Poisson regression approach[257-259], which can accommodate repeated measurements and is preferable to odds ratio in prospective designs. If the rate of improvement is very low, a zero-inflated alternative will be considered[210].

Secondary Hypotheses. **Specific Aim 2** is concerned with estimation of the effects of SARM administration 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 SARM on strength and physical function. As in Aims 1 and 2 we will utilize mixed effects regression.
We will also consider further exploratory analyses of the primary endpoint. For example, we will use linear regression to determine whether changes in muscle strength and measures of physical function correlate with changes in muscle mass and whether improvements in aerobic capacity are associated with improved fatigue scores. Appropriate techniques will assess assumptions of linearity and homoscedasticity.

12.4 Missing data

All subjects who are randomized will be included in the analyses. We will use multiple imputation using chained equations (MICE) to accommodate missing data. Further, our analyses will use simple linear mixed models that use additional intermediate time points when available. These methods use available information more efficiently, thus reducing type II error. We recognize that missingness may be associated with outcome, in which case there exists the potential for biased estimates of treatment effect. Sensitivity analyses will be employed to assess this possibility.

12.5 Sample Size Estimates and Power Considerations

Initially, we had estimated that 126 men will be needed to test the primary hypothesis based on assumptions of two sided type I error rate of 0.05, attrition rate of 20% and 90% power. Our primary outcome is change in sexual activity score derived from Harbor-UCLA Seven Day Sexual Function Questionnaire[221]. The primary targets of estimation was overall dose effect as well as the direct comparison of highest dose group (15 mg) to placebo, however due to stoppage of 15-mg dose group, the primary aim of this study will be comparison of 5-mg group to placebo. There are no randomized trial data on the effects of SARM on sexual function in men with prostate cancer. In several trials in hypogonadal men[178, 183-184], testosterone therapy increased sexual activity score by an average of 1.5 points. Here we assume that the difference of interest in the change in sexual activity score between the 15 mg dose and placebo over 3 months is 1.5 points with a standard deviation of 1.8 (1.27 within each group). We estimate that the difference between 1 mg and placebo is 0.3 points with SD 1.2 and, as previously assumed, between 5 mg and placebo is 1.2 with SD 1.8. Under these assumptions, group allocation of 36:28:36:14 (for placebo, 1mg, 5 mg and 15 mg groups, respectively) subjects per arm will achieve more than 95% power to reject the null hypothesis of no overall dose effect, and to detect the difference between the 15 mg group and placebo. As enrollment to 15-mg group has been stopped and insufficient number of participants were randomized to this group (N=14), there will not be any formal analysis testing difference between 15-mg arm to placebo.

We will similarly obtain good power to detect clinically meaningful effects on other measures of sexual function. We hypothesize that the mean difference in change in sexual desire scores between the 15 mg and placebo groups is 1.8 (SD 2.1). The proposed sample size has >95% power to detect this difference. Similarly, we will obtain >95% power to detect between group differences of 4 points in change in erectile function domain (EFD) of International Index of Erectile Dysfunction (IIEF) (assumed SD 6 points), a threshold deemed clinically significant[222-225]. The average increase in EFD score in trials of PDE5 inhibitors is 7[153, 226-228].

Assuming mean (SD) LBM changes of 0 (1) kg in placebo, 0.8 (1.2) at 1 mg, 1.5 (2.1) kg at 5 mg and 1.8 (2.1) kg at 15 mg dose, simulation results indicate that this design achieves more than 90% power to demonstrate an overall dose-response relationship and to detect the advantage of 15 mg dose over placebo**,** where both tests are performed at the 0.05 level. Using the Holm-Bonferroni correction for these two non-independent hypotheses (both hypotheses must be rejected at the 0.05 level, and at least one at the 0.025 level, preserving the overall type-I error rate of 0.05), results indicate that the design achieves more than 80% power to reject both nulls simultaneously. Recent SARM trials have reported average gains of ~1.5 kg in lean body mass[45, 48,116]. 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[173]. Testosterone trials in older men that used smaller doses of testosterone observed an increase of ~1.5 kg[186].

We anticipate that the change in leg press strength at 15 mg dose will be 15 kg (SD 18), at 5 mg dose 12 kg (SD 18 kg) and at the 1 mg dose 4 kg (SD 6 kg), while placebo group is assumed to have no increase (SD 6). This assumption is based on testosterone trials in older men[175,195], HIV-infected men[173], and in men with COPD[185]. A 15

kg increase in leg press strength is deemed clinically significant because a 10 kg increase in leg strength was associated with improvements in walking speed[232]. Under these assumptions, simulation results demonstrate that the planned randomization will provide >90% power to jointly detect an overall dose-response pattern and a significant difference between the5 mg and placebo groups. In a SARM trial[48], the increase in stair climbing power in men receiving enobosarm averaged 15% (SD 20%). The proposed sample size provides >80% power to detect a similar difference between 5 mg and placebo arms. For physical function domain of MOS-SF36, the difference of interest between 5 mg and placebo group is 4 points (SD 7 points), which is a moderate effect.

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[186]. Ware et al[233] have determined that a 4-point change in the physical function domain of the MOS SF36 score is clinically meaningful. A proposed sample size provides >80% power to detect this effect size between placebo and 5 mg dose group.

Absent intervention, the clinical PSA recurrence rate in this group of men should be <1% over 10 years[54-57], 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 SARM. To insure 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 15 mg group.

To accommodate attrition of up to 20%, we will enroll 37:25:37:36 men (for placebo, 1 mg, 5 mg and 15 mg groups, respectively) for a total of 135 men. Assumption of 20% attrition rate is conservative; the attrition in our testosterone trial in older men was 12%[174]. Even in a 3-year intervention trial to determine the effects of testosterone on atherosclerosis, the loss-to-follow-up has been <20%. The incorporation of 6-week measurement in the mixed effects model and the inclusion of all 114 subjects made possible by use of multiple imputation will provide even higher power than that claimed here.

12.6 DATA MANAGEMENT

The Data Management Center (DMC) will provide data management and statistical programming under the supervision of Dr. Travison. A randomization application will be available online. Upon completion of Eligibility Form, a subject ID will be generated, and the randomization table will be queried for study arm designation. Database will track subjects, provide documentation of eligibility and consent, and provide alerts to study staff about due dates. The database will reside on a secure, password protected server, and backed up on a nightly basis. The DMC will prepare standardized data collection forms to ensure that all data fields are unambiguous, items are easily read, response categories are in standardized units, and the instructions are clearly worded. Validation rules including built-in edits such as range and logic checks will be incorporated into the verification process. After forms have been verified, programming codes will check across-form internal inconsistencies. The statistical programmer will be responsible for cleaning the data, creating analytic data sets, standardized protocols for coding data, and a data dictionary of variables, and for writing the analysis code for all analyses.

The target sample size is 114 participants study-wide. In order to randomize 114 subjects, we estimate that we will need 450 subjects to enroll (sign consent). The study intervention includes placebo and three doses of LY SARM (1, 5 and 15 mg daily). It is planned for the recruitment to be split among the Brigham and Womens Hospital (BWH), the University of Florida (UFL), and Johns Hopkins Medical Institutes (JHMI). Ultimately, it is planned to have 68 subjects randomized at BWH, 27 subjects randomized at UFL, and 40 subjects randomized at Johns

Hopkins Medical Institute. A target sample size of 114 participants from two trial sites will have >90% power to test the primary hypothesis.

Randomization: After protocol amendment, last 10 subjects who meet the eligibility criteria will be randomized to either the placebo or 5mg SARM daily. Due to inclusion of new treatment arm (15 mg) in the study and stopping enrollment into the 1 mg group, and later stopping enrollment into the 15-mg group, participants will have been randomized in three stages. In the first stage, then=80 subjects were randomized to one of 3 groups: placebo, 1 mg and 5 mg, with allocation ratio of 1:1:1; this randomization scheme was ended after the amendment was approved. In the second stage, (according to protocol amendment, after stopping the enrolment in 1 mg group and inclusion of new 15 mg LYSARM dose group) N=24 participants were randomized with allocation ratio of 1:1:3 to placebo, 5 mg and 15 mg groups, respectively. In the third stage, after stopping the enrollment in 15-mg group, due to safety signal, we anticipate to randomize 10 more participants with allocation ratio 3:2 (6 in placebo and and 4 in 5-mg dose). At the end of the trial we expect to enroll 114 participants (80 in the first stage, 24 in the second stage and 10 in the third stage) with group allocation of 36:28:36:14 participants, for placebo, 1 mg, 5 mg and 15 mg groups, respectively.. The subject assignment will be based on the randomization tables, using permuted blocks with varying blocks sizes. Subjects will be stratified by age (19-50 and >50) and use of phosphodiesterase 5 inhibitors (PDEIs); PDEIs may influence sexual function (and mood and HRQOL) independently[228-231]. Stratification variables will be included as covariates in analyses.

12.7 Sample Size, Accrual Rate and Study Duration

The revised planned sample size is114. Enrollment is targeted to be completed in 3years from start of study initiation. We anticipate that enrollment will average 45 subjects per year over the three years. If enrollment is slower at the start, efforts will be enhanced to meet the 3 year enrollment goal. There is a 12-week intervention period after the screening and baseline measures are obtained. Section 9 of this document contains the Schedule of Events. Women are not eligible for this trial as this is a study of men with prostate cancer.

Accrual Targets

Ethnic Category	Sex/Gender							
	Females			Males			Total	
Hispanic or Latino	0		+	17		=	17	
Not Hispanic or Latino	0		+	118		=	118	
Ethnic Category: Total of all subjects	0	(A1)	+	135	(B1)	=	135	(C1)
Racial Category								
American Indian or Alaskan Native	0		+	1		=	1	
Asian	0		+	1		=	1	
Black or African American	0		+	13		=	13	
Native Hawaiian or other Pacific Islander	0		+	0		=	0	
White	0		+	120		=	120	
Racial Category: Total of all subjects	0	(A2)	+	135	(B2)	=	135	(C2)
	(A1 = A2)			(B1 = B2)			(C1 = C2)	

12.8 Stratification Factors

There is no stratification in this study design.

12.9 Interim Monitoring Plan

Please refer to the Data Safety Monitoring Plan in Section 11.

12.10 Analysis of Primary Endpoints

Please reference the analysis section 12 of this document.

12.11 Analysis of Secondary Endpoints

Please reference the analysis section 12 of this document.

12.12 Reporting and Exclusions

12.13 Evaluation of Toxicity

Please reference Section 5.5 of this document.

12.14 Evaluation of the Primary Efficacy Endpoint

Please reference Section 12 of this document.

13. PUBLICATION PLAN

The results will be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis.

REFERENCES

1. Morgentaler A 2009 Testosterone therapy in men with prostate cancer: scientific and ethical considerations. J Urol 181:972-979. PMID: 19150547
2. Morgentaler A 2007 Testosterone replacement therapy and prostate cancer. Urol Clin North Am 34:555-563, vii. PMID: 17983895
3. Morgentaler A 2008 Guilt by association: a historical perspective on Huggins, testosterone therapy, and prostate cancer. J Sex Med 5:1834-1840. PMID: 18547385
4. Khera M, E.D. G, Najari B, Colen JS, Mohamed O, D.J. L, Lipshultz LI 2009 Testosterone replacement therapy follwing radical prostatectomy. J Sex Med 6:1165-1170. PMID: 19207277
5. Khera M, Lipshultz LI 2007 The role of testosterone replacement therapy following radical prostatectomy. Urol Clin North Am 34:549-553, vi. PMID: 17983894
6. Kaufman JM, Graydon RJ 2004 Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men. J Urol 172:920-922. PMID: 15310998
7. Agarwal PK, Oefelein MG 2005 Testosterone replacement therapy after primary treatment for prostate cancer. J Urol 173:533-536. PMID: 15643240
8. Nabulsi O, Tal R, Gotto G, Narus J, Goldenberg L, Mulhall JP 2008 Outcomes analysis of testosterone supplementation in hypogonadal men following radical prostatectomy. J Urol 179 (suppl):406 (abstract 1181)
9. Davila HH, Arison CN, Hall MK, Salup P, Lockhart JL, Carrion RE 2008 Analysis of the PSA response after testosterone supplementation in patients who have previously received management for their localized prostate cancer, . J Urol 179 (suppl.) 428 (abstract 1247)
10. Kaufman J 2006 A rational approach to androgen therapy for hypogonadal men with prostate cancer. Int J Impot Res 18:26-31. PMID: 16208401
11. Khera M 2009 Androgens and erectile function: a case for early androgen use in postprostatectomy hypogonadal men. J Sex Med 6 Suppl 3:234-238. PMID: 19207279
12. Lane BR, Stephenson AJ, Magi-Galluzzi C, Lakin MM, Klein EA 2008 Low testosterone and risk of biochemical recurrence and poorly differentiated prostate cancer at radical prostatectomy. Urology 72:1240-1245. PMID: 18692874
13. Maliski SL, Kwan L, Elashoff D, Litwin MS 2008 Symptom clusters related to treatment for prostate cancer. Oncology nursing forum 35:786-793. PMID: 18765324
14. Maliski SL, Kwan L, Orecklin JR, Saigal CS, Litwin MS 2005 Predictors of fatigue after treatment for prostate cancer. Urology 65:101-108. PMID: 15667873
15. Stanford JL, Feng Z, Hamilton AS, Gilliland FD, Stephenson RA, Eley JW, Albertsen PC, Harlan LC, Potosky AL 2000 Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the Prostate Cancer Outcomes Study. Jama 283:354-360. PMID: 10647798
16. Helgason AR, Adolfsson J, Dickman P, Arver S, Fredrikson M, Steineck G 1997 Factors associated with waning sexual function among elderly men and prostate cancer patients. J Urol 158:155-159. PMID: 9186344
17. Clark JA, Rieker P, Propert KJ, Talcott JA 1999 Changes in quality of life following treatment for early prostate cancer. Urology 53:161-168. PMID: 9886606
18. Sanda MG, Dunn RL, Michalski J, Sandler HM, Northouse L, Hembroff L, Lin X, Greenfield TK, Litwin MS,

Saigal CS, Mahadevan A, Klein E, Kibel A, Pisters LL, Kuban D, Kaplan I, Wood D, Ciezki J, Shah N, Wei JT 2008 Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med 358:1250-1261. PMID: 18354103

19. Litwin MS, Gore JL, Kwan L, Brandeis JM, Lee SP, Withers HR, Reiter RE 2007 Quality of life after surgery, external beam irradiation, or brachytherapy for early-stage prostate cancer. Cancer 109:2239-2247. PMID: 17455209

20. Litwin MS, Hays RD, Fink A, Ganz PA, Leake B, Leach GE, Brook RH 1995 Quality-of-life outcomes in men treated for localized prostate cancer. Jama 273:129-135. PMID: 7799493

21. Litwin MS, Nied RJ, Dhanani N 1998 Health-related quality of life in men with erectile dysfunction. J Gen Intern Med 13:159-166. PMCID: PMC1496922

22. Penson DF, Latini DM, Lubeck DP, Wallace K, Henning JM, Lue T 2003 Is quality of 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. J Urol 169:1458-1461. PMID: 12629383

23. Litwin MS, Flanders SC, Pasta DJ, Stoddard ML, Lubeck DP, Henning JM 1999 Sexual function and bother after radical prostatectomy or radiation for prostate cancer: multivariate quality-of-life analysis from CaPSURE. Cancer of the Prostate Strategic Urologic Research Endeavor. Urology 54:503-508. PMID: 10475362

24. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM 2006 Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 91:1995-2010. PMID: 16720669

25. Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, Gooren LJ, Kaufman JM, Legros JJ, Lunenfeld B, Morales A, Morley JE, Schulman C, Thompson IM, Weidner W, Wu FC 2008 Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. Eur J Endocrinol 159:507-514. PMID: 18955511

26. Isaacs JT 1984 Antagonistic effect of androgen on prostatic cell death. Prostate 5:545-557. PMID: 6483690

27. Berry PA, Maitland NJ, Collins AT 2008 Androgen receptor signalling in prostate: effects of stromal factors on normal and cancer stem cells. Mol Cell Endocrinol 288:30-37. PMID: 18403105

28. Ergun A, Lawrence CA, Kohanski MA, Brennan TA, Collins JJ 2007 A network biology approach to prostate cancer. Molecular systems biology 3:82. PMCID: PMC1828752

29. Heinlein CA, Chang C 2004 Androgen receptor in prostate cancer. Endocr Rev 25:276-308. PMID: 15082523

30. Wu CP, Gu FL 1991 The prostate in eunuchs. Prog Clin Biol Res 370:249-255. PMID: 1924456

31. Ray G, Dhar G, Van Veldhuizen PJ, Banerjee S, Saxena NK, Sengupta K, Banerjee SK 2006 Modulation of cell-cycle regulatory signaling network by 2-methoxyestradiol in prostate cancer cells is mediated through multiple signal transduction pathways. Biochemistry 45:3703-3713. PMID: 16533053

32. Huggins C, Hodges CV 1941 Studies on prostate cancer. I. The effects of castration, of estrogen, and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. . Cancer Res 1:293

33. Fowler JE, Jr., Whitmore WF, Jr. 1981 The response of metastatic adenocarcinoma of the prostate to exogenous testosterone. J Urol 126:372-375. PMID: 7277602

34. Prout GR, Brewer WR 1967 Response of men with advanced prostatic carcinoma to exogenous administration of testosterone. Cancer 20:1871. PMID: 4168724

35. Roddam AW, Allen NE, Appleby P, Key TJ 2008 Endogenous sex hormones and prostate cancer: a

collaborative analysis of 18 prospective studies. J Natl Cancer Inst 100:170-183. PMID: 18230794

35. Shaneyfelt T, Husein R, Bubley G, Mantzoros CS 2000 Hormonal predictors of prostate cancer: a meta-analysis. J Clin Oncol 18:847-853. PMID: 10673527

36. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ 1996 Prospective study of sex hormone levels and risk of prostate cancer. J Natl Cancer Inst 88:1118-1126. PMID: 8757191

37. Comstock GW, Gordon GB, Hsing AW 1993 The relationship of serum dehydroepiandrosterone and its sulfate to subsequent cancer of the prostate. Cancer Epidemiol Biomarkers Prev 2:219-221. PMID: 8318873

38. Hsing AW, Comstock GW 1993 Serological precursors of cancer: serum hormones and risk of subsequent prostate cancer. Cancer Epidemiol Biomarkers Prev 2:27-32. PMID: 8420607

39. Vatten LJ, Ursin G, Ross RK, Stanczyk FZ, Lobo RA, Harvei S, Jellum E 1997 Androgens in serum and the risk of prostate cancer: a nested case-control study from the Janus serum bank in Norway. Cancer Epidemiol Biomarkers Prev 6:967-969. PMID: 9367072

40. Hoffman MA, DeWolf WC, Morgentaler A 2000 Is low serum free testosterone a marker for high grade prostate cancer? J Urol 163:824-827. PMID: 10687985

41. Marks LS, Mazer NA, Mostaghel E, Hess DL, Dorey FJ, Epstein JI, Veltri RW, Makarov DV, Partin AW, Bostwick DG, Macairan ML, Nelson PS 2006 Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. Jama 296:2351-2361. PMID: 17105798

42. Page ST, Lin DW, Mostaghel EA, Hess DL, True LD, Amory JK, Nelson PS, Matsumoto AM, Bremner WJ 2006 Persistent intraprostatic androgen concentrations after medical castration in healthy men.J Clin Endocrinol Metab 2006;91:3850-6.

43. Sarosdy MF 2007 Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy. Cancer 109:536-541. PMID: 17183557

44. Rhoden EL, Morgentaler A 2003 Testosterone replacement therapy in hypogonadal men at high risk for prostate cancer: results of 1 year of treatment in men with prostatic intraepithelial neoplasia. J Urol 170:2348. PMID: 14634413

45. Bhasin S, Calof OM, Storer TW, et al 2006 Drug insight: Testosterone and selective androgen receptor modulators as anabolic therapies for chronic illness and aging. Nature Clinical Practice Endocrinol Metab 2:146-159

46. Bhasin S, Jasuja R 2009 Selective androgen receptor modulators as function promoting therapies. Curr Opin Clin Nutr Metab Care 12(3):232-40.

47. Narayanan R, Mohler ML, Bohl CE, Miller DD, Dalton JT 2008 Selective androgen receptor modulators in preclinical and clinical development. Nuclear Receptor Signaling 6:e010

48. Dalton JT, Barnette KG, Bohl CE, et al 2011 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.J Cachexia Sarcopenia Muscle 2:153-161

49. Miner JN, Chang W, Chapman MS, et al 2007 An orally active selective androgen receptor modulator is efficacious on bone, muscle, and sex function with reduced impact on prostate. Endocrinology 148:363-373

50. Schmidt A, Kimmel DB, Bai C, et al 2010 Discovery of the selective androgen receptor modulator MK-0773 using a rational development strategy based on differential transcriptional requirements for androgenic anabolism versus reproductive physiology.J Biol Chem 285:17054-64.

51. Gao W, Dalton JT 2007 Expanding the therapeutic use of androgens via selective androgen receptor modulators (SARMs).Drug Discov Today 12(5-6):241-8.

52. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ 2008 Cancer statistics, 2008. CA Cancer J Clin 58:71-96. PMID: 18287387

53. Siegel R, Ward E, Brawley O, Jemal A 2011 Cancer statistics: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011;61:21236

54. Hernandez DJ, Nielsen ME, Han M, Trock BJ, Partin AW, Walsh PC, Epstein JI 2008 Natural history of pathologically organ-confined (pT2), Gleason score 6 or less, prostate cancer after radical prostatectomy. Urology 72:172-176. PMCID: PMC2603620

55. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, Tomaszewski JE, Renshaw AA, Kaplan I, Beard CJ, Wein A 1998 Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. Jama 280:969-974. PMID: 9749478

56. Stokes SH 2000 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 1;47:129-36.

57. Potosky AL, Davis WW, Hoffman RM, Stanford JL, Stephenson RA, Penson DF, Harlan LC 2004 Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. J Natl Cancer Inst 96:1358-1367. PMID: 15367568

58. Potosky AL, Legler J, Albertsen PC, Stanford JL, Gilliland FD, Hamilton AS, Eley JW, Stephenson RA, Harlan LC 2000 Health outcomes after prostatectomy or radiotherapy for prostate cancer: results from the Prostate Cancer Outcomes Study. J Natl Cancer Inst 92:1582-1592. PMID: 11018094

59. Dillioglugil O, Miles BJ, Scardino PT 1995 Current controversies in the management of localized prostate cancer. Eur Urol 28:85-101.

60. Ficarra V, Novara G, Galfano A, Stringari C, Baldassarre R, Cavalleri S, Artibani W 2006 Twelve-month self-reported quality of life after retropubic radical prostatectomy: a prospective study with Rand 36-Item Health Survey (Short Form-36). BJU Int 97:274-278. PMID: 16430628

61. Schapira MM, Lawrence WF, Katz DA, McAuliffe TL, Nattinger AB 2001 Effect of treatment on quality of life among men with clinically localized prostate cancer. Medical care 39:243-253. PMID: 11242319

62. Cookson MS, Aus G, Burnett AL, Canby-Hagino ED, D'Amico AV, Dmochowski RR, Eton DT, Forman J, Goldernberg SL, Hernandez J, Higano CS, Kraus SR, Moul JW, Tangen CM, Thrasher JB, Thomson I 2007 Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the AUA Guidelines for localized prostate cancer update panel report and recommendations for a standard in reporting surgical outcomes J Urol 177:540-545. PMID: 17222629

63. Schatzl G, Madersbacher S, Thurridl T, Waldmuller J, Kramer G, Haitel A, Marberger M 2001 High-grade prostate cancer is associated with low serum testosterone levels. Prostate 47:52-58. PMID: 11304729

64. Severi G, Morris HA, MacInnis RJ, English DR, Tilley W, Hopper JL, Boyle P, Giles GG 2006 Circulating steroid hormones and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 15:86-91. PMID: 16434592

65. Morgentaler A, Bruning CO, 3rd, DeWolf WC 1996 Occult prostate cancer in men with low serum testosterone levels. Jama 276:1904-1906. PMID: 8968017

66. Ahluwalia B, Jackson MA, Jones GW, Williams AO, Rao MS, Rajguru S 1981 Blood hormone profiles in prostate cancer patients in high-risk and low-risk populations. Cancer 48:2267-2273. PMID: 7296478.

67. Chen SS, Chen KK, Lin AT, Chang YH, Wu HH, Chang LS 2002 The correlation between pretreatment serum hormone levels and treatment outcome for patients with prostatic cancer and bony metastasis. BJU Int 89:710-713. PMID: 11966629

68. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR 2001 Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 86:724-731. PMID: 11158037

69. Orwoll E, Lambert LC, Marshall LM, Blank J, Barrett-Connor E, Cauley J, Ensrud K, Cummings SR 2006 Endogenous testosterone levels, physical performance, and fall risk in older men. Arch Intern Med 166:2124-2131. PMID: 17060543

70. Gray A, Feldman HA, McKinlay JB, Longcope C 1991 Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts Male Aging Study. J Clin Endocrinol Metab 73:1016-1025. PMID: 1719016

71. Simon D, Preziosi P, Barrett-Connor E, Roger M, Saint-Paul M, Nahoul K, Papoz L 1992 The influence of aging on plasma sex hormones in men: the Telecom Study. Am J Epidemiol 135:783-791. PMID: 1595678

72. Baumgartner RN, Waters DL, Morley JE, Patrick P, Montoya GD, Garry PJ 1999 Age-related changes in sex hormones affect the sex difference in serum leptin independently of changes in body fat. Metabolism 48:378-384. PMID: 10094117

73. Morley JE, Kaiser FE, Perry HM, 3rd, Patrick P, Morley PM, Stauber PM, Vellas B, Baumgartner RN, Garry PJ 1997 Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. Metabolism 46:410-413. PMID: 9109845

74. Wu FC, Tajar A, Pye SR, Silman AJ, Finn JD, O'Neill TW, Bartfai G, Casanueva F, Forti G, Giwercman A, Huhtaniemi IT, Kula K, Punab M, Boonen S, Vanderschueren D 2008 Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. J Clin Endocrinol Metab 93:2737-2745. PMID: 18270261

75. Zmuda JM, Cauley JA, Kriska A, Glynn NW, Gutai JP, Kuller LH 1997 Longitudinal relation between endogenous testosterone and cardiovascular disease risk factors in middle-aged men. A 13-year follow-up of former Multiple Risk Factor Intervention Trial participants. Am J Epidemiol 146:609-617. PMID: 9345114

76. Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB 2002 Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab 87:589-98.

77. Ferrini RL, Barrett-Connor E 1998 Sex hormones and age: a cross-sectional study of testosterone and estradiol and their bioavailable fractions in community-dwelling men. Am J Epidemiol 147:750-4.

78. Dai WS, Kuller LH, LaPorte RE, Gutai JP, Falvo-Gerard L, Caggiula A 1981 The epidemiology of plasma testosterone levels in middle-aged men. Am J Epidemiol 114:804-16.

79. Liverman CT, Blazer DG 2004 Testosterone and aging: clinical research directions. Washington, DC: National Academies Press.

80. Burnett AL 2005 Erectile dysfunction following radical prostatectomy. Jama 293:2648-2653. PMID: 15928287

81. Hyun JS. Prostate cancer and sexual function.World J Mens Health 2012;30:99-107. PMID: 596596

82. Basaria S 2008 Androgen deprivation therapy, insulin resistance, and cardiovascular mortality: an inconvenient truth. J Androl 29:534-539. PMID: 18567642

83. Basaria S 2009 Prostate cancer: Cardiovascular mortality and androgen deprivation. Nature reviews 6:252-253. PMID: 19424172

84. Basaria S, Lieb J, 2nd, Tang AM, DeWeese T, Carducci M, Eisenberger M, Dobs AS 2002 Long-term effects of androgen deprivation therapy in prostate cancer patients. Clin Endocrinol (Oxf) 56:779-786

85. Basaria S, Muller DC, Carducci MA, Egan J, Dobs AS 2006 Hyperglycemia and insulin resistance in men with prostate carcinoma who receive androgen-deprivation therapy. Cancer 106:581-588. PMID: 16388523

86. Basaria S, Muller DC, Carducci MA, Egan J, Dobs AS 2007 Relation between duration of androgen deprivation therapy and degree of insulin resistance in men with prostate cancer. Arch Intern Med 167:612-613. PMID: 17389294

87. Smith MR, Lee H, Nathan DM 2006 Insulin sensitivity during combined androgen blockade for prostate cancer. J Clin Endocrinol Metab 91:1305-1308. PMID: 16434464

88. Diamond TH, Higano CS, Smith MR, Guise TA, Singer FR 2004 Osteoporosis in men with prostate carcinoma receiving androgen-deprivation therapy: recommendations for diagnosis and therapies. Cancer 100:892-899. PMID: 14983482

89. Pirl WF, Siegel GI, Goode MJ, Smith MR 2002 Depression in men receiving androgen deprivation therapy for prostate cancer: a pilot study. Psycho-oncology 11:518-523. PMID: 12476433.

90. Smith JC, Bennett S, Evans LM, Kynaston HG, Parmar M, Mason MD, Cockcroft JR, Scanlon MF, Davies JS 2001 The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. J Clin Endocrinol Metab 86:4261-4267. PMID: 11549659

91. Smith MR 2002 Osteoporosis during androgen deprivation therapy for prostate cancer. Urology 60:79-85; discussion 86. PMID: 12231056

92. Smith MR 2004 Changes in fat and lean body mass during androgen-deprivation therapy for prostate cancer. Urology 63:742-745. PMID: 15072892

93. Smith MR, Fallon MA, Goode MJ 2003 Cross-sectional study of bone turnover during bicalutamide monotherapy for prostate cancer. Urology 61:127-131. PMID: 12559282

94. Smith MR, Finkelstein JS, McGovern FJ, Zietman AL, Fallon MA, Schoenfeld DA, Kantoff PW 2002 Changes in body composition during androgen deprivation therapy for prostate cancer. J Clin Endocrinol Metab 87:599-603. PMID: 11836291

95. Penson DF, Litwin MS 2003 The physical burden of prostate cancer. Urol Clin North Am 30:305-313. PMID: 12735506

96. Glickman L, Godoy G, Lepor H 2009 Changes in continence and erectile function between 2 and 4 years after radical prostatectomy. J Urol 181:731-735. PMID: 19091349

97. Masterson TA, Wedmid A, Sandhu JS, Eastham JA 2009 Outcomes after radical prostatectomy in men receiving previous pelvic radiation for non-prostate malignancies. BJU Int. PMID: 19239447

98. Mulhall JP 2008 Penile rehabilitation following radical prostatectomy. Current opinion in urology 18:613-620. PMID: 18832948

99. Mulhall JP 2009 Defining and reporting erectile function outcomes after radical prostatectomy: challenges and misconceptions. J Urol 181:462-471. PMID: 19084865

100. Penson DF, McLerran D, Feng Z, Li L, Albertsen PC, Gilliland FD, Hamilton A, Hoffman RM, Stephenson RA, Potosky AL, Stanford JL 2008 5-year urinary and sexual outcomes after radical prostatectomy: results from the Prostate Cancer Outcomes Study. J Urol 179:S40-44. PMID: 18405749

101. Talcott JA, Rieker P, Clark JA, Propert KJ, Weeks JC, Beard CJ, Wishnow KI, Kaplan I, Loughlin KR, Richie JP, Kantoff PW 1998 Patient-reported symptoms after primary therapy for early prostate cancer: results of a prospective cohort study. J Clin Oncol 16:275-283. PMID: 9440753

102. Talcott JA, Rieker P, Propert KJ, Clark JA, Wishnow KI, Loughlin KR, Richie JP, Kantoff PW 1997 Patient-reported impotence and incontinence after nerve-sparing radical prostatectomy. J Natl Cancer Inst 89:1117-1123. PMID: 9262249

103. Fowler FJ, Jr., Barry MJ, Lu-Yao G, Roman A, Wasson J, Wennberg JE 1993 Patient-reported complications and follow-up treatment after radical prostatectomy. The National Medicare Experience: 1988-1990 (updated June 1993). Urology 42:622-629. PMID: 8256394

104. Crawford ED, Blumenstein BA, Goodman PJ, Davis MA, Eisenberger MA, McLeod DG, Spaulding JT, Benson R, Dorr FA 1990 Leuprolide with and without flutamide in advanced prostate cancer. Cancer 66:1039-1044. PMID: 2118417

105. Crawford ED, Eisenberger MA, McLeod DG, Spaulding JT, Benson R, Dorr FA, Blumenstein BA, Davis MA, Goodman PJ 1989 A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. N Engl J Med 321:419-424. PMID: 2503724

106. Eisenberger MA, Blumenstein BA, Crawford ED, Miller G, McLeod DG, Loehrer PJ, Wilding G, Sears K, Culkin DJ, Thompson IM, Jr., Bueschen AJ, Lowe BA 1998 Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. N Engl J Med 339:1036-1042. PMID: 9761805

107. Maroni PD, Crawford ED 2008 The benefits of early androgen blockade. Best practice & research 22:317-329. PMID: 18471789

108. Kumar S, Shelley M, Harrison C, Coles B, Wilt TJ, Mason MD 2006 Neo-adjuvant and adjuvant hormone therapy for localised and locally advanced prostate cancer. Cochrane database of systematic reviews (Online):CD006019. PMID: 17054269

109. Meikle AW, Arver S, Dobs AS, Adolfsson J, Sanders SW, Middleton RG, Stephenson RA, Hoover DR, Rajaram L, Mazer NA 1997 Prostate size in hypogonadal men treated with a nonscrotal permeation-enhanced testosterone transdermal system. Urology 49:191-196. PMID: 9037280

110. Behre HM, Bohmeyer J, Nieschlag E 1994 Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal controls. Clin Endocrinol (Oxf) 40:341-349. PMID: 7514512

111. Bhasin S, Woodhouse L, Casaburi R, Singh AB, Bhasin D, Berman N, Chen X, Yarasheski KE, Magliano L, Dzekov C, Dzekov J, Bross R, Phillips J, Sinha-Hikim I, Shen R, Storer TW 2001 Testosterone dose-response relationships in healthy young men. Am J Physiol Endocrinol Metab 281:E1172-1181. PMID: 11701431

112. Bhasin S, Woodhouse L, Casaburi R, Singh AB, Mac RP, Lee M, Yarasheski KE, Sinha-Hikim I, Dzekov C, Dzekov J, Magliano L, Storer TW 2005 Older men are as responsive as young men to the anabolic effects of graded doses of testosterone on the skeletal muscle. J Clin Endocrinol Metab 90:678-688. PMID: 15562020.

113. Wu CP, Gu FL 1987 The prostate 41-65 years post castration. An analysis of 26 eunuchs. Chin Med J (Engl) 100:271-272

114. Wu CP, Gu FL 1991 The prostate in eunuchs. Prog Clin Biol Res 370;249-255 PMID: 1924456

115. Morgentaler A, Lipshultz LI, Bennett R, Sweeney M, Avila D Jr, Khera M 2011 Testosterone therapy in men

with untreated prostate cancer.J Urol 185:1256-60. PMID: 21334649

116. Basaria S, Collins L, Dillon EL, Orwoll K, Storer TW, Miciek R, Ulloor J, Zhang A, Eder R, Zientek H, Gordon G, Kazmi S, Sheffield-Moore M, Bhasin S 2012 The Safety, Pharmacokinetics, and Effects of LGD-4033, a novel nonsteroidal oral, selective androgen receptor modulator, in healthy young men.J Gerontol A Biol Sci Med Sci 2012 Mar 28. PMID: 11549629

117. Dobs AS, Boccia RV, Croot CC, Gabrail NY, Dalton JT, Hancock ML, Johnston MA, Steiner MS 2013 Effects of enobosarm on muscle wasting and physical function in patients with cancer: a double-blind, randomised controlled phase 2 trial.Lancet Oncol 14:335-45. PMID: 23499390

118. Han M, Partin AW, Zahurak M, Piantadosi S, Epstein JI, Walsh PC 2003 Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. J Urol 169:517-523. PMID: 12544300

119. Kupelian PA, Katcher J, Levin HS, Klein EA 1997 Stage T1-2 prostate cancer: a multivariate analysis of factors affecting biochemical and clinical failures after radical prostatectomy. Int J Radiat Oncol Biol Phys 37:1043-1052. PMID: 9169811

120. Bhasin S, Enzlin P, Coviello A, Basson R 2007 Sexual dysfunction in men and women with endocrine disorders. Lancet 369:597-611. PMID: 17307107

121. Davidson JM, Camargo CA, Smith ER 1979 Effects of androgen on sexual behavior in hypogonadal men. J Clin Endocrinol Metab 48:955-958. PMID: 447801

122. Davidson JM, Kwan M, Greenleaf WJ 1982 Hormonal replacement and sexuality in men. Clin Endocrinol Metab 11:599-623. PMID: 6814798

123. Kwan M, Greenleaf WJ, Mann J, Crapo L, Davidson JM 1983 The nature of androgen action on male sexuality: a combined laboratory-self-report study on hypogonadal men. J Clin Endocrinol Metab 57:557-562. PMID: 6874890

124. Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ, Weber T, Berman N, Hull L, Swerdloff RS 2004 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. J Clin Endocrinol Metab 89:2085-2098. PMID: 15126525

125. Wang C, Swedloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G, Matsumoto AM, Weber T, Berman N 2000 Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. Testosterone Gel Study Group. J Clin Endocrinol Metab 85:2839-2853. PMID: 10946892

126. Alexander GM, Sherwin BB 1991 The association between testosterone, sexual arousal, and selective attention for erotic stimuli in men. Horm Behav 25:367-381. PMID: 1937428

127. Arver S, Dobs AS, Meikle AW, Allen RP, Sanders SW, Mazer NA 1996 Improvement of sexual function in testosterone deficient men treated for 1 year with a permeation enhanced testosterone transdermal system. J Urol 155:1604-1608. PMID: 8627833

128. Carani C, Bancroft J, Granata A, Del Rio G, Marrama P 1992 Testosterone and erectile function, nocturnal penile tumescence and rigidity, and erectile response to visual erotic stimuli in hypogonadal and eugonadal men. Psychoneuroendocrinology 17:647-654. PMID: 1287683

129. Carani C, Granata AR, Bancroft J, Marrama P 1995 The effects of testosterone replacement on nocturnal penile tumescence and rigidity and erectile response to visual erotic stimuli in hypogonadal men.

Psychoneuroendocrinology 20:743-753. PMID: 8848520

130. Cunningham GR, Hirshkowitz M, Korenman SG, Karacan I 1990 Testosterone replacement therapy and sleep-related erections in hypogonadal men. J Clin Endocrinol Metab 70:792-797. PMID: 2307732

131. Shabsigh R, Kaufman, J, Aurora, CO, Steidle, C, Padma-Natha, H. 2003 Testosterone repalcement therapy with testosterone gel 1% converts sildenafil non-responders in men with hypogonadism and erectile dysfunction who failed prior sidlenafil therapy. J Urol 169:247 (854A)

132. Shabsigh R, Kaufman JM, Steidle C, Padma-Nathan H 2004 Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. J Urol 172:658-663. PMID: 15247755

133. Shabsigh R, Kaufman JM, Steidle C, Padma-Nathan H 2008 Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. J Urol 179:S97-S102. PMID: 18405769

134. Aversa A, Isidori AM, Spera G, Lenzi A, Fabbri A 2003 Androgens improve cavernous vasodilation and response to sildenafil in patients with erectile dysfunction. Clin Endocrinol (Oxf) 58:632-638. PMID: 12699447

135. Kalinchenko SY, Kozlov GI, Gontcharov NP, Katsiya GV 2003 Oral testosterone undecanoate reverses erectile dysfunction associated with diabetes mellitus in patients failing on sildenafil citrate therapy alone. Aging Male 6:94-99. PMID: 12898793

136. Trigo-Rocha F, Aronson WJ, Hohenfellner M, Ignarro LJ, Rajfer J, Lue TF 1993 Nitric oxide and cGMP: mediators of pelvic nerve-stimulated erection in dogs. Am J Physiol 264:H419-422. PMID: 8383456

137. Reilly CM, Stopper VS, Mills TM 1997 Androgens modulate the alpha-adrenergic responsiveness of vascular smooth muscle in the corpus cavernosum. J Androl 18:26-31. PMID: 9089065

138. Shabsigh R, Raymond JF, Olsson CA, O'Toole K, Buttyan R 1998 Androgen induction of DNA synthesis in the rat penis. Urology 52:723-728. PMID: 9763105

139. Fournier GR, Jr., Juenemann KP, Lue TF, Tanagho EA 1987 Mechanisms of venous occlusion during canine penile erection: an anatomic demonstration. J Urol 137:163-167. PMID: 3795360

140. Mills TM, Lewis RW 1999 The Role of Andorgens in the Erectile Response: A 1999 Perspective. Mol Urol 3:75-86. PMID: 10851308

141. Mills TM, Lewis RW, Stopper VS 1998 Androgenic maintenance of inflow and veno-occlusion during erection in the rat. Biol Reprod 59:1413-1418. PMID: 9828186

142. Mills TM, Stopper VS, Wiedmeier VT 1994 Effects of castration and androgen replacement on the hemodynamics of penile erection in the rat. Biol Reprod 51:234-238. PMID: 7948478

143. Reilly CM, Zamorano P, Stopper VS, Mills TM 1997 Androgenic regulation of NO availability in rat penile erection. J Androl 18:110-115. PMID: 9154504

144. Reilly CM, Lewis RW, Stopper VS, Mills TM 1997 Androgenic maintenance of the rat erectile response via a non-nitric-oxide-dependent pathway. J Androl 18:588-594. PMID: 9432131

145. Reilly CM, Stopper VS, Mills TM 1997 Androgens modulate the alpha-adrenergic responsiveness of vascular smooth muscle in the corpus cavernosum. J Androl 18:26-31. PMID: 9089065

146. Lugg JA, Rajfer J, Gonzalez-Cadavid NF 1995 Dihydrotestosterone is the active androgen in the maintenance of nitric oxide-mediated penile erection in the rat. Endocrinology 136:1495-1501. PMID: 7534702

147. Trigo-Rocha F, Aronson WJ, Hohenfellner M, Ignarro LJ, Rajfer J, Lue TF 1993 Nitric oxide and cGMP: mediators of pelvic nerve-stimulated erection in dogs. Am J Physiol 264:H419-422. PMID: 8383456

148. Fournier GR, Jr., Juenemann KP, Lue TF, Tanagho EA 1987 Mechanisms of venous occlusion during canine penile erection: an anatomic demonstration. J Urol 137:163-167. PMID: 3795360

149. Shabsigh R, Raymond JF, Olsson CA, O'Toole K, Buttyan R 1998 Androgen induction of DNA synthesis in the rat penis. Urology 52:723-728. PMID: 9763105

150. Jain P, Rademaker AW, McVary KT 2000 Testosterone supplementation for erectile dysfunction: results of a meta-analysis. J Urol 164:371-375. PMID: 10893588

151. Bolona ER, Uraga MV, Haddad RM, Tracz MJ, Sideras K, Kennedy CC, Caples SM, Erwin PJ, Montori VM 2007 Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc 82:20-28. PMID: 17285782

152. Buvat J, Montorsi F, Maggi M, Porst H, Kaipia A, Colson MH, Cuzin B, Moncada I, Martin-Morales A, Yassin A, Meuleman E, Eardley I, Dean JD, Shabsigh R 2011 Hypogonadal men nonresponders to the PDE5 inhibitor tadalafil benefit from normalization of testosterone levels with a 1% hydroalcoholic testosterone gel in the treatment of erectile dysfunction (TADTEST study).J Sex Med 8:284-93

153. Spitzer M, Basaraia S, Travison TG, Davda M, Mazer NA, Paley A, Mohammed N, Hanka S, Knapp P, Rosen R, DeRogatis L, Bhasin S 2012 The effect of testosterone on response to sildeanfil in men with erectile dysfunciton: a randomized controlled trial. Ann Intern Med in press

154. Barrett-Connor E, Von Muhlen DG, Kritz-Silverstein D 1999 Bioavailable testosterone and depressed mood in older men: the Rancho Bernardo Study. J Clin Endocrinol Metab 84:573-577. PMID: 10022418

155. Seidman SN, Araujo AB, Roose SP, McKinlay JB 2001 Testosterone level, androgen receptor polymorphism, and depressive symptoms in middle-aged men. Biol Psychiatry 50:371-376. PMID: 11543741

156. Seidman SN, Araujo AB, Roose SP, Devanand DP, Xie S, Cooper TB, McKinlay JB 2002 Low testosterone levels in elderly men with dysthymic disorder. Am J Psychiatry 159:456-459. PMID: 11870011

157. Wang C, Alexander G, Berman N, Salehian B, Davidson T, McDonald V, Steiner B, Hull L, Callegari C, Swerdloff RS 1996 Testosterone replacement therapy improves mood in hypogonadal men--a clinical research center study. J Clin Endocrinol Metab 81:3578-3583. PMID: 8855804

158. Pope HG, Jr., Cohane GH, Kanayama G, Siegel AJ, Hudson JI 2003 Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. Am J Psychiatry 160:105-111. PMID: 12505808

159. Shifren JL, Braunstein GD, Simon JA, Casson PR, Buster JE, Redmond GP, Burki RE, Ginsburg ES, Rosen RC, Leiblum SR, Caramelli KE, Mazer NA 2000 Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. N Engl J Med 343:682-688. PMID: 10974131

160. Arlt W, Callies F, van Vlijmen JC, Koehler I, Reincke M, Bidlingmaier M, Huebler D, Oettel M, Ernst M, Schulte HM, Allolio B 1999 Dehydroepiandrosterone replacement in women with adrenal insufficiency. N Engl J Med 341:1013-1020. PMID: 10502590

161. Wagner GJ, Rabkin JG, Rabkin R 1998 Testosterone as a treatment for fatigue in HIV+ men. Gen Hosp Psychiatry 20:209-13.

162. Rabkin JG, Wagner GJ, Rabkin R 2000 A double-blind, placebo-controlled trial of testosterone therapy for HIV-positive men with hypogonadal symptoms. Arch Gen Psychiatry 57:141-147; discussion 155-146. PMID: 10665616

163. Rosen RC, Araujo AB, Connor MK, Elstad EA, McGraw SA, Guay AT, Morgentaler A, Miner MM 2009 Assessing symptoms of hypogonadism by self-administered questionnaire: qualitative findings in patients and controls. Aging Male 12:77-85.

164. Rabkin J, Wagner G, McElhiney M, Rabkin R, Lin S 2004 Testosterone versus fluoxetine for depression and fatigue in HIV/AIDS: a placebo-controlled trial. Journal of Clinical Psychopharmacology 24:379-385.

165. Rabkin JG, Ferrando SJ, Wagner GJ, Rabkin R 2000 DHEA treatment for HIV+ patients: effects on mood, androgenic and anabolic parameters. Psychoneuroendocrinology 25:53-68.

166. Knapp PE, Storer TW, Herbst KL, Singh AB, Dzekov C, Dzekov J, LaValley M, Zhang A, Ulloor J, Bhasin S 2008 Effects of a supraphysiological dose of testosterone on physical function, muscle performance, mood, and fatigue in men with HIV-associated weight loss. Am J Physiol Endocrinol Metab 2008;294(6):E1135-43.

167. http://www.hiv.va.gov/provider/manual-primary-care/androgen-deficiency.asp.

168. http://www.savvyhealth.com/disp.asp?doc_id=544.

169. http://www.aidsmeds.com/articles/Fatigue_4832.shtml.

170. http://www.thebody.com/Forums/AIDS/Fatigue/Q214266.html.

171. Bhasin S, Storer TW, Berman N, Callegari C, Clevenger B, Phillips J, Bunnell TJ, Tricker R, Shirazi A, Casaburi R 1996 The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 335:1-7. PMID: 8637535

172. Bhasin S, Storer TW, Berman N, Yarasheski KE, Clevenger B, Phillips J, Lee WP, Bunnell TJ, Casaburi R 1997 Testosterone replacement increases fat-free mass and muscle size in hypogonadal men. J Clin Endocrinol Metab 82:407-413. PMID: 9024227

173. Bhasin S, Storer TW, Javanbakht M, Berman N, Yarasheski KE, Phillips J, Dike M, Sinha-Hikim I, Shen R, Hays RD, Beall G 2000 Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. Jama 283:763-770. PMID: 10683055

174. Bhasin S, Woodhouse L, Casaburi R, Singh AB, Bhasin D, Berman N, Chen X, Yarasheski KE, Magliano L, Dzekov C, Dzekov J, Bross R, Phillips J, Sinha-Hikim I, Shen R, Storer TW 2001 Testosterone dose-response relationships in healthy young men. Am J Physiol Endocrinol Metab 281:E1172-1181. PMID: 11701431

175. Bhasin S, Woodhouse L, Casaburi R, Singh AB, Mac RP, Lee M, Yarasheski KE, Sinha-Hikim I, Dzekov C, Dzekov J, Magliano L, Storer TW 2005 Older men are as responsive as young men to the anabolic effects of graded doses of testosterone on the skeletal muscle. J Clin Endocrinol Metab 90:678-688. PMID: 15562020

176. Storer TW, Magliano L, Woodhouse L, Lee ML, Dzekov C, Dzekov J, Casaburi R, Bhasin S 2003 Testosterone dose-dependently increases maximal voluntary strength and leg power, but does not affect fatigability or specific tension. J Clin Endocrinol Metab 88:1478-1485. PMID: 12679426

177. Storer TW, Woodhouse LJ, Sattler F, Singh AB, Schroeder ET, Beck K, Padero M, Mac P, Yarasheski KE, Geurts P, Willemsen A, Harms MK, Bhasin S 2005 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. J Clin Endocrinol Metab 90:4474-4482. PMID: 15914526

178. Steidle C, Schwartz S, Jacoby K, Sebree T, Smith T, Bachand R 2003 AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. J Clin Endocrinol Metab 88:2673-2681. PMID: 12788872

179. Woodhouse LJ, Reisz-Porszasz S, Javanbakht M, Storer TW, Lee M, Zerounian H, Bhasin S 2003 Development

of models to predict anabolic response to testosterone administration in healthy young men. Am J Physiol Endocrinol Metab 284:E1009-1017. PMID: 12517741

180. Brodsky IG, Balagopal P, Nair KS 1996 Effects of testosterone replacement on muscle mass and muscle protein synthesis in hypogonadal men--a clinical research center study. J Clin Endocrinol Metab 81:3469-3475. PMID: 8855787

181. Katznelson L, Finkelstein JS, Schoenfeld DA, Rosenthal DI, Anderson EJ, Klibanski A 1996 Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. J Clin Endocrinol Metab 81:4358-4365. PMID: 8954042

182. Snyder PJ, Peachey H, Berlin JA, Hannoush P, Haddad G, Dlewati A, Santanna J, Loh L, Lenrow DA, Holmes JH, Kapoor SC, Atkinson LE, Strom BL 2000 Effects of testosterone replacement in hypogonadal men. J Clin Endocrinol Metab 85:2670-2677. PMID: 10946864

183. Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ, Weber T, Berman N, Hull L, Swerdloff RS 2004 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. J Clin Endocrinol Metab 89:2085-2098. PMID: 15126525

184. Wang C, Swedloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G, Matsumoto AM, Weber T, Berman N 2000 Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. Testosterone Gel Study Group. J Clin Endocrinol Metab 85:2839-2853. PMID: 10946892

185. Casaburi R, Bhasin S, Cosentino L, Porszasz J, Somfay A, Lewis MI, Fournier M, Storer TW 2004 Effects of testosterone and resistance training in men with chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine 170:870-878. PMID: 15271690

186. Bhasin S, Calof O, Storer TW, al. E 2006 Drug insights: anabolic applications of testosterone and selective androgen receptor modulators in aging and chronic illness. Nature CPEM 2:133-140. PMID: 19011296

187. Blazer DG, Liverman C 2004 The Institute of Medicine Expert Panel Report on the Future of Testosterone Research in Older Men. The National Academies Press, Washington, DC.

188. Page ST, Amory JK, Bowman FD, Anawalt BD, Matsumoto AM, Bremner WJ, Tenover JL 2004 Exogenous Testosterone (T) Alone or with Finasteride Increases Physical Performance, Grip Strength, and Lean Body Mass in Older Men with Low Serum T. J Clin Endocrinol Metab. PMID: 15572415

189. Brill KT, Weltman AL, Gentili A, Patrie JT, Fryburg DA, Hanks JB, Urban RJ, Veldhuis JD 2002 Single and combined effects of growth hormone and testosterone administration on measures of body composition, physical performance, mood, sexual function, bone turnover, and muscle gene expression in healthy older men. J Clin Endocrinol Metab 87:5649-5657. PMID: 15579792

190. Ware JE. **SF-36® Health Survey Update. Version 2.**

191. Watson D, Clark LA 1984 Negative affectivity: the disposition to experience aversive emotional states. Psychological bulletin 96:465-490. PMID: 6393179

192. Watson D, Clark LA, Carey G 1988 Positive and negative affectivity and their relation to anxiety and depressive disorders. Journal of abnormal psychology 97:346-353. PMID: 3192830

193. Crawford JR, Henry JD 2004 The positive and negative affect schedule (PANAS): construct validity, measurement properties and normative data in a large non-clinical sample. The British journal of clinical psychology / the British Psychological Society 43:245-265. PMID: 15333231

194. Almagor M, Ben-Porath YS 1989 The two-factor model of self-reported mood: a cross-cultural replication. J Pers Assess 53:10-21. PMID: 2918447

195. Basaria S, Coviello A, Travison TG, Storer TW, Farwell WR, Jette A, Eder R, Tennstedt S, Ulloor J, Zhang A, Choong K, Lakshman K, Mazer NA, Miciek R, Krasnoff J, Elmi A, Knapp P, Brooks B, Bhasin G, Appleman E, Aggarwal S, Collins L, LeBrasseur N, Fiore L, Bhasin S 2010 Adverse effects associated with testosterone administration in older men. N Engl J Med 363:109-22. PMID 2059229

196. Bhasin S, Storer TW, Berman N, Hays R, Beall G 2000 Effects of testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. JAMA 283:756-762. PMID: 1068305

197. Bhasin S, Travison TG, Storer TW, Lakshman K, Kaushik M, Mazer NA, Ngyuen AH, Davda MN, Jara H, Aakil A, Anderson S, Knapp PE, Hanka S, Mohammed N, Daou P, Miciek R, Ulloor J, Zhang A, Brooks B, Orwoll K, Hede-Brierley L, Eder R, Elmi A, Bhasin G, Collins L, Singh R, Basaria S 2012 Effect of testosterone supplementation with and without a dual 5α-reductase inhibitor on fat-free mass in adult men with suppressed testosterone production: a randomized trial. JAMA 307:931-9. PMID: 22396515

198. Berry D, Halpenny B, Hong F, et al 2011 The Personal Patient Profile-Prostate for Men With Newly Diagnosed Localized Prostate Cancer: A Multi-center Randomized Trial. Urologic Oncology; E-pub ahead of print, 7 Dec, 2011; PMID: 22153756.

199. Berry D, Blumenstein B, Halpenny B, Wolpin S, Fann JR, Austin-Seymour M. Bush N, Karras BT, Lober WB, McCorkle R 2011 Enhancing Patient-Provider Communication with the Electronic Self-Report Assessment for Cancer (ESRA-C): A Randomized Trial. J Clin Oncol 29:1029-35.

200. Hussain M, Tangen CM, Berry DL, Higano CS, Crawford ED, Liu G, Wilding G, Prescott S, Kanaga Sundaram S, Small EJ, Dawson NA, Donnelly BJ, Venner PM, Vaishampayan UN, Schellhammer PF, Quinn DI, Raghavan D, Ely B, Moinpour CM, Vogelzang NJ, Thompson IM Jr 2013 Intermittent versus continuous androgendeprivation in prostate cancer.N Engl J Med 368:1314-25.

201. Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG 2000 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 56:899-905. PMID: 11113727

202. Buena F, Swerdloff RS, Steiner BS, Lutchmansingh P, Peterson MA, Pandian MR, Galmarini M, Bhasin S 1993 Sexual function does not change when serum testosterone levels are pharmacologically varied within the normal male range. Fertil Steril 59:1118-1123. PMID: 8486184

203. Bhasin S, Woodhouse L, Casaburi R, Singh AB, Bhasin D, Berman N, Chen X, Yarasheski KE, Magliano L, Dzekov C, Dzekov J, Bross R, Phillips J, Sinha-Hikim I, Shen R, Storer TW 2001 Testosterone dose-response relationships in healthy young men. Am J Physiol Endocrinol Metab 281:E1172-1181. PMID: 15827094

204. Fielder TJ, Peacock NR, McGivern RF, Swerdloff RS, Bhasin S 1989 Testosterone dose-dependency of sexual and nonsexual behaviors in the gonadotropin-releasing hormone antagonist-treated male rat. J Androl 10:167-173. PMID: 2501257

205. Bhasin S, Fielder T, Peacock N, Sod-Moriah UA, Swerdloff RS 1988 Dissociating antifertility effects of GnRH-antagonist from its adverse effects on mating behavior in male rats. Am J Physiol 254:E84-91. PMID: 3276216

206. Bhasin S, Zhang A, Coviello A, Jasuja R, Ulloor J, Singh R, Vesper H, Vasan RS 2008 The impact of assay quality and reference ranges on clinical decision making in the diagnosis of androgen disorders. Steroids 73:1311-1317 PMID: 18687348

207. Vesper HW, Bhasin S, Wang C, Tai SS, Dodge LA, Singh RJ, Nelson J, Ohorodnik S, Clarke NJ, Salameh WA,

Parker CR, Jr., Razdan R, Monsell EA, Myers GL 2009 Interlaboratory comparison study of serum total testoserone measurements performed by mass spectrometry methods. Steroids 74:498-503 PMID: 19428438

208. Bhasin S, Pencina M, Jasuja GK, Travison TG, Coviello A, Orwoll E, Wang PY, Nielson C, Wu F, Tajar A, Labrie F, Vesper H, Zhang A, Ulloor J, Singh R, D'Agostino R, Vasan RS 2011 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.J Clin Endocrinol Metab 2011;96:2430-9. PMID: 21697255

209. Berry DL, Moinpour CM, Pauler Ankerst D, Jiang CS, Petrylak DP, Vinson LV, Lara PN, Lanier S, Taplin ME, Burch PA, Hussain MHA and Crawford ED. Quality of Life and Pain in Advanced Stage Prostate Cancer: Results of a Southwest Oncology Group Randomized Trial Comparing Docetaxel/estramustine to Mitoxantrone/prednisone. J Clin Oncology 2006; 2418:2828-35.

210. Berry DL, Ellis WJ, Russell KJ, Blasko JC, Bush N. Blumenstein BA, Lange PH. Factors That Predict Treatment Choice and Satisfaction with the Decision in Men with Localized Prostate Cancer. Clinical Genitourinary Cancer 2006; 5: 219-226. PMC 3189855

211. Burnett AL, Aus G, Canby-Hagino ED, Cookson MS, D'Amico AV, Dmochowski RR, Eton DT, Forman JD, Goldenberg SL, Hernandez J, Higano CS, Kraus S, Liebert M, Moul JW, Tangen C, Thrasher JB, Thompson I; American Urological Association Prostate Cancer Guideline Update Panel 2007 Erectile function outcome reporting after clinically localized prostate cancer treatment. J Urol 178(2):597-601.

212. Cookson MS, Roth BJ, Dahm P, Engstrom C, Freedland SJ, Hussain M, Lin DW, Lowrance WT, Murad MH, Oh WK, Penson DF, Kibel AS. 2013. Castration-Resistant Prostate Cancer: AUA Guideline.J Urol S0022-5347(13)04327-9. PMID: 23665272

213. Nepple KG, Stephenson AJ, Kallogjeri D, Michalski J, Grubb RL 3rd, Strope SA, Haslag-Minoff J, Piccirillo JF, Ciezki JP, Klein EA, Reddy CA, Yu C, Kattan MW, Kibel AS 2013 Mortality After Prostate Cancer Treatment with Radical Prostatectomy, External-Beam Radiation Therapy, or Brachytherapy in Men Without Comorbidity.Eur Urol S0302-2838(13)00229-7.

214. Kibel AS, Ciezki JP, Klein EA, Reddy CA, Lubahn JD, Haslag-Minoff J, Deasy JO, Michalski JM, Kallogjeri D, Piccirillo JF, Rabah DM, Yu C, Kattan MW, Stephenson AJ 2012 Survival among men with clinically localized prostate cancer treated with radical prostatectomy or radiation therapy in the prostate specific antigen era.J Urol 187:1259-65.

215. Rebbeck TR, Devesa SS, Chang BL, Bunker CH, Cheng I, Cooney K, Eeles R, Fernandez P, Giri VN, Gueye SM, Haiman CA, Henderson BE, Heyns CF, Hu JJ, Ingles SA, Isaacs W, Jalloh M, John EM, Kibel AS, Kidd LR, Layne P, Leach RJ, Neslund-Dudas C, Okobia MN, Ostrander EA, Park JY, Patrick AL, Phelan CM, Ragin C, Roberts RA, Rybicki BA, Stanford JL, Strom S, Thompson IM, Witte J, Xu J, Yeboah E, Hsing AW, Zeigler-Johnson CM 2013 Global patterns of prostate cancer incidence, aggressiveness, and mortality in men of african descent.Prostate Cancer 2013:560857

216. Travison TG, Basaria S, Storer TW, Jette AM, Miciek R, Farwell WR, Choong K, Lakshman K, Mazer NA, Coviello AD, Knapp PE, Ulloor J, Zhang A, Brooks B, Nguyen A-H, Eder R, LeBrasseur N, Elmi A, Appleman E, Hede-Brierley L, Bhasin G, Bhatia A, Lazzari A, Davis S, Ni P, Collins L, Bhasin S 2011 Clinical meaningfulness of the changes in muscle performance and physical function associated with testosterone administration in older men with mobility limitation. J. Gerontol. A Biol. Sci. Med. Sci 66:1090–9.

217. Bachman E, Feng R, Travison TG, Li M, Olbina G, Ostland V, Ulloor J, Zhang A, Basaria S, Ganz T, Westerman M, Bhasin S 2010 Testosterone suppresses hepcidin in men: a potential mechanism for testosterone-induced erythrocytosis. J Clin Endocrinol Metab 95:4743–7.

218. Coviello AD, Lakshman K, Mazer NA, Bhasin S 2006 Differences in the apparent metabolic clearance rate of testosterone in young and older men with gonadotropin suppression receiving graded doses of testosterone. J Clin Endocrinol Metab 91:4669-75.

219. Coviello AD, Kaplan B, Lakshman KM, Chen T, Singh AB, Bhasin S 2008 Effects of graded doses of testosterone on erythropoiesis in healthy young and older men. J Clin Endocrinol Metab 93:914-9.

220. Gray PB, Singh AB, Woodhouse LJ, Storer TW, Casaburi R, Dzekov J, Dzekov C, Sinha-Hikim I, Bhasin S 2005 Dose-dependent effects of testosterone on sexual function, mood, and visuospatial cognition in older men. J Clin Endocrinol Metab 90:3838-46.

221. Lee KK, Berman N, Alexander GM, Hull L, Swerdloff RS, Wang C 2003 A simple self-report diary for assessing psychosexual function in hypogonadal men.J Androl 24:688-98.

222. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A 1997 The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 49:822-830. PMID: 9187685

223. Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Pena BM 1999 Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res 11:319-326. PMID: 10637462

224. Cappelleri JC, Rosen RC, Smith MD, Mishra A, Osterloh IH 1999 Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. Urology 54:346-351. PMID: 10443736

225. Rosen RC, Catania J, Pollack L, Althof S, O'Leary M, Seftel AD 2004 Male Sexual Health Questionnaire (MSHQ): scale development and psychometric validation. Urology 64:777-782.

226. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA 1998 Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. N Engl J Med 338:1397-1404 PMID: 9580646.

227. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA 2002 Oral sildenafil in the treatment of erectile dysfunction. 1998. J Urol 167:1197-1203; discussion 1204. PMID: 11905901

228. Padma-Nathan H, McMurray JG, Pullman WE, Whitaker JS, Saoud JB, Ferguson KM, Rosen RC 2001 On-demand IC351 (Cialis) enhances erectile function in patients with erectile dysfunction. Int J Impot Res 13:2-9. PMID: 11313831

229. Shabsigh R, Kaufman JM, Steidle C, Padma-Nathan H 2004 Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. J Urol 172:658-663. PMID: 15247755

230. Shabsigh R, Kaufman JM, Steidle C, Padma-Nathan H 2008 Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. J Urol 179:S97-S102. PMID: 18405769

231. Kalinchenko SY, Kozlov GI, Gontcharov NP, Katsiya GV 2003 Oral testosterone undecanoate reverses erectile dysfunction associated with diabetes mellitus in patients failing on sildenafil citrate therapy alone. Aging Male 6:94-99. PMID: 12898793

232. Fiatarone MA, Marks EC, Ryan ND, Meredith CN, Lipsitz LA, Evans WJ 1990 High-intensity strength training in nonagenarians. Effects on skeletal muscle. Jama 263:3029-3034. PMID: 2342214

233. Ware JE.SF-36® Health Survey Update. Version 2.

234. Travison TG, Morley JE, Araujo AB, O'Donnell AB, McKinlay JB 2006 The relationship between libido and testosterone levels in aging men. J Clin Endocrinol Metab 91:2509-2513. PMID: 16670164

235. Guralnik JM, Ferrucci L, Pieper CF, Leveille SG, Markides KS, Ostir GV, Studenski S, Berkman LF, Wallace RB 2000 Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. J Gerontol A Biol Sci Med Sci 55:M221-231. PMID: 10811152

236. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB 1995 Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med 332:556-561. PMID: 7838189

237. Lai JS, Crane PK, Cella D 2006 Factor analysis techniques for assessing sufficient unidimensionality of cancer related fatigue. Qual Life Res 15:1179-1190. PMID: 17001438

238. Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE 2002 Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. Journal of pain and symptom management 24:547-561. PMID: 12551804

239. Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J 2005 Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. The Journal of rheumatology 32:811-819. PMID: 1586861

240. Cella D, Zagari MJ, Vandoros C, Gagnon DD, Hurtz HJ, Nortier JW 2003 Epoetin alfa treatment results in clinically significant improvements in quality of life in anemic cancer patients when referenced to the general population. J Clin Oncol 21:366-373. PMID: 12525531

241. Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG 2000. 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 56:899-905.

242. Szymanski KM, Wei JT, Dunn RL, Sanda MG 2010 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 76(5):1245-50.

243. Wagner G, Fugl-Meyer KS, Fugl-Meyer AR 2000 Impact of erectile dysfunction on quality of life: patient and partner perspectives. Int J Impot Res 12 Suppl 4:S144-146. PMID: 11035403

244. Watson D, Clark LA, Tellegen A 1988 Development and validation of brief measures of positive and negative affect: the PANAS scales. Journal of personality and social psychology 54:1063-1070. PMID: 3397865

245. Watson D, Clark LA, Carey G 1988 Positive and negative affectivity and their relation to anxiety and depressive disorders. Journal of abnormal psychology 97:346-353. PMID: 3192830

246. Watson D, Clark LA 1984 Negative affectivity: the disposition to experience aversive emotional states. Psychological bulletin 96:465-490. PMID: 6393179

247. Smith BW, Zautra AJ 2002 The role of personality in exposure and reactivity to interpersonal stress in relation to arthritis disease activity and negative affect in women. Health Psychol 21:81-88. PMID: 11846348

248. Lord SR, Menz HB 2002 Physiologic, psychologic, and health predictors of 6-minute walk performance in older people. Arch Phys Med Rehabil 83:907-911. PMID: 12098148

249. Voogt E, van der Heide A, van Leeuwen AF, Visser AP, Cleiren MP, Passchier J, van der Maas PJ 2005 Positive and negative affect after diagnosis of advanced cancer. Psycho-oncology 14:262-273. PMID: 15386769

250. Koller M, Kussman J, Lorenz W, Jenkins M, Voss M, Arens E, Richter E, Rothmund M 1996 Symptom reporting in cancer patients: the role of negative affect and experienced social stigma. Cancer 77:983-995. PMID: 8608494

251. LeBrasseur NK, Bhasin S, Miciek R, Storer TW 2008 Tests of muscle strength and physical function: reliability and discrimination of performance in younger and older men and older men with mobility limitations. J Am Geriatr Soc 56:2118-23.

252. Mitchell JH, Sproule BJ, Chapman CB. The physiological meaning of the maximal oxygen intake test. J Clin Invest 1958;37(4):538-47.

253. Taylor Hl, Buskirk E, Henschel A. Maximal oxygen intake as an objective measure of cardio-respiratory performance. J Appl Physiol 1955;8(1):73-80.

254. Whipp BJ, Davis JA, Torres F, Wasserman K. A test to determine parameters of aerobic function during exercise. J Appl Physiol 1981;50(1):217-21.

255. Vestergaard S, Nayfield SG, Patel KV, Eldadah B, Cesari M, FerrucciL,Ceresini G, Guralnik JM. Fatigue in a representative population of older persons and its association with functional impairment, functional limitation, and disability. J Gerontol A Biol Sci Med Sci 2009;64:76-82.

256. Wood S 2006 Generalized Additive Models: An Introduction with R. 1st ed. Chapman and Hall/CRC.

257. van Buuren S 2007 Multiple imputation of discrete and continuous data by fully conditional specification. Statistical Methods in Medical Research 16(3):219–242.

258. White IR, Royston P, Wood AM 2011 Multiple imputation using chained equations: Issues and guidance for practice. Statistics in Medicine 30:377–399.

259. Buuren S, Groothuis-Oudshoorn K 2011 MICE: multivariate imputation by chained equations in R. Journal of Statistical Software. 2011;45(3). Available at: http://doc.utwente.nl/78938/. Accessed September 8, 2012.

260. Zeger SL, Liang K-Y 1986 Longitudinal Data Analysis for Discrete and Continuous Outcomes.Biometrics 42(1):121–130.

261. Yelland LN, Salter AB, Ryan P 2011 Performance of the modified Poisson regression approach for estimating relative risks from clustered prospective data. Am. J. Epidemiol 174(8):984–992.

258. Zou G 2004 A modified poisson regression approach to prospective studies with binary data.Am. J. Epidemiol 159:702–706.

259. Zou GY, Donner A 2011 Extension of the modified Poisson regression model to prospective studies with correlated binary data. Stat Methods Med Res. 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22072596. Accessed March 1, 2012.

260. Hall DB 2000 Zero-inflated Poisson and binomial regression with random effects: a case study. Biometrics 56(4):1030–1039.

261. Harada ND, Chiu V, Stewart AL 1999 Mobility-related function in older adults: assessment with a 6-minute walk test. Arch Phys Med Rehabil 80:837-841. PMID: 10414771

262. Jylha M, Guralnik JM, Balfour J, Fried LP 2001 Walking difficulty, walking speed, and age as predictors of self-rated health: the women's health and aging study. J Gerontol A Biol Sci Med Sci 56:M609-617. PMID: 11584033

263. Melzer D, Lan TY, Guralnik JM 2003 The predictive validity for mortality of the index of mobility-related limitation--results from the EPESE study. Age and ageing 32:619-625. PMID: 14600003

264. Newman AB, Simonsick EM, Naydeck BL, Boudreau RM, Kritchevsky SB, Nevitt MC, Pahor M, Satterfield S,

Brach JS, Studenski SA, Harris TB. Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability.JAMA. 2006 May 3;295(17):2018-26.

265. Kennedy DM, Stratford PW, Wessel J, Gollish JD, Penney D 2005 Assessing stability and change of four performance measures: a longitudinal study evaluating outcome following total hip and knee arthroplasty. BMC musculoskeletal disorders 6:3. PMID: 15679884

266. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH 1997 Interpreting small differences in functional status: the Six Minute Walk test in chronic lung disease patients. American journal of respiratory and critical care medicine 155:1278-1282. PMID: 9105067

267. Perera S, Mody SH, Woodman RC, Studenski SA 2006 Meaningful change and responsiveness in common physical performance measures in older adults. J Am Geriatr Soc 54:743-749. PMID: 16696738

268. Margaria R, Aghemo P, Rovelli E 1966 Measurement of muscular power (anaerobic) in man. J Appl Physiol 21:1662-1664. PMID: 5923240

269. Heymsfield SB, Smith R, Aulet M, Bensen B, Lichtman S, Wang J, Pierson RN, Jr. 1990 Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry. Am J Clin Nutr 52:214-218. PMID: 2375286

270. Heymsfield SB, Wang J, Lichtman S, Kamen Y, Kehayias J, Pierson RN, Jr. 1989 Body composition in elderly subjects: a critical appraisal of clinical methodology. Am J Clin Nutr 50:1167-1175; discussion 1231-1165. PMID: 2683725

271. Kim J, Wang Z, Heymsfield SB, Baumgartner RN, Gallagher D 2002 Total-body skeletal muscle mass: estimation by a new dual-energy X-ray absorptiometry method. Am J Clin Nutr 76:378-383. PMID: 12145010

272. Wang ZM, Pierson RN, Jr., Heymsfield SB 1992 The five-level model: a new approach to organizing body-composition research. Am J Clin Nutr 56:19-28. PMID: 1609756

273. Silva AM, Shen W, Wang Z, Aloia JF, Nelson ME, Heymsfield SB, Sardinha LB, Heshka S 2004 Three-compartment model: critical evaluation based on neutron activation analysis. Am J Physiol Endocrinol Metab 287:E962-969. PMID: 15186997

274. Schoeller DA, Tylavsky FA, Baer DJ, Chumlea WC, Earthman CP, Fuerst T, Harris TB, Heymsfield SB, Horlick M, Lohman TG, Lukaski HC, Shepherd J, Siervogel RM, Borrud LG 2005 QDR 4500A dual-energy X-ray absorptiometer underestimates fat mass in comparison with criterion methods in adults. Am J Clin Nutr 81:1018-1025. PMID: 15883424

275. Soriano JM, Ioannidou E, Wang J, Thornton JC, Horlick MN, Gallagher D, Heymsfield SB, Pierson RN 2004 Pencil-beam vs fan-beam dual-energy X-ray absorptiometry comparisons across four systems: body composition and bone mineral. J Clin Densitom 7:281-289. PMID: 15319498

276. Cooper, CB and Storer, TW 2001 Exercise testing and Interpretation: a Practical Approach. Cambridge, UK. Cambridge University Press.

277. Buchfuhrer MJ, Hansen JE, Robinson TE, Sue DY, Wasserman K, Whipp BJ 1983 Optimizing the exercise protocol for cardiopulmonary assessment. J Appl Physiol 55:1558-64. PMID: 1264567

278. Casaburi R, Storer TW, Ben-Dov I, Wasserman K 1987 Effect of endurance training on possible determinants of VO2 during heavy exercise. . J Appl Physiol 62:199-207. PMID: 2397864

279. Forster HV DJ, Thomson J, Vidruk E, DoPico GA 1972 Estimation of arterial PO2, PCO2, pH, and lactate from arterialized venous blood. J Appl Physiol 32(1):134-7.

280. Wasserman K, Hansen JE, Sue DY, Stringer WW, Sietzema K, Sun X-G, Whipp, BJ 2012 Principles of Exercise

Testing and Interpretation. 5th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins. 2012.

281. Pescatello LS, ed. 2012 ACSM's Guidelines for Exercise Testing and Prescription. 9th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins.

282. ATS/ACCP Statement on Cardiopulmonary Exercise Testing. Am J Respir Crit Care Med Vol 167. pp 211–277, 2003.

283. Ickovics JR, Meisler AW. Adherence in AIDS clinical trials: A framework for clinical research and clinical practice. J Clin Epidemiol 1997;50:385-391. PMID: 9179096

284. Miller L, Hays RD 2000 Measures of adherence to antiretroviral drugs in clinical trials. HIV Clinical Trials 2000; 1:36-46. PMID: 11590488

285. Davis LL, Broome ME, Cox RP. Maximizing retention in community-based clinical trials. Journal of Nursing Scholarship. 2002; 34:47-53 PMID: 11901967

286. Wilcox S, Shumaker SA, Bowen DJ, Naughton MJ, Rosal MC, Ludlam SS, Dugan E, Hunt JR, Stevens S 2001 Promoting adherence and retention to clinical trials in special populations: A Women's Health Initiative Workshop. Controlled Clinical Trials 22:279-28. PMID: 11384790

287. McDonald AM, Treweek S, Shakur H, Free C, Knight R, Speed C, Campbell MK 2011 Using a business model approach and marketing techniques for recruitment and retention to clinical trials.Trials. 11;12:74. PMID: 21396088

288. Campbell MK, Snowdon C, Francis D, Elbourne D, McDonald AM, Knight R, Entwistle V, Garcia J, Roberts I, Grant A, Grant A; STEPS group 2007 Recruitment to randomised trials: strategies for trial enrollment and participation study. The STEPS study.Health Technol Assess 11:iii, ix-105. PMID: 17999843

289. Treweek S, Pitkethly M, Cook J, Kjeldstrøm M, Taskila T, Johansen M, Sullivan F, Wilson S, Jackson C, Jones R, Mitchell E 2010. Strategies to improve recruitment to randomised controlled trials.Cochrane Database Syst Rev MR000013. PMID: 23396504

290. Reddy P, White CM, Dunn AB, Moyna NM, Thompson PD 2000 The effect of testosterone on health-related quality of life in elderly males - a pilot study. Journal of clinical pharmacy and therapeutics 25:421-426. PMID: 11123495

291. Brock G, Heiselman D, Maggi M, Kim SW, Rodríguez Vallejo JM, Behre HM, McGettigan J, Dowsett SA, Hayes RP, Knorr J, Ni X, Kinchen K.2015Effect of Testosterone Solution 2% on Testosterone Concentration, Sex Drive and Energy in Hypogonadal Men: Results of a Placebo Controlled Study. J Urol. (15)05023-5 [Epub ahead of print]. PMID: 26498057

292. Hayes RP, Henne J, Kinchen KS2015Establishing the content validity of the Sexual Arousal, Interest, and Drive Scale and the Hypogonadism Energy Diary. International Journal of Clinical Practice.69(4):454-65. PMID: 25382263

293. Cohen DR, Todd S, Gregory WM, Brown JM. Adding a treatment arm to an ongoing clinical trial: a review of methodology and practice. Trials. 2015 Apr 22;16:179. PMID: 25897686

294. Elm JJ, Palesch YY, Koch GG, Hinson V, Ravina B, Zhao W. Flexible analytical methods for adding a treatment arm mid-study to an ongoing clinical trial. J Biopharm Stat. 2012;22(4):758-72. PMID: 22651113

DFCI IRB Protocol #: 15-120

APPENDIX A

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

APPENDIX A-TABLE OF CONTENTS

1. INTRODUCTION

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: Brigham and Women's Hospital (BWH))

DF/HCC Sponsor: Shalender Bhasin, MD

Participating Institutions: Johns Hopkins Medical Institute and the University of Florida

Supporting Referral Site to BWH: Beth Israel Deaconess Medical Center

Coordinating Center: Brigham and Women's Hospital

DF/HCC Office of Data Quality: ODQ

2. GENERAL ROLES AND RESPONSIBILITIES

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, Shalender Bhasin, MD accepts responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC, NINR, and FDA reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA (investigator-held IND trials)

- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence.
- Review registration materials for eligibility and register participants from Participating Institutions with DF/HCCODQ.
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
  Conduct regular communications with all Participating Institutions (conference calls, emails, etc) with relevant documentation maintained.

2.3 Participating Institution

The Johns Hopkins Medical Institute and the University of Florida are expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities of the Participating Institution include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per local requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.

- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

Participating Institutions will send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members or responsible study members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent to interventional trials (i.e. drug and/or device trials).

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution's IRB.
- Participating Institution's IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not receive from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information. Subject confidentiality will be maintained except as may be required by law. All identifying information will be kept in a secure area at all times. Consent form(s) will be maintained in a separate folder from original Case Report Forms at the conclusion of the study. Only de-identified data will be used for analyses.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports submitted to the Coordinating Center should be de-identified. It is recommended that the assigned DF/HCC ODQ case number be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 Participant Registration and Randomization

The following documents will be completed by the Participating Institution and e-mailed to the Coordinating Center, Maricelle Ramirez (mramirez5@partners.org)

- Copy of required laboratory tests including: **CBC, PSA, chemistry panel, TSH, total and free testosterone**
- Copy of the signed informed consent document (original to remain on site)
- HIPAA authorization form (if separate from the informed consent document)

- Other appropriate forms: Eligibility Screening Worksheet, Registration form

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC ODQ
- Upon receiving confirmation of registration by the ODQ, the Coordinating Center will inform the Participating Institution and provide the study specific participant case number. The QACT will communicate the treatment assignment directly to the site's research pharmacy.

Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.

- It should be noted that subjects referred through BIDMC to BWH will be registered via the BWH registration procedures.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC ODQ before receiving treatment. Treatment may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

The DF/HCC ODQ will make no exceptions to the eligibility requirements for randomized trials.

3.8 DF/HCC Protocol Case Number

At the time of registration, ODQ requires the following identifiers for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.8.1 Protocol Deviations, Exceptions and Violations

The site investigators are not allowed to initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. Any departure from the defined procedures set forth in the IRB approved protocol must be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

3.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.8.3 Reporting Procedures

DF/HCC Sponsor, Shalender Bhasin, MD, is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission.

All protocol violations must be sent to the Coordinating Center in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

3.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include complete blood counts, blood chemistries, PSA, periodic physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in the Data and Safety Monitoring Plan (appended to this document).

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB

Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

3.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.10 Data Management

The trial's Data Coordinating Center in collaboration with the study team will develop case report forms (CRF), for use with the protocol. These forms are designed to collect data for each study. Each institution is responsible for its own data quality and review.

Data is required to be entered within 14 days of data collection.

4. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol section 8.0.

5. MONITORING: QUALITY CONTROL

The Coordinating Center, with the aid of the ODQ provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring will occur during protocol performance and through study completion. Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol departures, pharmacy records, response assessments, and data management.

Monitoring will occur every 6 months during the first year and then annually. Additional monitoring may occur at the discretion of the DF/HCC Sponsor if incidences of non-compliance are discovered.

Participating institutions will be required to participate in monthly Coordinating Center initiated teleconferences.

Source documentation verification (SDV) will be conducted by having access to participants' complete study records and source documents.

5.2 Monitoring Reports

The DF/HCC Sponsor, Shalender Bhasin, MD, will review all monitoring reports for on-site and remote monitoring of Participating Institutions to ensure protocol compliance. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Each site will accrue at least 3 subjects per year. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

6. AUDITING: QUALITY ASSURANCE

6.1 Audit Plan: NCI Sponsored Trials

Not applicable

6.2 Audit Plan: DF/HCC Sponsored Trials

One on-site audit will be scheduled by the ODQ, assuming at least three participants have been treated on protocol at the site. Approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.3 Audit Notification

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.4 Audit Reports

The DF/HCC Sponsor, Shalender Bhasin, MD, will review all final audit reports and corrective action plans if applicable. The Coordinating Center, will forward these reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the DF/HCC Sponsor to implement recommendations or require further follow-up. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.5 Participating Institution Performance

The DF/HCC Sponsor is charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

6.5.1 Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation

of participation. A DF/HCC Sponsor may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.

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APPENDIX B- NINR Data and Safety Monitoring Plan

DATA AND SAFETY MONITORING PLAN
1RO1NR014502-01A1, PI: Bhasin, Shalender

The Data and Safety Monitoring Plan (DSMP) for this trial, described below, will be reviewed and approved by the NINR staff prior to the commencement of any human subjects activities in this trial. The DSMP approved by the NINR staff will then be submitted to the local IRB for its review and approval. It is understood that the IRB approval of the NINR-approved DSMP is required before human subjects activities can take place within the trial, and that the awardee institution is responsible for approving the DSMB.
The responsibility for compliance with the DSMP rests with the PI. The oversight of the monitoring activity described in the DSMP is the responsibility of the NINR staff. NINR will be notified within 7 days if the human subjects research or DSMP is changed prior to or during the implementation of the clinical trial. The NINR program staff must approve the changes prior to implementation.

The essential components of the DSM Plan are the following:

a. A Data and Safety Monitoring Board (DSMB), an independent committee charged with reviewing safety and trial progress and providing advice with respect to study continuation, modification, and termination, will assume oversight of the study, in accordance with NINR policy, once the study is underway. The procedures that will be used for data and safety monitoring are outlined below.

b. The DSMB will include <u>five individuals,</u> including a chair and a separate executive secretary. All five members will be voting members. The DSMB members will have expertise in prostate cancer, androgen biology, biostatistical analysis of clinical trials data, and the conduct and oversight of clinical trials in prostate cancer patients. These individuals will be approved by the institutional review board for human subjects research (IRB) after review of their expertise and potential conflicts of interest. The composition of the DSMB will consist of the following:

- Two nationally or internationally recognized experts in prostate cancer and clinical trials of men with prostate cancer
- An expert with nursing background and experience in symptom management including fatigue and other outcomes being assessed in this trial
- An endocrinologist with expertise in clinical trials of androgens in men
- A biostatistician with expertise in the design and analysis of clinical trials

<u>Safety Review Procedures:</u>

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

2.) Generation of safety reports. The Study's PI, with the assistance of the Data Management Center (DMC) will prepare and submit the safety reports for DSMB review, This will be done in a blinded fashion, while protecting the confidentiality of participant data. The reports will be given to an independent third party who will add a code (A, B, or C) to the data for each treatment group. The third party will place the finished report into an envelope, seal the envelope and sign across the seal.

He/she will place this envelope containing the coded safety report into Fed Ex envelopes, pre-prepared by the research coordinators, and seal those. The reports will be sent, by Fed Ex, to the various DSMB members. This will allow the DSMB to review the safety data by individual treatment groups. The third party will store, in a locked cabinet, the code for the trial. In the event that the DSMB requests unblinding of the study, the code will be sent from the third party directly to the DSMB. Thus, the DSMB members can have access to the categorized data, while the investigating team remains blinded.

3.) Review of all adverse events will be performed by treatment group (coded A, B, or C).

4.) Each safety 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 NIH, FDA, and 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 also be provided to the DSMB members. The summary of all adverse events will allow for a comprehensive overview or analysis 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 patients cannot be identified.

5.) Each DSMB meeting will be comprised of 2 portions. Research personnel will arrange and be present for the "open discussions" at the start of the DSMB meetings. The initial "open" portion of the meeting will have study personnel available to give a brief update on the status of the trial 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 have independent deliberations. Provisions will be made for study personnel to be available to the DSMB committee during these deliberations, should their input be required.

6.) In addition to these review procedures the DSMB will receive copies of all serious adverse events, with study group assignment (A or B), as they occur.

Transmission of DSMB Recommendations and Summary Reports of Adverse Events to IRBs
A summary of the DSMB review and recommendations without treatment assignment information will be sent to the Principal Investigator after each DSMB meeting. The PI will then forward the DSMB report, including the DSMB's assessment of adverse events within the trial, to the IRBs of the participating institutions.
Transmission of Summary of Closed Deliberations to the NINR Staff

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

Procedures for monitoring study safety:

1. Monitoring schedule
   a. Adverse events are solicited and recorded by study staff at each study visit.
   b. PSA is measured at screening and weeks 2, 4, 6, and 12.
   c. Other safety labs – complete blood counts and chemistries – are measured at screening, baseline and during weeks 6 and 12.
2. Auditing of selected cases for compliance with IRB requirements, conformance with informed consent requirements, verification of source documents, and investigator compliance will be performed by Brigham and Women's Hospital's institutional compliance officer annually.

3. Procedures for minimizing research-associated risk.

All subjects will be monitored by frequent physical examinations, blood counts, chemistries and PSA levels. We will follow hematocrit, 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. The subjects will be instructed in proper technique and the risks minimized by careful supervision. Patients will be screened with cardiopulmonary exercise testing with continuous monitoring of the ECG to rule out cardiac ischemia and serious arrhythmias. This test will be administered and supervised according to current American Heart Association guidelines[1]. The likelihood of musculoskeletal injury from exercise testing will be minimized by providing a warm-up period preceding each exercise session including low speed treadmill walking and stretching exercises. Further, a certified exercise physiologist will oversee all exercise testing sessions.

The risks of SARM therapy will be minimized by close monitoring with serial physical examinations, 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 selection of LY SARM, which not only spares the prostate but has been shown in preclinical models to act as an androgen antagonist on the prostate, induce prostate atrophy in a canine model, inhibit the growth of prostate cancer explants in mice, and lower PSA in men.
b. The inclusion and exclusion criteria will assure selection of subjects at very low risk of disease recurrence.
c. We have established rigorously defined criteria for biochemical recurrence and for progression from stage 1.
d. We have established *a priori* stopping rules based on PSA change.
e. We will perform frequent PSA measurements to ensure early detection of biochemical recurrence.
f. We will designate study clinicians to monitor PSA and other laboratory tests at each site.
g. An independent DSMB will oversee the study after its initiation

Protecting the confidentiality of participant data

Subject confidentiality will be maintained except as may be required by law. All identifying information will be kept in a secure area at all times. Consent form(s) will be maintained in a separate folder from original Case Report Forms at the conclusion of the study. Only de-identified data will be used for analyses.

Procedures for identifying, reviewing, and reporting of adverse events and unanticipated problems to the IRB, NINR, and FDA

The adverse events will be identified by the study staff and reviewed by a study physician on an ongoing basis. Serious adverse events will be reported by the study PI to the DSMB Chair, FDA and NINR staff. Unanticipated problems will be reported to the DSMB, IRB, FDA, and NINR staff by the study's PI.

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 hematocrit above 54%, if confirmed by a repeated test, would warrant discontinuation of treatment.
- Transaminase elevation above 3 times the upper limit of normal, if confirmed by a repeated test, 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.

Procedures ensuring compliance with the monitoring plan and reporting requirements across sites

As this is a three-site study, a study monitor will visit each of the three sites to monitor compliance with the study protocol, monitoring plan, and reporting requirements. These visits will take place every 6 months in the first year and then annually.

An assessment of external factors or relevant information that may have an impact on safety of the participants or on the ethics of the study.

The study team will provide this assessment to the DSMB (6-monthly) and IRB (annual) reports.

Interim or Futility Analysis

There are no plans for an interim or futility analysis.

Additional Components of the DSM Plan
The PI will provide reporting to the NINR staff of the following. All personal identifiers will be removed from any documents sent to NINR staff.

1. Unanticipated problems or unexpected serious adverse events that may be related to the study protocol
2. IRB-approved revisions to the study protocol that indicate a change in risks to the participants
3. A summary of recommendations made by the DSMB and if applicable, an action plan for response
4. Notice of any actions taken by the IRB or regulatory bodies regarding the research and any responses to those actions

REFERENCES

Myers J, Forman DE, Balady GJ, Franklin BA, Nelson-Worel J, Martin BJ, Herbert WG, Guazzi M, Arena R 2014, Sept 16. Supervision of exercise testing by nonphysicians: a scientific statement from the American Heart Association. American Heart Association Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention of the Council on Clinical Cardiology, Council on Lifestyle and Cardiometabolic Health, Council on Epidemiology and Prevention, and Council on Cardiovascular and Stroke Nursing. 130 (12): 1014-1027. PMID: 25223774

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APPENDIX C- Study Questionnaires

FACIT Fatigue Questionnaire

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

IIEF Questionnaire

INSTRUCTIONS: These questions ask about your sex life over the past 4 weeks. Please answer the following questions as honestly and clearly as possible. In answering these questions, the following definitions apply:

Sexual activity includes intercourse, caressing, foreplay, masturbation, or any other types of sex
Sexual intercourse is defined as penetration of the partner (you entered your partner)
Sexual stimulation includes situations like foreplay with a partner, looking at erotic pictures, etc.
Ejaculate the ejection of semen from the penis (or the feeling of this)

Circle ONLY one answer (number) per question.

Q1) Over the past 4 weeks, how often were you able to get an erection during sexual activity?

0 = No sexual activity
1 = Almost never / never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always / always

Q2) Over the past 4 weeks, when you had erections with sexual stimulation, how often were your erections hard enough for penetration?

0 = No sexual activity
1 = Almost never / never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always / always

Q3) Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?

0 = Did not attempt intercourse
1 = Almost never / never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always / always

Q4) Over the past 4 weeks, during sexual intercourse, *how often* were you able to maintain your erection after you had penetrated (entered) your partner?.

0 = Did not attempt intercourse

1 = Almost never / never

2 = A few times (much less than half the time)

3 = Sometimes (about half the time)

4 = Most times (much more than half the time)

5 = Almost always / always

Q5) Over the past 4 weeks, during sexual intercourse, *how difficult* was it to maintain your erection to completion of intercourse?

0 = Did not attempt intercourse

1 = Extremely difficult

2 = Very difficult

3 = Difficult

4 = Slightly difficult

5 = Not difficult

Q6) Over the past 4 weeks, how many times have you attempted sexual intercourse?

0 = No attempts

1 = One to two attempts

2 = Three to four attempts

3 = Five to six attempts

4 = Seven to ten attempts

5 = Eleven+ attempts

Q7) Over the past 4 weeks, when you attempted sexual intercourse, how often was it satisfactory for you?

0 = Did not attempt intercourse

1 = Almost never / never

2 = A few times (much less than half the time)

3 = Sometimes (about half the time)

4 = Most times (much more than half the time)

5 = Almost always / always

Q8) Over the past 4 weeks, when you attempted sexual intercourse, how much have you enjoyed sexual intercourse?

0 = No intercourse

1 = No enjoyment

2 = Not very enjoyable

3 = Fairly enjoyable

4 = Highly enjoyable

5 = Very highly enjoyable

Q9) Over the past four weeks, when you had sexual stimulation *or* intercourse, how often did you ejaculate?

0 = No sexual stimulation / intercourse

1 = Almost never / never

2 = A few times (much less than half the time)

3 = Sometimes (about half the time)

4 = Most times (much more than half the time)

5 = Almost always / always

Q10) Over the past 4 weeks, when you had sexual stimulation *or* intercourse, how often did you have the feeling of orgasm or climax?

0 = No sexual stimulation / intercourse

1 = Almost never / never

2 = A few times (much less than half the time)

3 = Sometimes (about half the time)

4 = Most times (much more than half the time)

5 = Almost always / always

Q11) Over the past 4 weeks, how often have you felt sexual desire?

1 = Almost never / never

2 = A few times (much less than half the time)

3 = Sometimes (about half the time)

4 = Most times (much more than half the time)

5 = Almost always / always

Q12) Over the past 4 weeks, how would you rate your level of sexual desire?

1 = Very low / not at all

2 = Low

3 = Moderate

4 = High

5 = Very high

Q13) Over the past 4 weeks, how satisfied have you been with your overall *sex life*?

1 = Very dissatisfied

2 = Moderately dissatisfied

3 = About equally satisfied and dissatisfied

4 = Moderately satisfied

5 = Very satisfied

Q14) Over the past 4 weeks, how satisfied have you been with your *sexual relationship* with your partner?

1 = Very dissatisfied

2 = Moderately dissatisfied

3 = About equally satisfied and dissatisfied

4 = Moderately satisfied

5 = Very satisfied

Q15) Over the last 4 weeks, how would you rate your *confidence* that you could get and keep an erection?

1 = Very low

2 = Low

3 = Moderate

4 = High

5 = Very high

IPSS - International Prostate Symptom Score

Put an X in the box (beside the number) that most closely corresponds to your response for each question.

1.) Incomplete emptying: Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

2.) Frequency: Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

3.) Intermittency: Over the last month, how often have you found that you stopped and started again several times when you urinated?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

4.) Urgency: Over the last month, how difficult have you found it to postpone urination?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

5.) Weak-stream: Over the past month, how often have you had a weak urinary stream?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

6.) Straining: Over the past month, how often have you had to push or strain to begin urination?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

7.) Nocturia: Over the past month, how many times did you typically get up to urinate from the time you went to bed until the time you got up in the morning?

1 time	2 times	3 times	4 times	5 times
1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

8.) Quality of life due to urinary symptoms	Delighted	Pleased	Mostly satisfied	Mixed – about equally satisfied and dissatisfied	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Subject initials and Date: _____

FOR STUDY STAFF ONLY

Total Score_____

Note: Only score questions 1-7

1-7 mildly symptomatic; 8-19 moderately symptomatic; 20-35 severely symptomatic.

EPIC

The Expanded Prostate Cancer Index Composite

This questionnaire is designed to measure Quality of Life issues in patients with Prostate cancer. To help us get the most accurate measurement, it is important that you answer all questions honestly and completely.

Remember, as with all medical records, information contained within this survey will remain strictly confidential.

Today's Date (please enter date when survey completed): Month___Day_____Year_____

Study ID: _____

Do Not Mark in This Space

URINARY FUNCTION

This section is about your urinary habits. Please consider **ONLY THE LAST 4 WEEKS**.

1. Over the **past 4 weeks**, how often have you leaked urine?

   More than once a day 1
   About once a day 2
   More than once a week..... 3 (Circle one number) 23/
   About once a week.....4
   Rarely or never..... 5

2. Over the **past 4 weeks**, how often have you urinated blood?

   More than once a day 1
   About once a day 2
   More than once a week..... 3 (Circle one number) 24/
   About once a week 4
   Rarely or never 5

3. Over the **past 4 weeks**, how often have you had pain or burning with urination?

   More than once a day 1
   About once a day 2
   More than once a week..... 3 (Circle one number) 25/
   About once a week 4
   Rarely or never 5

4. Which of the following best describes your urinary control **during the last 4 weeks**?

   No urinary control whatsoever 1
   Frequent dribbling.....2 (Circle one number) 26/
   Occasional dribbling..... 3
   Total control..... 4

5. How many pads or adult diapers per day did you usually use to control leakage
   1. **during the last 4 weeks**?

None	0		
1 pad per day.....	1		
2 pads per day.....	2	(Circle one number)	
3 or more pads per day.....	3		27/

6. How big a problem, if any, has each of the following been for you **during the last 4 weeks**?

(Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Dripping or leaking urine ….....	0	1	2	3	4	28/
b. Pain or burning on urination.....	0	1	2	3	4	29/
c. Bleeding with urination.....	0	1	2	3	4	30/
d. Weak urine stream or incomplete emptying……..	0	1	2	3	4	31/
e. Waking up to urinate……..	0	1	2	3	4	32/
f. Need to urinate frequently during the day ……..	0	1	2	3	4	33/

7. Overall, how big a problem has your urinary function been for you **during the last 4 weeks**?

No problem.....	.1		
Very small problem.....	.2		
Small problem.....	3	(Circle one number)	34/
Moderate problem.	.4		
Big problem	.5		

BOWEL HABITS

The next section is about your bowel habits and abdominal pain. Please consider **ONLY THE LAST 4 WEEKS**.

8. How often have you had rectal urgency (felt like I had to pass stool, but did not) **during the last 4 weeks**?

More than once a day	1	
About once a day	2	
More than once a week	3 (Circle one number)	42/
About once a week	4	
Rarely or never	5	

9. How often have you had uncontrolled leakage of stool or feces?

More than once a day	1	
About once a day	2	
More than once a week	3 (Circle one number)	43/
About once a week	4	
Rarely or never	5	

10. How often have you had stools (bowel movements) that were loose or liquid (no form, watery, mushy) **during the last 4 weeks**?

Never	1	
Rarely	2	
About half the time	3 (Circle one number)	44/
Usually	4	
Always	5	

11. How often have you had bloody stools **during the last 4 weeks**?

Never.	1	
Rarely	2	
About half the time	3 (Circle one number)	45/
Usually	4	
Always	5	

Do Not Mark in This Space

12. How often have your bowel movements been painful **during the last 4 weeks**?

Never. 1
Rarely.....2
About half the time..... 3 (Circle one number) 46/
Usually.....4
Always 5

13. How many bowel movements have you had on a typical day **during the last 4 weeks**?

Two or less.....1
Three to four.....2 (Circle one number) 47/
Five or more 3

14. How often have you had crampy pain in your abdomen, pelvis or rectum **during the last 4 weeks**?

More than once a day.....1
About once a day 2
More than once a week..... 3 (Circle one number) 48/
About once a week.....4
Rarely or never..... 5

15. How big a problem, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Urgency to have a bowel movement	0	1	2	3	4	49/
b. Increased frequency of bowel movements.....	0	1	2	3	4	50/
c. Watery bowel movements.....	0	1	2	3	4	51/
d. Losing control of your stools.....	0	1	2	3	4	52/
e. Bloody stools	0	1	2	3	4	53/
f. Abdominal/ Pelvic/Rectal pain...	0	1	2	3	4	54/

16. Overall, how big a problem have your bowel habits been for you **during the last 4 weeks**?

No problem..... 1
Very small problem..... 2
Small problem..... 3 (Circle one number) 55/
Moderate problem. 4
Big problem 5

SEXUAL FUNCTION

The next section is about your **current** sexual function and sexual satisfaction. Many of the questions are very personal, but they will help us understand the important issues that you face every day. Remember, THIS SURVEY INFORMATION IS COMPLETELY **CONFIDENTIAL**. Please answer honestly about **THE LAST 4 WEEKS ONLY**.

17. How would you rate each of the following during the last 4 weeks? (Circle one number on each line)

	Very Poor to None	Poor	Fair	Good	Very Good	
a. Your level of sexual desire?	1	2	3	4	5	56/
b. Your ability to have an erection?	1	2	3	4	5	57/
c. Your ability to reach orgasm (climax)?	1	2	3	4	5	58/

18. How would you describe the usual QUALITY of your erections **during the last 4 weeks**?

None at all..... 1
Not firm enough for any sexual activity..... 2
Firm enough for masturbation and foreplay only..... 3 (Circle one number) 59/
Firm enough for intercourse..... 4

19. How would you describe the FREQUENCY of your erections **during the last 4 weeks**?

I NEVER had an erection when I wanted one..... 1
I had an erection LESS THAN HALF the time I wanted one..... 2
I had an erection ABOUT HALF the time I wanted one ..... 3 (Circle one number) 60/
I had an erection MORE THAN HALF the time I wanted one..... 4
I had an erection WHENEVER I wanted one..... 5

20. How often have you awakened in the morning or night with an erection **during the last 4 weeks**?

Never …..... 1
Less than once a week..... 2
About once a week..... 3 (Circle one number) 61/
Several times a week..... 4
Daily……..... 5

21. **During the last 4 weeks**, how often did you have <u>any</u> sexual activity?

Not at all	1		
Less than once a week	2		
About once a week	3	(Circle one number)	62/
Several times a week	4		
Daily	5		

22. **During the last 4 weeks**, how often did you have sexual intercourse?

Not at all	1		
Less than once a week	2		
About once a week	3	(Circle one number)	63/
Several times a week	4		
Daily	5		

23. Overall, how would you rate your ability to function sexually **during the last 4 weeks**?

Very poor	1		
Poor	2		
Fair	3	(Circle one number)	64/
Good	4		
Very good	5		

24. How big a problem **during the last 4 weeks**, if any, has each of the following been for you?

(Circle one number on each line)

	<u>No Problem</u>	<u>Very Small Problem</u>	<u>Small Problem</u>	<u>Moderate Problem</u>	<u>Big Problem</u>	
a. Your level of sexual desire.....	0	1	2	3	4	65/
b. Your ability to have an erection.	0	1	2	3	4	66/
c. Your ability to reach an orgasm.	0	1	2	3	4	67/

25. Overall, how big a problem has your sexual function or lack of sexual function been for you **during the last 4 weeks**?

No problem	1		
Very small problem	2		
Small problem	3	(Circle one number)	68/
Moderate problem	4		
Big problem	5		

HORMONAL FUNCTION

The next section is about your hormonal function. Please consider **ONLY THE LAST 4 WEEKS**.

26. **Over the last 4 weeks,** how often have you experienced hot flashes?

More than once a day.....1
About once a day 2
More than once a week..... 3 (Circle one number) 69/
About once a week.....4
Rarely or never.....5

27. How often have you had breast tenderness **during the last 4 weeks**?

More than once a day.....1
About once a day 2
More than once a week..... 3 (Circle one number) 70/
About once a week.....4
Rarely or never.....5

28. **During the last 4 weeks,** how often have you felt depressed?

More than once a day.....1
About once a day 2
More than once a week..... 3 (Circle one number) 71/
About once a week.....4
Rarely or never.....5

29. **During the last 4 weeks,** how often have you felt a lack of energy?

More than once a day.....1
About once a day 2
More than once a week..... 3 (Circle one number) 72/
About once a week.....4
Rarely or never.....5

30. How much change in your weight have you experienced **during the last 4 weeks**, if any?

Gained 10 pounds or more……..1
Gained less than 10 pounds …..…….2
No change in weight……. ….…….. 3 (Circle one number) 73/
Lost less than 10 pounds …..…….….4
Lost 10 pounds or more…….…..……5

31. How big a problem **during the last 4 weeks**, if any, has each of the following been for you?

(Circle one number on each line)

		No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a.	Hot flashes…….....	0	1	2	3	4	74/
b.	Breast tenderness/enlargement..	0	1	2	3	4	75/
c.	Loss of Body Hair...….....	0	1	2	3	4	76/
d.	Feeling depressed..….....	0	1	2	3	4	77/
e.	Lack of energy.....….....	0	1	2	3	4	78/
f.	Change in body weight	0	1	2	3	4	79/

Overall Satisfaction

32. Overall, how satisfied are you with the treatment you received for your prostate cancer?

Extremely dissatisfied.....1
Dissatisfied.....2
Uncertain..... 3 (Circle one number) 80/
Satisfied 4
Extremely satisfied 5

THANK YOU VERY MUCH!!

Men's Sexual Health Questionnaire (MSHQ)

INTRODUCTION: These next questions ask about your urge or desire to have sex with **your MAIN PARTNER**. Some people refer to this as "feeling horny". In answering these questions, we only want to know about the sexual urges you have felt toward your MAIN PARTNER, and not whether you actually had sex. Some of these questions might be difficult to answer, but we would appreciate you being as honest as possible. Remember, all of your answers are confidential.

Do you have a "MAIN PARTNER"? __ Yes __ No
IF YOU DO NOT HAVE A MAIN PARTNER, PLEASE ANSWER ALL QUESTIONS WITHOUT THE REFERENCE TO "MAIN PARTNER" UNLESS OTHERWISE DIRECTED.

1. **In the last month,** how often have you felt an urge or desire to have sex with your MAIN PARTNER?

Would you say (Check only one):
__ All of the time
__ Most of the time
__ About half of the time
__ Less than half of the time
__ None of the time

2. **In the last month,** how would you rate your urge or desire to have sex with your MAIN PARTNER?

(Check only one)
__ Very high
__ High
__ Moderate
__ Low
__ Very low or none at all

3. **In the last month,** have you been bothered by your level of sexual desire?

Have you been… (Check only one):
__ Not at all bothered
__ A little bit bothered
__ Moderately bothered
__ Very bothered
__ Extremely bothered

4. Compared to **ONE month ago,** has your urge or desire for sex with your MAIN PARTNER increased or decreased?

Has it… (Check only one):
__ Increased a lot
__ Increased moderately
__ Neither increased nor decreased
__ Decreased moderately
__ Decreased a lot

INTRODUCTION: The next set of questions asks about the sexual activity you have had **in the last month**. In answering these questions, we want to know about all of the sexual activity you have had with your MAIN PARTNER, with other partners, or masturbating. By sexual activity, we mean any type of sex you may have had, including intercourse, oral sex, or any other sexual activities that could lead to ejaculation or cumming.

5. **In the last month,** how often have you had sexual activity, including masturbating, intercourse, oral sex, or any other type of sex?

(Check only one):
__ 0 times per month
__ 1-3 times per month
__ 4-6 times per month
__ More than 6 times per month
__ Daily or almost daily

If your answer is "0" for item 5, please answer the following questions:

A. When was the last time you had sex? (Check only one)
__1-3 months ago
__ 4-6 months ago
__ 7-12 months ago
__ More than 1 year to 2 years ago
__ More than 2 years ago

B. What are the reasons you have not had sex?
- I could not have sex because I could not get an erection: __ Yes __ No
- I could not have sex because I could not ejaculate or "cum": __ Yes __ No
- I had no partner: __ Yes __ No

Other (specify): _____

6. Compared to **ONE month ago,** has the number of times you have had sexual activity increased or decreased?

Would you say it has… (Check only one):
__ Increased a lot
__ Increased moderately
__ Neither increased nor decreased
__ Decreased moderately
__ Decreased a lot

7. **In the last month,** have you been bothered by these changes in the number of times you have had sexual activity?

Have you been… (Check only one):
__ Not at all bothered
__ A little bit bothered
__ Moderately bothered
__ Very bothered
__ Extremely bothered

INTRODUCTION: These next questions deal with various aspects of your ability to have sex. In answering these questions, we want to know about all of the sexual activity you have had with your MAIN PARTNER, with other partners, or masturbating. By sexual activity, we mean any type of sex you may have had, including intercourse, oral sex, or any other sexual activities that could lead to ejaculation or cumming. Some of these questions might be difficult to answer. We hope that you can answer as many of them as possible, and be as honest as possible when answering them. Please remember that all of your answers are confidential. First, we would like to ask you a few questions about your erections, which some people refer to as "hard-ons".

In the last month have you taken Viagra or any similar drugs for problems with your erection? __ Yes __ No

8. **In the last month,** without using drugs like Viagra, how often have you been able to get an erection when you wanted to?

Would you say… (Check only one):
__ All of the time
__ Most of the time
__ About half of the time
__ Less than half of the time
__ None of the time
__ Used Viagra or similar drug with every sexual encounter

9. **In the last month,** if you were able to get an erection without using drugs like Viagra, how often were you able to stay hard as long as you wanted to?

Would you say… (Check only one):
__ All of the time
__ Most of the time
__ About half of the time
__ Less than half of the time
__ None of the time
__ Used Viagra or similar drug with every sexual encounter

10. **In the last month,** if you were able to get an erection, without using drugs like Viagra, how would you rate the hardness of your erection?

Would you say they were… (Check only one):
__ Completely hard
__ Almost completely hard
__ Mostly hard, but can be slightly bent
__ A little hard, but bends easily
__ Not at all hard
__ Used Viagra or similar drug with every sexual encounter

11. **In the last month,** if you have had difficulty getting hard or staying hard without using drugs like Viagra, have you been bothered by this problem?…

(Check only one):
__ Not at all bothered/Did not have a problem with erection
__ A little bit bothered
__ Moderately bothered
__ Very bothered
__ Extremely bothered

INTRODUCTION: The next section deals with male ejaculation and the pleasure you have with ejaculation. Ejaculation or cumming is the release of semen or cum during sexual climax. In answering these questions, we want to know about all of your ejaculations when having sexual activity. These could include ejaculations you have had with your MAIN PARTNER, as well as with other partners, or ejaculations you could have had when masturbating.

12. **In the last month,** how often have you been able to ejaculate or cum when having sexual activity?

(Check only one)
__ All of the time
__ Most of the time
__ About half of the time
__ Less than half of the time
__ None of the time/Could not ejaculate

13. **In the last month,** when having sexual activity, how often have you felt like you were ejaculating or cumming but no fluid came out?

Would you say… (Check only one)
__ All of the time
__ Most of the time
__ About half of the time
__ Less than half of the time
__ None of the time
__ Could not ejaculate

14. **In the last month,** when having sexual activity, how often did you feel that you took too long to ejaculate or cum?

Would you say… (Check only one)
__ All of the time
__ Most of the time
__ About half of the time
__ Less than half of the time
__ None of the time
__ Could not ejaculate

15. **In the last month**, when having sexual activity, how often did you feel that you ejaculated or came faster than you would have wanted to?

(Check only one)
__ All of the time
__ Most of the time
__ About half of the time
__ Less than half of the time
__ None of the time
__ Could not ejaculate

16. Compared to **ONE month ago**, would you say the amount of time it takes from when you first start ejaculating or cumming to when you have stopped ejaculating or cumming has...

(Check only one)
__ Increased a lot
__ Increased moderately
__ Neither increased nor decreased
__ Decreased moderately
__ Decreased a lot
__ Could not ejaculate

17. Some men have a medical condition called retrograde ejaculation. Men with this condition say it feels like their ejaculation goes backwards into their bladder rather than out through their penis. **In the last month**, when having sexual activity, how often did you feel that your ejaculation or cum was going backwards?

Would you say… (Check only one)
__ All of the time
__ Most of the time
__ About half of the time
__ Less than half of the time
__ None of the time
__ Could not ejaculate

18. **In the last month,** how would you rate the strength or force of your ejaculation? Would you say it is…

(Check only one)
__ As strong as it always was
__ A little less strong than it used to be
__ Somewhat less strong than it used to be
__ Much less strong than it used to be
__ Very much less strong than it used to be
__ Could not ejaculate

19. **In the last month,** how would you rate the amount or volume of semen or fluid when you ejaculate?

Would you say it is… (Check only one)
__ As much as it always was
__ A little less than it used to be
__ Somewhat less than it used to be
__ Much less than it used to be
__ Very much less than it used to be
__ Could not ejaculate

20. **Compared to ONE month ago,** would you say the physical pleasure you feel when you ejaculate or cum has…

(Check only one)
__ Increased a lot
__ Increased moderately
__ Neither increased nor decreased
__ Decreased moderately
__ Decreased a lot
__ Could not ejaculate

21. **In the last month**, when having sexual activity, how much physical pleasure did you have when you were ejaculating or cumming?

Would you say… (Check only one)
__ A great deal
__ A moderate amount
__ A slight amount
__ Very little
__ None
__ Could not ejaculate

22. **In the last month**, when having sexual activity, how pleasurable has the feeling of ejaculating or cumming been?

Would you say… (Check only one)
__ Very pleasurable
__ Somewhat pleasurable
__ Neither pleasurable nor unpleasurable
__ Somewhat unpleasurable
__ Very unpleasurable
__ Could not ejaculate

23. Do you think that the amount of physical pleasure you have when you ejaculate or cum is dependent <u>on the amount or volume</u> of your ejaculation?

Would you say it is… (Check only one)
__ Very dependent
__ Dependent
__ Somewhat dependent
__ Not very dependent
__ Not at all dependent
__ Could not ejaculate

24. Do you think the amount of physical pleasure you have when you ejaculate or cum is dependent on the strength or force of your ejaculation?

Would you say it is… (Check only one)
__ Very dependent
__ Dependent
__ Somewhat dependent
__ Not very dependent
__ Not at all dependent
__ Could not ejaculate

25. **In the last month**, have you experienced any physical pain or discomfort when you ejaculated or came?

Would you say you have… (Check only one)
__ No pain at all
__ Slight amount of pain or discomfort
__ Moderate amount of pain or discomfort
__ Strong amount of pain or discomfort
__ Extreme amount of pain or discomfort
__ Could not ejaculate

26. **In the last month,** if you have had any ejaculation difficulties or have been unable to ejaculate or cum, have you been bothered by this?

Would you say… (Check only one)
__ Not at all bothered/ Did not have a problem with ejaculation
__ A little bit bothered
__ Moderately bothered
__ Very bothered
__ Extremely bothered

These next few questions ask about your relationship with your MAIN PARTNER over the **last month**. Some of these questions are about your sexual relationship only, while others are about your general relationship, and not just your sexual relationship. **SKIP NEXT SIX QUESTIONS IF NO MAIN PARTNER**

27. Generally, how satisfied are you with the overall sexual relationship you have with your MAIN PARTNER?

Would you say you are… (Check only one)
__ Extremely Satisfied
__ Moderately Satisfied
__ Neither Satisfied nor Unsatisfied
__ Moderately Unsatisfied
__ Extremely Unsatisfied

28. Generally, how satisfied are you with the quality of the sex life you have with your MAIN PARTNER?

Would you say you are… (Check only one)
__ Extremely Satisfied
__ Moderately Satisfied
__ Neither Satisfied nor Unsatisfied
__ Moderately Unsatisfied
__ Extremely Unsatisfied

29. Generally, how satisfied are you with the number of times you and your MAIN PARTNER have sex?

Would you say you are… (Check only one)
__ Extremely Satisfied
__ Moderately Satisfied
__ Neither Satisfied nor Unsatisfied
__ Moderately Unsatisfied
__ Extremely Unsatisfied

30. Generally, how satisfied are you with the way you and your MAIN PARTNER show affection during sex?

Would you say you are… (Check only one)
__ Extremely Satisfied
__ Moderately Satisfied
__ Neither Satisfied nor Unsatisfied
__ Moderately Unsatisfied
__ Extremely Unsatisfied

31. Generally, how satisfied are you with the way you and your MAIN PARTNER communicate about sex?

Would you say you are… (Check only one)
__ Extremely Satisfied
__ Moderately Satisfied
__ Neither Satisfied nor Unsatisfied
__ Moderately Unsatisfied
__ Extremely Unsatisfied

32. Generally, not counting your sexual relationship, how satisfied are you with all other aspects of the relationship you have with your MAIN PARTNER?

Would you say you are… (Check only one):
__ Extremely Satisfied
__ Moderately Satisfied
__ Neither Satisfied nor Unsatisfied
__ Moderately Unsatisfied
__ Extremely Unsatisfied

Harbor-UCLA 7-day Sexual Function Questionnaire

Psychosexual Daily Questionnaire

(a) Center No.: ☐ (b) Subject No.: ☐ (c) Visit No.: ☐ (d) Day: ☐ (e) Date: ☐

1. Please rate your overall level of sexual desire today by circling the appropriate number below:

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7
none very low very high

2. Please rate highest level of enjoyment or pleasure of any sexual activity that you experienced today.
(a) without a partner (e.g., masturbationl sexual fantasies) and/or (b) with a partner (e.g., kissing, intercourse) by circling the appropriate number below.

(a) Without a partner
0 — 1 — 2 — 3 — 4 — 5 — 6 — 7
none very high enjoyment/pleasure

(b) With a partner
0 — 1 — 2 — 3 — 4 — 5 — 6 — 7
none very high enjoyment/pleasure

(c) Please indicate if partner is available ☐ yes ☐ no

3. Please rate your mood by writing the number that corresponds to the scale below. For each item 0 indicates that the descriptor is not at all true; 7 indicates that the descriptor is very true for you today.

not at all true 0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 very true

(a) Angry? ___
(b) Alert? ___
(c) Irritable?___
(d) Full of pep/energetic?___
(e) Sad or Blue?_____
(f) Tired? _____
(g) Friendly?_____
(h) Nervous?_____
(i) Well/good?_____

4. For all of the items below check yes if you have experienced (or are experiencing) today, otherwise check no.

	Yes	No		Yes	No		Yes	No	
(a)	☐	☐	sexual daydreams	(e)	☐	☐	orgasm	(i)	☐	☐	masturbation
(b)	☐	☐	anticipation of sex	(f)	☐	☐	flirting (by others toward you)	(j)	☐	☐	night spontaneous erection
(c)	☐	☐	sexual interactions with partner	(g)	☐	☐	ejaculation	(k)	☐	☐	day spontaneous erection
(d)	☐	☐	flirting (by you)	(h)	☐	☐	intercourse	(l)	☐	☐	erection in response to sexual activity

Answer the following two questions only if you experienced an erection as shown in No. 4. j-l above.

5. If you experienced an erection today, indicate the % full erection that you experienced by circling the appropriate number below (make a reasonable estimate):

%= 0 10 20 30 40 50 60 70 80 90 100

6. If you experienced an erection today, indicate whether it was maintained for a satisfactory duration by circling the appropriate number below:

not satisfactory 0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 very satisfactory

Day is the relative day of the reporting period/week (i.e., 1,2,3,4,5,6, or 7)

PANAS

This scale consists of a number of words that describe different feelings and emotions. Read each item and then circle the appropriate answer next to that word. Indicate to what extent you have felt this way during the past week.

Use the following scale to record your answers.

(1) = Very slightly or not at all (2) = A little (3) = Moderately (4) = Quite a bit (5) = Extremely

	Very slightly or not at all	A little	Moderately	Quite a bit	Extremely
1. Interested	1	2	3	4	5
2. Distressed	1	2	3	4	5
3. Excited	1	2	3	4	5
4. Upset	1	2	3	4	5
5. Strong	1	2	3	4	5
6. Guilty	1	2	3	4	5
7. Scared	1	2	3	4	5
8. Hostile	1	2	3	4	5
9. Enthusiastic	1	2	3	4	5
10. Proud	1	2	3	4	5
11. Irritable	1	2	3	4	5
12. Alert	1	2	3	4	5
13. Ashamed	1	2	3	4	5
14. Inspired	1	2	3	4	5
15. Nervous	1	2	3	4	5
16. Determined	1	2	3	4	5
17. Attentive	1	2	3	4	5
18. Jittery	1	2	3	4	5
19. Active	1	2	3	4	5
20. Afraid	1	2	3	4	5

Your Health and Well-Being SF-36

For each of the following questions, please select the appropriate response.

1. In general, would you say your health is:
   - ☐ 1 Excellent
   - ☐ 2 Very Good
   - ☐ 3 Good
   - ☐ 4 Fair
   - ☐ 5 Poor

2. Compared to one year ago, how would you rate your health in general now?
   - ☐ 1 Much better now than one year ago
   - ☐ 2 Somewhat better now than one year ago
   - ☐ 3 About the same as one year ago
   - ☐ 4 Somewhat worse now than one year ago
   - ☐ 5 Much worse now that one year ago

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stopping	☐ 1	☐ 2	☐ 3
g. Walking more than a mile	☐ 1	☐ 2	☐ 3
h. Walking several hundred yards	☐ 1	☐ 2	☐ 3
i. Walking one hundred yards	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

5

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious).?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family friends, neighbors, or groups?

☐ 1 Not at all ☐ 2 Slightly ☐ 3 Moderately ☐ 4 Quite a Bit ☐ 5 Extremely

7. How much bodily pain have you had during the past 4 weeks?

☐ 1 None ☐ 2 Very Mild ☐ 3 Mild ☐ 4 Moderate ☐ 5 Severe ☐ 6 Very Severe

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

☐ 1 None ☐ 2 A little bit ☐ 3 Moderately ☐ 4 Quite a Bit ☐ 5 Extremely

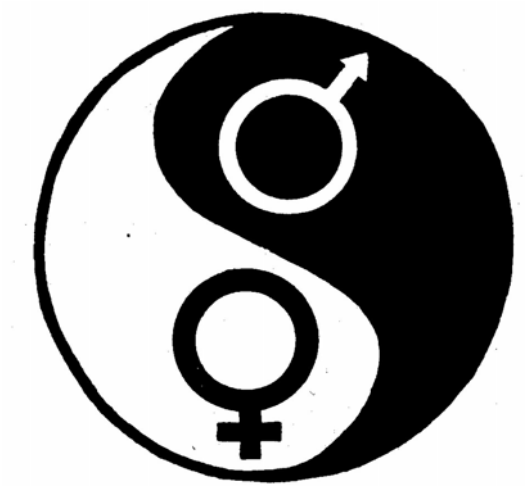
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes close to the way you have been feeling

How much of the time during the past 4 weeks….	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.) ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

11. How TRUE or FALSE is each of the following statements for you?	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

DISF-SR II



DEROGATIS INTERVIEW FOR SEXUAL FUNCTION II

(Male Version)

DISF-SR II (M)

NAME: _____ **DATE:** _____ **LOCATION** _____

AGE: _____ **EDUCATION:** _____ **MAR. STAT:** _____ **ID NO.** _____

INSTRUCTIONS

Below are listed a brief set of questions that ask about your sexual thoughts and activities. The questions are divided into five sections that ask about different aspects of your sexual experiences.

Some questions request that you answer in terms of "how often" you engage in certain sexual activities. Other questions ask you to report "how intense" some of your sexual experiences are. A third type of question inquires about how much you "enjoyed" or were "satisfied" by different aspects of your sexual activities and relationship.

For each Section, there are one or more scale definition boxes located alongside the questions. Indicators at the tops of the boxes tell you which questions the particular scale definition should be used with.

The inventory is quite brief, so please take your time in answering all the questions. **Please circle the scale number for each question that best describes your personal experience.** If you have any questions, please ask the person who gave you the inventory for help or clarification.

SECTION I – SEXUAL DESIRE

During the last 30 days, or since the last time you completed this inventory,

1.1 How often did you have thoughts or fantasies about sexual, romantic, or erotic situations?
0 1 2 3 4 5 6 7

1.2 How often did you feel sexual desire?
0 1 2 3 4 5 6 7

1.3 How often did you want to be involved in sexual activities?
0 1 2 3 4 5 6 7

1.4 With the partner of your choice, how often did you want to have sexual intercourse?
0 1 2 3 4 5 6 7

Questions 1.1 – 1.4

7= 2 or more times a day
6= once a day
5= 4 to 6 times a week
4= 2 or 3 times a week
3= once a week
2= once or twice a month 1= less than once a month 0=

Question 1.5

1.5 Usually, how strong was your sexual desire?
0 1 2 3 4 5

5= intense
4= very strong
3= strong
2= moderate
1= mild
0= absent

[ ] = Sum of 1.1 thru 1

SECTION II – SEXUAL AROUSAL

During the past 30 days, or since the last time you filled out this inventory,

2.1 How often did you feel sexually aroused , that is have a satisfactory erection with or without your partner?

0 1 2 3 4 5 6 7

2.2 How often did you have a full erection upon awakening In the morning?

0 1 2 3 4 5 6 7

2.3 How often did you have an erection that enabled you to penetrate your partner during intercourse?

0 1 2 3 4 5 6 7

2.4 How often were you able to maintain a good erection to your satisfaction throughout sexual intercourse?

0 1 2 3 4 5 6 7

2.5 Please rate your ability your ability to get and maintain an erection during this period?

0 1 2 3 4 5

Questions 2.1 – 2.4

7= 2 or more times a day
6= once a day
5= 4 to 6 times a week
4= 2 or 3 times a week
3= once a week
2= once or twice a month 1= less than once a month 0=

Question 2.5

5= excellent
4= good
3= fair
2= weak
1= very poor
0=absent

[ ] = Sum of 2.1 to 2.5

SECTION III – SEXUAL ACTIVITY

During the last 30 days, or since the last time you filled out this inventory,

3.1 How often have you engaged in kissing, petting or sexual touching with your partner?

0 1 2 3 4 5 6 7

3.2 How often have you engaged in masturbation?

0 1 2 3 4 5 6 7

3.3 How often have you initiated sexual experiences with your partner?

0 1 2 3 4 5 6 7

3.4 How often have you had sexual intercourse that led to orgasm for you or your partner?

0 1 2 3 4 5 6 7

3.5 How often have you engaged in other sexual activities that led to orgasm for you or your partner?

0 1 2 3 4 5 6 7

Questions 3.1-3.5

7= 2 or more times a day
6= once a day
5= 4 to 6 times a week
4= 2 or 3 times a week
3= once a week
2= once or twice a month 1= less than once a month 0=

[ ] = Sum =0 3.1-3.5

SECTION IV – ORGASM

During the last 30 days, or since the last time you filled out this inventory,
(NOTE: If you did not experience an orgasm during this period circle "0" for these items)

4.1 How easy was it for you to have an orgasm?

0 1 2 3 4

4.2 Typically, how intense were your orgasms?

0 1 2 3 4

4.3 How good was the control or timing of your orgasms?

0 1 2 3 4

Questions 4.1, 4.2, 4.3

4= extremely (easy, intense, good)
3= very (easy, intense, good)
2= moderately (easy, intense, good)
1= minimally (easy, intense, good) 0= not at all (easy, intense, good)

4.4 How often did you experience an orgasm?
0 1 2 3 4 5 6 7

4.5 How often did you experience a sense of relaxation and feeling good after orgasm?
0 1 2 3 4 5 6 7

Questions 4.4 and 4.5

7= 2 or more times a day
6= once a day
5= 4 to 6 times a week
4= 2 to 3 times a week
3= once a week
2= once or twice a month 1= less than once a month 0= not at all

[ ] = Sum of 4.1 to 4.5

SECTION V – SEXUAL SATISFACTION

During the past 30 days, or since the last time you filled out this form,

5.1 How satisfied have you been with your sexual relationship with your partner?
0 1 2 3 4 5

5.2 How satisfied have you been with the emotional Intimacy and closeness you have shared with your partner?
0 1 2 3 4 5

5.3 How satisfied have you been with how often you have had sex?
0 1 2 3 4 5

5.4 How satisfied have you been with the variety of your sexual experiences?
0 1 2 3 4 5

5.5 How satisfied have you been with the sexual Sum of enjoyment you have experienced with your partner?
0 1 2 3 4 5

Questions 5.1– 5.5

5= highly satisfied
4= satisfied
3= somewhat satisfied
2= somewhat dissatisfied
1= dissatisfied
0= highly dissatisfied

[ ] = Sum of 5.1– 5.5

SEXUAL ACTIVITY, INTEREST, AND DESIRE SCALE

The following questions ask about your interest in sexual activities and your sexual desire during the past 7 days. The first set of questions are about **THINKING** about sex, the second set of questions are about **BEING SEXUALLY AROUSED**, and the third set of questions are about **SEXUAL ACTIVITY**. Please answer the following questions by checking the box under the phrase that best describes your answer**.** In answering these questions, the following definition applies:

Sexual activity includes intercourse, oral sex, caressing, foreplay, and masturbation.

1. Thinking About Sex (But Not Engaging in Sexual Activity)

During the past 7 days to what extent:	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**A great deal**
1a …did you THINK about sexual activity?	☐	☐	☐	☐	☐
1b …did you FANTASIZE about sexual activity?	☐	☐	☐	☐	☐

2. Becoming PHYSICALLY Sexually Aroused (But Not Engaging in Sexual Activity)

During the past 7 days:	**None of the time**	**Once or twice**	**A few times**	**Several times**	**Many times**
2a …when seeing a sexually attractive person or seeing something sexual (for example a picture or a movie), how often did you PHYSICALLY FEEL a sense of sexual arousal, or a PHYSICAL stirring or tingling of arousal?	☐	☐	☐	☐	☐

During the past 7 days:	**0 days or nights**	**1-2 days or nights**	**3-4 days or nights**	**5-6 days of nights**	**7 days or**
2b ...how often did you wake up from sleeping with an erection (either in the morning or in the middle of the night)	☐	☐	☐	☐	☐

3. Engaging in Sexual Activity.

During the past 7 days:	**0 times**	**1-2 times**	**3-4 times**	**5-6 times**	**7 or more times**
3a …how many times did you masturbate?	☐	☐	☐	☐	☐
3b …how many times did you have some type of sexual activity with another person?	☐	☐	☐	☐	☐

For the next two questions, please circle the number that corresponds with the way that you felt **during the past 7 days.**

1. In general, thinking of everything you've thought, said, and done how would you rate your level of interest in sex during the last 7 days?

0	1	2	3	4	5	6	7	8	9	10
No interest at all										Extremely high interest

2. How would you rate your level of sexual desire during the last 7 days?

0	1	2	3	4	5	6	7	8	9	10
No desire at all										Extremely high desire

HYPOGONADISM ENERGY DIARY

For the next 4 questions, thinking about **how you feel now**, please circle the number under the phrase that best describes how much you feel each word or phrase.

1. ***Right now,*** how energetic do you feel?

0	1	2	3	4	5	6	7	8	9	10
No energy at all										Full of energy

2. ***Right now,*** how tired or exhausted do you feel?

0	1	2	3	4	5	6	7	8	9	10
Extremely tired (Totally exhausted)										Not at all tired

3. ***Right now,*** how lethargic or sluggish do you feel?

0	1	2	3	4	5	6	7	8	9	10
Extremely lethargic/ sluggish										Not at all lethargic/ sluggish

4. ***Right now,*** how focused (able to concentrate) do you feel?

0	1	2	3	4	5	6	7	8	9	10
Not at all focused										Extremely focused/ able to concentrate