RADIATION THERAPY ONCOLOGY GROUP

RTOG 0831

A RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED PHASE III TRIAL TO EVALUATE THE EFFECTIVENESS OF A PHOSPHODIESTERASE 5 INHIBITOR, TADALAFIL, IN PREVENTION OF ERECTILE DYSFUNCTION IN PATIENTS TREATED WITH RADIOTHERAPY FOR PROSTATE CANCER

[Prevention of Erectile Dysfunction Study (PEDS)]

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RTOG 0831

A Randomized, Double-Blinded, Placebo-Controlled Phase III Trial to Evaluate the Effectiveness of a Phosphodiesterase 5 Inhibitor, Tadalafil, in Prevention of Erectile Dysfunction in Patients Treated With Radiotherapy for Prostate Cancer

[Prevention of Erectile Dysfunction Study (PEDS)]

SCHEMA (8/20/10)

STRATIFY	**Age** 1. ≤65 years 2. >65 years **RT Treatment** 1. External radiation therapy 2. Brachytherapy*	**RANDOMIZE**	**Arm 1** Tadalafil started within 7 days after the start of radiation therapy* and continued for 168 days (24 weeks) **Arm 2** Placebo started within 7 days after the start of radiation therapy* and continued for 168 days (24 weeks)

*RT start date for brachytherapy patients is the date of the procedure

See Section 5.0 for pre-registration requirements.

Patient Population: (See Section 3.0 for Eligibility) Men with clinical stage T1b-T2b (AJCC, 6th ed.) adenocarcinoma of the prostate and no distant metastases (M0), and their spouses/partners

Required Sample Size: 218 men

RTOG Institution #
RTOG 0831 **ELIGIBILITY CHECKLIST (11/16/09) (8/20/10) (9/7/10)**
Case # **(page 1 of 4)**

1. ___(Y) Is the clinical stage T1b-T2b (AJCC, 6th ed.; Appendix IV) adenocarcinoma of the prostate within 6 months of registration?

2. ___(Y/NA) Clinically negative lymph nodes established by imaging, nodal sampling or dissection within 3 months prior to registration?

3. ___(Y) No evidence of bone metastases (M0) on bone scan within 3 months prior to registration?

4. ___(Y) Is the baseline serum PSA value performed with an FDA-approved assay (e.g., Abbott, Hybritech) within 3 months prior to registration?

5. ___(Y) Are there any of the following combinations of factors (Note: tumor found in 1 or both lobes on biopsy, but not palpable, will not alter T stage):
   - T1b-T2b disease, Gleason <7 and serum total PSA that is <20 ng/ml **or**
   - T1b-T2b disease, Gleason ≥7 and PSA that is <15 ng/ml

6. ___(Y) Is the testosterone level prior to the initiation of RT within normal range according to institutional guidelines?

7. ___(Y) Is the Zubrod Performance Status 0 or 1 (Appendix III)?

8. ___(Y) Is the patient's age ≥ 18 years?

9. ___(Y) Will treatment consist of either external radiotherapy alone to the prostate ± seminal vesicles only at a dose between 75 Gy and 79.2 Gy or brachytherapy alone?

10. ___(Y) Is the entire IIEF form (QF Form) completed prior to registration?

11. ___(Y) Is there pretreatment (before starting prostate cancer treatment) erectile function as measured by IIEF (QF Form) Question 1, "How often were you able to get an erection during sexual activity?" – with responses of:
    - "sometimes (about half the time)" [response 3] **or**
    - "most times (much more than half the time)" [response 4] **or**
    - "almost always/always" [response 5]

12. ___(Y/N) Is there history of prior tadalafil use: Document usual dosage per sexual encounter, date of last dose, and patient's response (No; Yes—Unsatisfactory Response; Yes—Satisfactory Response)? Regardless of past experience, the patient is eligible if he agrees to adhere to protocol and take only tadalafil or placebo prescribed on study.

13. ___(Y) Has the patient and/or partners (willing to participate) provided study-specific informed consent?

14. ___(N) Is the patient participating in another medical research study that involves the treatment of ED?

15. ___(N) Does the patient have a history of myocardial infarction within the last year?

16. ___(N) Has the patient experienced heart failure in the last 6 months?

17. ___(N) Has the patient had uncontrolled arrhythmias, hypotension (<90/50mm Hg), or uncontrolled hypertension (>170/100 mm Hg)?

18. ___(N) Stroke within the last 6 months?

19. ___(N) Is there known moderate to severe renal insufficiency or end-stage renal disease?

20. ___(N) Is there known severe hepatic impairment?

21. ___(N) Current use of any organic nitrate or as needed nitrates (e.g., use of nitroglycerin)?

22. ___(N) Current use of cimetidine, ketoconazole, itraconazole, erythromycin, or ritonavir?

23.___(N) Use of LHRH agonist androgen suppression (e.g., Lupron, Zoladex), anti-androgen (e.g., Casodex, Eulexin, Nilandron), or estrogenic (e.g., diethylstilbestrol) agents within the last 6 months?

24. ___(N) Does the patient have a previous or concomitant invasive cancer (AJCC Stage >0), other than localized basal cell or squamous cell skin carcinoma (AJCC Stage 0-II), or a hematological malignancy (e.g., leukemia, lymphoma, myeloma) unless continually disease free for at least 5 years?

25. ___(Y) Has the use of mechanical (vacuum) devices, intracorporeal, intraurethral, topical, or oral (sildenafil, tadalafil, vardenafil) agents as therapy for erectile dysfunction (ED) or supplements to enhance sexual function been discontinued within 5-7 days prior to the start of radiation therapy?

26. ___(N) Is there pretreatment (before starting prostate cancer treatment) ED as measured by IIEF (QF Form) Question 1, "How often were you able to get an erection during sexual activity?" – with responses of:
- "no sexual activity" [response 0] **or**
- "almost never/never" [response 1] **or**
- a few times (much less than half the time)" [response 2]

27. __(N) Does the patient have a history of prior penile implant or history of bilateral orchiectomy?

28.__(N) Does the patient have a history of prior prostatectomy, prostatic cryosurgery or high-intensity focused ultrasound (HIFU), radionuclide prostate brachytherapy, or chemotherapy for prostate cancer?

29. ___(N) Prior or anticipated combined external RT and brachytherapy?

30.___(N) Prior or anticipated external RT to the pelvic ± para-aortic lymph nodes?

31. __(N) Does the patient have any of the following?

- Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immunocompromised patients.
- Anatomical genital abnormalities or concurrent conditions that in the estimation of the physician would prohibit sexual intercourse or prevent study completion
- Major medical or psychiatric illness which, in the opinion of the investigator, would prevent completion of treatment or would interfere with follow up

The following questions will be asked at Study Registration:

IMRT AND/OR BRACHYTHERAPY CREDENTIALING IS REQUIRED BEFORE REGISTRATION ONLY IF IMRT AND/OR BRACHYTHERAPY WILL BE USED

_____ 1. Name of institutional person registering this case?

_____(Y) 2. Has the Eligibility Checklist (above) been completed?

_____(Y) 3. Is the patient eligible for this study?

_____ 4. Date the patient provided study-specific consent prior to study entry

_____ 5. Patient's Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]

_____ 6. Verifying Physician

_____ 7. Patient's ID Number

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)

_____ 11. Gender

_____ 12. Patient's Country of Residence

_____ 13. Zip Code (U.S. Residents)

_____ 14. Patient's Insurance Status

_____ 15. Will any component of the patient's care be given at a military or VA facility?

_____ 16. Calendar Base Date

_____ 17. Registration/randomization date: This date will be populated automatically.

(Continued on the next page)

_____(Y/N) 18. Blood kept for cancer research?

_____(Y/N) 19. Blood kept for medical research?

_____(Y/N) 20. Allow contact for future research?

_____(N/Y) 21. Did the patient agree to participate in the quality of life component?

_____ If no, please specify the reason from the following:
1. Patient refused due to illness
2. Patient refused for other reason: specify _____
3. Not approved by institutional IRB
4. Tool not available in patient's language
5. Other reason: specify_____

_____(N/Y) 22. Did the patient's spouse/partner agree to participate in the quality of life component?

_____ If no, please specify the reason from the following:
1. Spouse/partner refused due to illness
2. Spouse/partner refused for other reason: specify _____
3. Not approved by institutional IRB
4. Tool not available in spouse/partner's language
5. Other reason: specify_____

23. Age
_____ 1. ≤ 65
_____ 2. > 65

24. RT Treatment
_____ 1. External radiation therapy
(If yes):
_____Will IMRT be used? **(Credentialing required only if this modality will be used)**
_____ 2. Brachytherapy **(Credentialing required only if this method will be used)**

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Prostate Cancer Therapy and Erectile Dysfunction

Erectile dysfunction (ED) has been reported in 40% to 60% of men after radiation therapy (RT).[1,2] By comparison, radical prostatectomy has at least an 85% risk of ED,[3] and reports of ED after nerve-sparing radical prostatectomy have ranged widely from 25% to 79%.[4] In one study of 287 patients that compared the rate of ED after conformal RT (doses ranging from 62 to 73.8 Gray [Gy]) to nerve-sparing radical prostatectomy, 29% of the RT patients versus 34% of the surgery patients experienced ED. For patients older than 70 years, 39% of RT patients and 67% of surgery patients experienced ED after treatment. At months 1, 20, 40, and 60, actuarial ED rates for the conformal RT group were 4%, 25%, 41%, and 47%, respectively. Factors identified as significant predictors of post-RT ED included pre-treatment ED, diabetes, coronary artery disease, and antiandrogen medication usage.[5] In our own work with patients receiving brachytherapy (prescription dose of 145 Gy), the percentage of men who reported the ability to have an erection decreased from 73% at baseline (65% unassisted, 8% assisted) to 57% at 1 year (36% unassisted, 21% assisted).[6] Further, 69% of men treated with surgery and 62% of men treated with RT have reported dissatisfaction with posttreatment sexual function.[7]

Although the specific mechanism by which RT reduces erections is uncertain, it has been suggested that RT does not damage the corporal nerves, but rather it causes vascular damage. This, in time, interferes with penile hemodynamics which results in ED, even though desire and sexual sensations may be present.[8] Erectile function has been found to be related to a number of factors including patient age, pretreatment sexual function, and comorbidities.

It is important to distinguish between age-related ED and its treatment-induced counterpart. For example, one study of 43 men (mean age 67.7 years) found that almost 63% were impotent prior to therapy.[9] By contrast, in a study of 67 men treated with RT (mean age 68 years), only 37% had pretreatment ED.[4] In this study, ED was preserved in 67% of patients at 24 months after the end of RT, although 50% observed worsening erectile function.[4]

Although prostate cancer is primarily thought of as a disease of advancing age, recent data suggests that the increase in prostate cancer diagnosis among younger men in the United States has been significant. One study analyzed the age-specific detection rate of prostate cancer diagnosed from 324,684 biopsies and found, for the age group 50-59 years, a 45% increase in the detection of prostate cancer from a baseline of approximately 11% in 1995 to greater than 16% in 2001. By contrast, for the age group 70-79 years, detection of prostate cancer decreased from a baseline of 41% in 1995 to 36% in 2001. The increase is likely multifactorial, and the authors suggest it may be attributable to prostate-specific antigen (PSA) and prostate cancer screening efforts.[10] The differentiation between age- and treatment-related ED is particularly important in light of recent work showing a high and increasing level of ED in the general population by decade. Results of a study of male aging indicated that 40% of men age 40 years had minimal, moderate, or complete ED while 67% of men age 70 years were similarly affected. The most recently reported population study of physiologic ED demonstrated age to be the most significant independent predictor of ED.[11]

In addition, studies have demonstrated that men who are potent and sexually active prior to external beam RT tended to maintain their erectile function after RT was completed. One study found that erectile function was related to the initial frequency and quality of intercourse. For men with sexual activity that amounted to more than 3 times per month, the prognosis remained good, whereas for others, it was poor. In this study, the patient's age was a predictive factor for the frequency of intercourse.[4]

1.2 Quality of Life

One of the consequences of prostate cancer therapy is that men with an otherwise long life expectancy may have to live with side effects for the rest of their lives. This also means that the adverse side effects of therapy and their impact on quality of life (QOL) have greater importance as the anticancer therapy prolongs survival duration.[12] One significant QOL concern that has received much attention after prostate cancer therapy is ED. The importance of sexual functioning as a QOL issue should not be underestimated. In a study of 413 impotent men and 109 controls, satisfaction with sexual life was found to be a powerful predictor of satisfaction with

life as a whole.[13] Further, the importance of sexual functioning as a major issue in patient decision making regarding prostate cancer treatment has been demonstrated. Quality versus quantity of life trade-offs have been documented in up to two-thirds of men with prostate cancer who are willing to accept at least a 10% decrement in survival for a treatment that offered a better chance of preserving erectile function.[14] The long-term impact of cancer treatments also highlights the consequences of cure on QOL. One study, which used a battery of QOL instruments, concluded that cancer survivors enjoy QOL similar to their neighbors in all but 1 aspect of daily life: sexual functioning.[15]

1.3 Therapies for Erectile Dysfunction

Despite these well-documented levels of ED following prostate cancer therapy, there had been, until the relatively recent availability of phosphodiesterase type 5 (PDE5) inhibitors, a deficit in acceptable interventions for maintaining erectile function. Pharmacological and nonpharmacological interventions such as intracavernous vasoactive injections, oral drug therapy with yohimbine, vacuum constriction devices, penile prosthesis implants, and venous and arterial surgery that can restore voluntary erectile function for sexual intercourse have been available for years but have gained little attention from physicians and patients alike, probably due to inconvenience and cost (physical and financial).

Despite all of the aforementioned options available to treat ED, there has been a poor overall success rate in patient acceptance of medical and surgical techniques used in the treatment of ED.[16] The risks and obvious difficulties with compliance with the previously discussed alternative treatments, along with the small samples of subjects and lack of prostate cancer specific studies, suggest the need for evaluating other potential agents in the treatment of ED after prostate cancer therapy.

1.4 PDE5 Inhibitors

The Food and Drug Administration (FDA) has approved 3 PDE5 inhibitors: sildenafil, vardenafil, and tadalafil, all with almost identical pharmacological action but slightly different pharmacokinetics. Tadalafil (Cialis®) is an oral agent that has demonstrated significant improvement in the treatment of ED in patients with various ED etiologies (e.g., diabetes mellitus, hypertension) including prostate cancer.[17]

Sildenafil, vardenafil, and tadalafil all work by enhancing the effect of nitric oxide by inhibiting PDE5, which causes increased levels of cyclic guanosine monophosphate (cGMP) in the corpus cavernosum and results in smooth muscle relaxation and inflow of blood. This occurs in conjunction with sexual stimulation. Tadalafil is rapidly absorbed following oral administration over a dose range of 2.5 mg to 20 mg (Eli Lilly, package insert) and steady state plasma concentrations are attained within 5 days of once-daily dosing.[18] Absolute bioavailability of tadalafil following oral dose administration has not yet been determined. The maximum observed plasma concentration (C_{max}) of tadalafil is achieved within 30 minutes to 6 hours (median time=2 hours) after oral administration of 20 mg. Tadalafil is readily distributed into tissues following oral administration, and at therapeutic concentrations 94% of tadalafil in plasma is bound to proteins. The rate and extent of absorption of tadalafil (C_{max}, systemic exposure or plasma half-life) are not influenced by food or alcohol consumption. Mean terminal half-life for tadalafil metabolites has been found to be 17.5 hours in healthy individuals. Tadalafil is predominately excreted in the feces and, to a lesser extent, in the urine.

To assess the efficacy and safety of tadalafil for the treatment of ED, an integrated analysis of 5 randomized, double-blind, placebo-controlled, parallel group trials were conducted in the US.[19] One thousand one hundred and twelve men with ED of varying severity and etiology were randomized to placebo or tadalafil as needed without food or alcohol restriction, at fixed daily doses ranging from 2.5 mg to 20 mg. The main outcomes were changes from baseline in the erectile function domain of the International Index of Erectile Function (IIEF) and the proportion of 'yes' responses to selected questions on the Sexual Encounter Profile (SEP). Compared to placebo, tadalafil significantly enhanced all efficacy outcomes, e.g., patients receiving 20 mg experienced a significant mean improvement in the erectile function domain score versus placebo (P<.001). There were also greater numeric improvements with increasing doses of tadalafil on all efficacy outcomes.

Eardley et al. reported on the efficacy and safety of on-demand 20 mg tadalafil in a double-blind, placebo-controlled study over a period of 12 weeks in men with ED of a broad etiologic spectrum (not including RT or antiandrogens).[20] Two hundred twenty patients from two countries (the United Kingdom and Italy) were randomized to receive treatment with placebo (52 men) or tadalafil (168 men). Concomitant medical conditions included hypertension (19%) and diabetes mellitus (10%). Patients randomized to treatment received 20 mg of tadalafil or placebo for 12 weeks. Efficacy was, as in the previous analysis, based on patient response to the IIEF and the SEP. Treatment with tadalafil significantly improved patients' abilities to achieve and maintain an erection compared to treatment with placebo (*P*<.001). In addition, approximately 74% of sexual intercourse attempts were successful in tadalafil-treated patients compared to 30% in placebo-treated patients (*P*<.001). Tadalafil significantly improved overall intercourse satisfaction and overall satisfaction scores compared to placebo (*P*<.001).

1.5 Tadalafil and Age

Studies including geriatric participants have shown that healthy elderly subjects (≥65 years) had a lower oral clearance of tadalafil that resulted in 25% higher exposure with no effect on C_{max} relative to that observed in healthy subjects 19 to 45 years of age. Dose adjustment based solely on age is not necessary (Eli Lilly, package insert). However, a greater awareness of possible contraindications to medications prescribed to older individuals is warranted, since higher plasma levels may increase both the efficacy and the incidence of adverse events.

Wespes et al. reported the results of a multinational, multicenter, crossover, open-label study of 4,262 European men with ED of any severity, randomized to 2 treatment regimens of tadalafil (20 mg on demand before sexual intercourse or 2-3 times per week for 5-6 weeks).[21] Sexual attempts, efficacy, and safety were evaluated over the 2 regimens across age groups with the IIEF and SEP diaries. Patterns of sexual activity were similar across all age groups for both treatment regimens: the mean per-patient rate of successful attempts decreased with increasing age (≥75% at age ≤60 years, ≥68% at age 61-70 years, and ≥60% at age >70 years). Tadalafil was effective for up to 36 hours after dosing and was well tolerated for all age and treatment groups.[21]

1.6 PDE5 Inhibitors and ED Prevention

Pertinent to this proposal studies have begun to assess PDE5 inhibitors as preventative agents. For example, nocturnal erections, which occur at all ages, contribute to the maintenance of the integrity of smooth muscle cells within the corpora cavernosa. Although the exact mechanism of PDE5 inhibitors' ability to improve or even prevent ED is unknown, it may, like nocturnal erections, contribute to the maintenance of the integrity of smooth muscle cells within the corpora cavernosa by allowing for regular filling. The improved blood flow carries oxygen and nutrients which may maintain a healthy smooth muscle environment. A recent double-blind, crossover, placebo-controlled study evaluated the effect on nocturnal erections of sildenafil (100 mg) versus a placebo taken at bedtime in 30 patients with ED. ED etiology was vasculogenic in 22 patients (73%) and psychogenic in 8 patients (27%). Sleep-related erectile activity was assessed with polysomnographic recording of nocturnal erections. Twenty-three patients (77%) showed a significantly improved nocturnal erectile rigidity and tumescence after the administration of sildenafil (*P*<.01), 5 patients (17%) showed no difference in nocturnal erections with sildenafil and placebo, and 2 patients (6%) showed a significantly improved nocturnal erectile activity after taking the placebo (*P*<.05). Although the number of erectile episodes was greater with the use of sildenafil (mean ± SE; sildenafil 3.8 ± 0.8 vs. placebo 3.0 ± 0.5), this did not reach statistical significance. In this study, sildenafil versus placebo taken at bedtime produced a significantly improved nocturnal erectile activity. However, further studies are needed to verify whether this preliminary finding may constitute the basis for the use of sildenafil, or any other PDE5 inhibitor, such as tadalafil, as a tool for preventing ED.[22]

Promising preliminary data for the prevention of ED in patients treated with surgery for early-stage prostate cancer has recently emerged. In a primary prevention trial, sildenafil (randomized to either 50 mg or 100 mg or placebo) was studied using nightly administration after a bilateral nerve-sparing prostatectomy. Patients had normal preoperative erectile function, defined as having a combined score of >8 for IIEF questions 3 and 4. Patients began sildenafil treatment 4

weeks postsurgery and continued on once an evening dosing for 36 weeks. Response was measured in the same way at week 48 postsurgery (week 44 post sildenafil treatment). Results indicated almost a 7-fold improvement in return of spontaneous, normal erectile function 2 months after drug discontinuation. Twenty-seven percent of the patients treated with sildenafil versus 4% of those treated with placebo were able to have spontaneous erections off drug at 2 months (*P*=.023). The response was thought to be mediated by properties unique to sildenafil that include improved endothelial function and neuronal regeneration and neuroprotection.[23] Although these two promising studies in ED prevention have been conducted with sildenafil, there is little reason to think the results would be unique to this drug since all three of the PDE5 inhibitors that are currently on the market have similar mechanisms of action.

1.7 PDE5 Inhibitors and Prostate Cancer (8/20/10)

In 1998, sildenafil was the first PDE5 inhibitor to be approved by the Food and Drug Administration (FDA) for the treatment of erectile dysfunction. Most studies in the literature assessing PDE5 inhibitors for ED from any cause, including prostate cancer therapies, have been conducted with sildenafil. However, subsequent studies demonstrate that efficacy data are similar in terms of improvements in erectile function among the 3 FDA-approved PDE5 inhibitors: sildenafil, vardenafil, and tadalafil.[24]

With similar efficacy among PDE5 inhibitors, we first report on studies in prostate cancer conducted with the longest-available drug, sildenafil. A small series of studies were undertaken to assess the efficacy of sildenafil in patients treated with RT for prostate cancer (Table 1).

Table 1: Studies of Sildenafil in the Improvement of Erections Post-Radiation Therapy

Author	N	Age	Age Range	Treatment	+ Response
Kedia[25]	21	Mean 65	---	Implant n=2 3D-CRT n=19	71%
Weber[26]	30	Mean 69	54-79 years	4-6 field RT	77%
Zelefsky[27]	50	Median 68	54-78 years	3D-CRT	70%
Merrick[28]	62	Mean 65	50-78 years	Implant	81%
Valicenti[29]	24	Median 68	51-77 years	3D-CRT	91%
Incrocci[30]	60	Mean 68	56-79 years	3D-CRT	55%

The first 5 studies in Table 1 were open-label, nonrandomized trials using small convenience samples. In these 5 studies, an improved response in erections was seen in approximately 70-80% of patients, about twice the rate Pfizer reported after radical prostatectomy. Across all of the Pfizer-sponsored randomized trials, sildenafil improved erections in 43% of radical prostatectomy patients compared to 15% with placebo. However, in the Incrocci study, the only double-blinded randomized RT report to date, the positive response rate of 55% was closer to the randomized radical prostatectomy reports than the nonrandomized earlier RT studies. In addition, only 1 study assessed partner satisfaction in this setting.

In all studies permitting dose titration 80 to 90% of patients required the dose adjustment to 100 mg of sildenafil.[25-30] Therapy was generally well-tolerated across all studies, with flushing, transient headache, and dyspepsia as the most frequently reported side effects and few if any patients discontinuing sildenafil due to side effects. Studies permitting dose titration of tadalafil also found that most patients (regardless of ED etiology) required dose escalation to the 20 mg daily maximum for greatest treatment effect, once patients have ED. (In the proposed study, we are trying to prevent ED in men with normal precancer-treatment sexual function and will therefore start at a lower dose of 5 mg, as explained in further detail in the section on dosing).

In 2003, tadalafil (Cialis®) received FDA approval. A recent study indicates a long-term (45-day) single daily dose of tadalafil prevents corporal veno-occlusive dysfunction (CVOD) and the underlying corporal fibrosis [the hypothesized mechanism of RT damage] caused by cavernosal nerve damage induced in the rat, as effectively as the previously reported continuous treatment with vardenafil or sildenafil. It works through the same cGMP-related mechanism that appears to be independent of inducible nitric oxide synthase induction.[31] Long-term safety and efficacy of tadalafil 5 mg dosed once daily for the treatment of ED has been established.[32] A study of

patients with ED of any severity or etiology receiving tadalafil 5 mg once daily during open-label extensions of two previously reported studies reported 96% improved erections and 92% improved ability to engage in sexual activity at the conclusion of the 2-year open-label extension. Overall, 208/234 (88.9%) and 139/238 (58.4%) patients completed the 1- and 2-year open-label extensions, respectively. No study drug-related serious adverse events were observed. Treatment-emergent adverse events observed in ≥ 5% of the patients during the first year of either open-label extension were dyspepsia, headache, back pain, and influenza.[33]

Tadalafil has an extended period of effectiveness compared with its competitors—up to 36 hours—and, while it appears to have efficacy similar to sildenafil and vardenafil, men appear to prefer the longer duration of effect. One study of men who were using sildenafil and switched to tadalafil found that men preferred to remain on tadalafil by a ratio of 9:1. However, there were limitations to the study that included different dosage levels and different dosage instructions.[34] Preference for tadalafil is most likely due to the longer amount of time of its effectiveness compared with sildenafil and vardenafil.

There are 2 randomized studies in the literature assessing tadalafil for the improvement of ED after radical prostatectomy. In one study, 4,262 patients were randomized to either on-demand or 3-times-per-week dosage regimens of tadalafil 20 mg. Either was equally efficacious in returning those with ED to normal erectile function (60% and 62% of patients reported normal erectile function scores, respectively).[35] In a second study, a total of 303 men (mean age 60 years) with preoperative normal erectile function who had undergone a bilateral nerve-sparing radical retropubic prostatectomy 12 to 48 months before study were randomized (2:1) to tadalafil (20 mg on demand; n=201) or placebo (n=102). For all patients who received tadalafil, mean percentage of successful penetration attempts was 54%, and the mean percentage of successful intercourse attempts was 41%. Of all patients randomized to tadalafil, 62% reported improved erections. Patients receiving tadalafil reported greater treatment satisfaction than those receiving placebo. The most commonly reported side effects were mild and included headache (21%), dyspepsia (13%), and myalgia (7%).[36]

There is one additional randomized study in the literature assessing tadalafil for the improvement of ED after RT. Sixty patients who completed three-dimensional conformal external-beam RT (3DCRT) at least 12 months before the study were entered on a double-blind, placebo-controlled, crossover study lasting 12 weeks. They received 20 mg of on-demand tadalafil or placebo for 6 weeks and then switched to the alternative. Mean age at study entry was 69 years. Outcomes were significantly improved with tadalafil, with 67% of the patients reporting an improvement of erectile function with tadalafil versus 20% with placebo and 48% reporting successful intercourse with tadalafil versus 9% with placebo.[37]

There has been some controversy over patient satisfaction with PDE-5 inhibitors. The Determinants of Continued Use of Tadalafil (DETECT) study, a 12-month, prospective, pan-European, observational trial of 1,900 patients with ED treated with tadalafil reported that 84% of patients continued using tadalafil after 12 months. However, only 8% of the patients in the DETECT study had been treated for prostate cancer (with surgery) and men were a mean of 56.7 years.[38] In contrast, a recent Italian non-randomized, observational study of a convenience sample of 100 consecutive prostate cancer patients treated with bilateral nerve sparing surgery indicated that 72.5% of those patients (mean age 61 years) who decided to start PDE-5 inhibitor therapy (either an on-demand or rehabilitative regimen with no formal counseling) discontinued the treatment during the 18-month follow-up.[39] At 6-months, 38% of those who chose to start a PDE-5 inhibitor had stopped. The number one reason for discontinuation of drug was treatment effect below expectations (reported by 28/37 or 75.7% of men). Of these, none asked for titration of the drug. The next highest reason was related to partner's causes (i.e., women's hypoactive sexual desire disorders – 13.5%).[39] In an open-labeled follow-up to a double-blind crossover study of sildenafil vs placebo, 24% of prostate cancer patients (mean age 68 years at study entry) were still using the drug 2 years after trial entry.[40] This data suggests that older men (compared to the Perimenis et al 2009 study) with prostate cancer may have a lower rate of continuing PDE-5 inhibitor use over time compared to younger men with mixed etiology ED. However, if treatment effect below expectations is the primary reason for discontinuation, evidence of preventative effects of a drug and the knowledge that taking it prophylactically may increase the likelihood of

"normal" erectile function off drug may appeal to patients. Although there is no data on the psychological appeal of a prevention strategy versus a treatment strategy, one could argue that having to take a therapy for 6 months to prevent ED may be more attractive than an alternative on-demand strategy that would need to continue indefinitely. It must be acknowledged that a prevention strategy cannot be expected to prevent ED for the rest of a man's life expectancy after prostate cancer therapy because risk of ED does increase with age. However, ED prevention after prostate cancer therapy may provide a significant period (to be assessed in the current protocol) of "normal" functioning off drug that may increase quality of erectile function in the years just prior to the rapid rise of comorbidities (age 73-92 years).[41] The approximate 5 years between the diagnosis of prostate cancer (mean age 68) and the average onset of increasing number of morbidities associated with older age, therefore, represent a high priority period for the maintenance of health, functioning and quality of life.

In summary, PDE5 inhibitors appear to have efficacy in the treatment of prostate cancer treatment-related ED, and there is promising early pilot data suggesting maintenance of spontaneous erections with use earlier in the treatment trajectory. While the 3 available PDE5 inhibitors have reported similar efficacy in the treatment of ED, patients appear to have a greater preference for the longer-acting tadalafil. This provides clear rationale for what we believe to be the first proposal to assess tadalafil as an ED prevention intervention for patients treated with RT for prostate cancer.

1.8 Genetic Predictors Associated with Erectile Dysfunction (ED)

Evidence that possession of genetic variants is associated with the development of adverse effects resulting from RT comes from several studies. In one case/control study of 141 prostate cancer patients treated with RT, patients were screened for single nucleotide polymorphisms (SNPs) in TGFB1.[42] Those subjects who possessed either the T/T genotype at position -509, the C/C genotype at position 869, or the G/C genotype at position 915 were significantly associated with the development of a decline in erectile function compared with those who did not have these genotypes. These subjects were also genotyped for SNPs in SOD2, XRCC1, and XRCC3.[43] Patients possessing the XRCC1 rs25489 G/A genotype were more likely to develop erectile dysfunction following irradiation compared to patients who had the G/G genotype. Taken together, the results of these two studies provide a basis suggestive for the role of genetic factors in the ability to predict which prostate cancer patients will exhibit ED following RT. However, it is likely that these studies were too narrowly focused in that only several genes were screened. They were limited because it had not been practical to perform whole genome SNP screening at the time these studies were conducted. However, this can now be accomplished with the identification of a large proportion of the estimated ten million SNPs present in the human genome by the HapMap project[44] and the availability of low cost SNP genotyping through the development and use of high density SNP arrays.[45]

1.9 Partners' Satisfaction with Tadalafil

Erectile dysfunction affects and is affected by not only the patient, but also his partner and their relationship. Despite the fact that pharmaceutical breakthroughs allow for renewed or expanded sexual activity among many couples, the psychosocial impact of these agents on the dyad has largely been ignored. Yet, the few studies conducted in this area have indicated that the couples' relationship is prognostic for both the incidence and the success or failure of the treatment of ED.[26] A recent analysis pooled data from 4 double-blind, placebo-controlled 12-week trials that included 746 couples to evaluate patient and female partner satisfaction with tadalafil. Patients were randomized to placebo or tadalafil at doses of 10 or 20 mg. Efficacy was evaluated by assessing the concordance between patient/partner "yes" responses to questions regarding erection achievement, penetration, and overall satisfaction. Tadalafil significantly improved the responses for the patients' and partners' overall satisfaction with sexual activity. The percentage of agreement by couple was approximately 98% for erection achievement and penetration and 85% for overall satisfaction. Partners reported significantly improved overall sexual satisfaction and corroborated the man's report of improved erections and penetration ability with tadalafil 10 mg or 20 mg.[46]

On the other hand, the media is replete with stories of relationship conflicts associated with at least one PDE5 inhibitor, sildenafil. The literature cites multiple case reports of psychosocial and

interpersonal problems associated with sildenafil. Two cases occurred in couples whose marital situation worsened after the husband refused to take sildenafil for ED following radical prostatectomy.[47] Two additional cases of homicidal ideation toward their wives were documented in men in their mid-seventies who took sildenafil. In one case, a wife's rejection of her husband's advances seemed to uncover many hidden resentments that they bore toward each other. In the other, sildenafil failed to restore potency to a patient with diabetes, and he developed a jealous delusion that his wife was having an affair. Both men required admission to a locked psychiatry unit.[48] Most recently (03/29/2007), the Midlands News Service of Omaha, Nebraska, reported on a murder trial in which the alleged murderer told the court that the victim with whom he had been having a relationship was breaking up with him, told him she had slept with other men, and taunted him about his use of Viagra®. As one author affirmed, the scientific community's emphasis on erection ignores the relationship issues and education/counseling efforts important to the successful treatment of sexual dysfunction. According to Westheimer and colleagues, "The most significant factors affecting sexual performance are not physical but psychological. Therefore, the same scientific rigor applied to the physical side of sexual function must be applied to the emotional and psychological aspects as well."[49] This provides rationale for the assessment of partner satisfaction with the patient's use of tadalafil.

1.10 Rationale for Choice of Primary Endpoint

We originally considered using the same outcome as described in the Padma-Nathan et al[23] study of prevention of ED after radical prostatectomy, which used a combined score of >8 for the International Index of Erectile Function Questionnaire (IIEF) Questions 3 and 4. However, not all sexual activity involves vaginal penetration. In fact, as prostate cancer is a disease of aging men at risk for some degree of ED unrelated to prostate cancer or prostate cancer therapy, sexual activity may involve erectile pleasures unrelated to penetration, as was the focus of the Padma-Nathan study. Further, even if erectile function is maintained for sexual pleasure, men may have aging partners that have decreasing interest in vaginal penetration for any number of reasons such as vaginal atrophy, dyspareunia, or lack of lubrication associated with menopause, but who engage in other forms of pleasuring such as oral gratification. We have therefore chosen to focus on the maintenance of erectile function as measured by IIEF Question 1.

2.0 OBJECTIVES

2.1 Primary Objective

To determine whether tadalafil maintains spontaneous (off-drug) erectile function, as measured by the International Index of Erectile Function (IIEF), as compared to placebo at weeks 28-30 after initiation of radiation therapy for prostate cancer

2.2 Secondary Objectives

2.2.1 Determine the difference in spontaneous (off-drug) erectile function between tadalafil and placebo arms at 1 and 2 years

2.2.2 Determine the difference in overall sexual function (as measured by the IIEF) between tadalafil and placebo arms at weeks 28-30 and 1 and 2 years

2.2.3 Determine differences in patient and partner overall sexual satisfaction (as measured by the Sexual Adjustment Questionnaire [SAQ]) between tadalafil and placebo arms at weeks 28-30 and 1 and 2 years

2.2.4 Determine differences in patient and partner marital adjustment (as measured by Locke's Marital Adjustment Test [LMAT]) between tadalafil and placebo arms at weeks 28-30 and 1 and 2 years

2.2.5 Determine associations between patient and partner overall sexual satisfaction (as measured by SAQ) and patient and partner marital adjustment (as measured by LMAT) at weeks 28-30 and 1 and 2 years

2.2.6 Determine patient-related factors (age, pretreatment sexual response, tobacco use, and comorbidities) that may predict response to tadalafil therapy at weeks 28-30 and 1 and 2 years

2.2.7 Determine differences in adverse events between tadalafil and placebo according to CTCAE criteria (CTEP Active Version)

2.2.8 Determine predictive and prognostic biomarkers of erectile dysfunction

2.3 Tertiary (Exploratory) Objectives

2.3.1 Characterization of preference and erectile function among patients who choose to stay on (or if on placebo, to start) tadalafil, a PDE5 inhibitor other than tadalafil, a non-PDE5-inhibitor erectile aide, or no PDE5 inhibitor or erectile aide at 28-30 weeks and 1 and 2 years

2.3.2 Identification of RT factors (modality, prescribed total dose, planning target volume margin, penile bulb dose-volume parameters) associated with erectile function

2.3.3 Evaluation of the number of patients screened for eligibility, the number eligible that are presented the protocol, the number who refuse, and the number who are accrued

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

Pretreatment evaluations are to be conducted within 3 months prior to administration of protocol therapy unless otherwise noted.

3.1 Conditions for Patient Eligibility (8/20/10)

3.1.1 Clinical stage T1b-T2b (AJCC, 6th ed.; Appendix IV) adenocarcinoma of the prostate within 6 months of registration

3.1.2 Clinically negative lymph nodes as established by imaging (pelvic ± abdominal CT or MR), nodal sampling, or dissection within 3 months prior to registration. Patients with lymph nodes equivocal or questionable by imaging are eligible if the nodes are ≤ 1.5 cm. Lymph node assessment is optional, and at investigator discretion, for patients with Gleason Score <7.

3.1.3 No evidence of bone metastases (M0) on bone scan within 3 months prior to registration. Equivocal bone scan findings are allowed if plain films are negative for metastasis. Bone metastases assessment is optional, and at investigator discretion, for patients with Gleason Score <7.

3.1.4 Baseline serum PSA value performed with an FDA-approved assay (e.g., Abbott, Hybritech) within 3 months prior to registration.

3.1.4.1 Any of the following combinations of factors (NOTE: tumor found in 1 or both lobes on biopsy, but not palpable, will not alter T stage):

- T1b-T2b disease, Gleason Score <7 and serum total PSA that is <20 ng/ml **or**
- T1b-T2b disease, Gleason Score ≥7 and PSA that is <15 ng/ml

3.1.5 Serum total testosterone level prior to the initiation of RT within normal range according to institutional guidelines

3.1.6 Zubrod Performance Status 0 or 1 (Appendix III)

3.1.7 Age ≥ 18 years

3.1.8 Treatment that will consist of either external beam RT alone to the prostate ± seminal vesicles only at a dose between 75 Gy and 79.2 Gy or brachytherapy alone (NOTE: treatment with combined external RT and brachytherapy excludes patient participation)

3.1.9 Completion of entire IIEF Form (QF Form) prior to registration

3.1.10 Pretreatment (before starting prostate cancer treatment) erectile function as measured by IIEF (QF form) Question 1, "How often were you able to get an erection during sexual activity?" – with responses of:

- "sometimes (about half the time)" [response 3] **or**
- "most times (much more than half the time)" [response 4] **or**
- "almost always/always" [response 5]

3.1.11 History of prior tadalafil use: Document usual dosage per sexual encounter, date of last dose, and patient's response (No; Yes—Unsatisfactory Response; Yes—Satisfactory Response). Regardless of past experience, the patient is eligible if he agrees to adhere to protocol and take only tadalafil or placebo prescribed on study.

3.1.12 Although patients with partners are targeted for recruitment, patients without partners or without partners willing to participate are eligible. Patients (and spouses/partners, if willing to participate) must be able to provide study-specific informed consent.

3.2 Conditions for Patient Ineligibility

3.2.1 The patient's participation in another medical research study that involves the treatment of ED

3.2.2 Previous or concomitant invasive cancer (AJCC Stage >0), other than localized basal cell or squamous cell skin carcinoma (AJCC Stage 0-II), or a hematological malignancy (e.g., leukemia, lymphoma, myeloma) unless continually disease free for at least 5 years

3.2.3 History of myocardial infarction within the last year

3.2.4 Heart failure in the last 6 months

3.2.5 Uncontrolled arrhythmias, hypotension (<90/50mm Hg), or uncontrolled hypertension (>170/100 mm Hg)

3.2.6 Stroke within the last 6 months

3.2.7 Use of LHRH agonist androgen suppression (e.g., Lupron, Zoladex), anti-androgen (e.g., Casodex, Eulexin, Nilandron), or estrogenic (e.g., diethylstilbestrol) agents within the last 6 months

3.2.8 Current use of any organic nitrate or as needed nitrates (e.g., use of nitroglycerin)

3.2.9 Current use of cimetidine, ketoconazole, itraconazole, erythromycin, or ritonavir

3.2.10 Known moderate to severe renal insufficiency or end-stage renal disease

3.2.11 Known severe hepatic impairment

3.2.12 Use of mechanical (vacuum) devices, intracorporeal, intraurethral, topical, or oral (sildenafil, tadalafil, vardenafil) agents as therapy for ED or supplements to enhance sexual function within 5-7 days prior to the start of RT. Patients who discontinue these therapies remain eligible if they can meet eligibility in Section 3.1

3.2.13 Pretreatment (before starting prostate cancer treatment) ED as measured by IIEF (QF form) Question 1, "How often were you able to get an erection during sexual activity?" – with responses of:

- "no sexual activity" [response 0] **or**
- "almost never/never" [response 1] **or**
- "a few times (much less than half the time)" [response 2]

3.2.14 Prior penile implant or history of bilateral orchiectomy

3.2.15 Prior prostatectomy, prostatic cryosurgery or high-intensity focused ultrasound (HIFU), radionuclide prostate brachytherapy, or chemotherapy for prostate cancer

3.2.16 Prior or anticipated combined external RT and brachytherapy

3.2.17 Prior or anticipated external RT to the pelvic ± para-aortic lymph nodes

3.2.18 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immunocompromised patients.

3.2.19 Anatomical genital abnormalities or concurrent conditions that in the estimation of the physician would prohibit sexual intercourse or prevent study completion

3.2.20 Major medical or psychiatric illness which, in the opinion of the investigator, would prevent completion of treatment or would interfere with follow-up

3.3 Spouse/Partner Eligibility Criteria

3.3.1 A male or female partner is eligible.

3.3.2 Signed study-specific informed consent (Appendix IA)

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

Note: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management

See Appendix II for a summary of study assessments and time frames. Pretreatment evaluations are to be conducted within 3 months prior to administration of protocol therapy unless otherwise noted. "Day 1," the start of "Week 1," corresponds to the date of initiation of external RT for patients receiving external RT or the date of brachytherapy implantation for patients receiving brachytherapy. Tadalafil or placebo will be started within 7 days after the initiation of RT. Pretreatment evaluations will include the following:

4.1.1 History/physical examination (including a digital rectal examination) and toxicity assessment within 60 days prior to registration assessment

4.1.2 History of prior PDE5 inhibitor (sildenafil, tadalafil, verdanafil) use: document which drug, usual dosage per sexual encounter, date of last dose, and patient's response (No; Yes—Unsatisfactory Response; Yes—Satisfactory Response).

5.0 REGISTRATION PROCEDURES (8/20/10)

5.1 Pre-Registration Requirements for IMRT Treatment Approach

NOTE: IMRT credentialing is required only if IMRT will be used.

5.1.1 In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the Radiological Physics Center (RPC) web site. Visit http://rpc.mdanderson.org/rpc and select "Credentialing" and "Credentialing Status Inquiry". **Institutions previously credentialed for IMRT on other RTOG trials do not need to be re-credentialed to use IMRT for this study.**

An IMRT phantom study with the RPC must be successfully completed (if the institution has not previously met this IMRT credentialing requirement). Instructions for requesting and irradiating the phantom are available on the RPC web site at http://rpc.mdanderson.org/rpc/; select "Credentialing" and "RTOG". Upon review and successful completion of the phantom irradiation, the RPC will notify both the registering institution and RTOG Headquarters that the institution has completed this requirement. Subsequently, RTOG Headquarters will notify the institution that the site can enroll patients on the study.

5.1.2 The institution must have an updated IMRT Facility Questionnaire on file at the RTOG prior to entering any cases. Institutions not previously credentialed for 3D-CRT or IMRT need to set up an SFTP account for digital data submission. Instructions for setting up an SFTP account and the Facility questionnaire are available on the Image-Guided Center (ITC) web site at http://atc.wustl.edu. Upon review and successful completion of the "Dry-Run" QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study.

5.2 Pre-Registration Requirements for 3D-CRT Treatment Approach

NOTE: 3D-CRT credentialing is required only if 3D-CRT will be used.

5.2.1 Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in 3D-CRT Quality Assurance Guidelines may enter patients onto this study.

5.2.2 An updated Facility Questionnaire (one per institution, available on the ATC website at http://atc.wustl.edu) is to be sent to RTOG for review prior to entering any cases. Institutions not previously credentialed for 3D-CRT or IMRT need to set up an SFTP account for digital data submission. Upon review and successful completion of a "Dry-Run" QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study. Institutions that have previously enrolled patients on 3D-CRT trials of this same disease site may enroll patients on this study without further credentialing. **Institutions previously credentialed for 3D-CRT on other RTOG trials do not need to be re-credentialed to use 3D-CRT for this study.**

5.3 Pre-Registration Requirements for Brachytherapy Treatment Approach

NOTE: Brachytherapy credentialing is required only if Brachytherapy will be used.

Institutions must be credentialed by the Radiological Physics Center (RPC) prior to registering any cases to this study. The credentialing materials may be found on the RPC website at http://rpc.mdanderson.org under the "credentialing" tab.

5.3.1 If an institution was credentialed for a previous RTOG prostate brachytherapy trial (RTOG 98-05, RTOG P-0019, RTOG 0232, or RTOG 0526), they do not have to be re-credentialed for this trial if the radiation oncologist and physicist are the same as on the approved credentialing request, and the institution is using the same seed model and planning system as on the approved credentialing request. A change of physician will require submission of the Knowledge Assessment Form and Clinical Test Case. A change in physicist will require submission of the Knowledge Assessment Form, the Credentialing Questionnaire, and the Reference Cases. A change in either the treatment planning computer or brachytherapy source model will require resubmission of only the Reference Cases.

5.4 Regulatory Pre-Registration Requirements

5.4.1 **U.S. and Canadian institutions** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206) along with the completed CTSU-IRB/REB Certification Form

(http://www.rtog.org/pdf_file2.html?pdf_document=CTSU-IRBCertifForm.pdf) prior to registration of the institution's first case:

- IRB/REB approval letter
- IRB/REB approved consent (English and native language versions*)
  ***Note**: Institutions must provide certification of consent translation to RTOG Headquarters
- IRB/REB assurance number

5.4.2 *Pre-Registration Requirements FOR CANADIAN INSTITUTIONS*

5.4.2.1 Prior to clinical trial commencement, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.

5.4.3 *Pre-Registration Requirements for the Initial Shipment of Tadalafil:*

5.4.3.1 **U.S. and Canadian Institutions:**

All pre-registration requirements must be met before calling to register the first case. Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the RTOG web site, www.rtog.org (next to the protocol). U.S. and Canadian institutions must fax the SASF to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified.

5.5 Registration

5.5.1 Online Registration

Patients can be registered only after eligibility criteria are met.

Each individual user must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via http://phrp.nihtraining.com/users/login.php).
- A representative from the institution must complete the Password Authorization Form at www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (http://www.rtog.org), going to "Data Center Login" and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient's record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study's database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

Institutions can contact RTOG web support for assistance with web registration at: websupport@acr-arrs.org or 800-227-5463 ext. 4189 or 215-574-3189.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday,

8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site's user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY (8/20/10)

Protocol treatment must begin within 6 weeks after randomization.

NOTE: Credentialing for IMRT, 3D-CRT, or brachytherapy is required only if IMRT, 3D-CRT, or brachytherapy will be used.

6.1 External Beam Radiotherapy

6.1.1 Dose Specification: The prescription dose is the minimum such that ≥98% of the planning target volume (PTV) receives the target dose, i.e., V100 ≥98%. The cumulative target dose of 75-79.2 Gy is delivered in once daily 1.8-2.0 Gy fractions with a forward or inversely planned 3DCRT or IMRT approach. The maximum dose to the PTV should not exceed the prescription dose by more than 7% and should not fall within critical normal structures. ICRU reference points are located in the central part of the PTV and secondly on or near the central axis of the beams, typically at the intersection of the beam axes.

6.1.2 Technical Factors: Treatment will be administered on an isocentrically mounted megavoltage unit with photon energy ≥6 MV. A minimum isocenter distance (i.e., SAD) of 100 cm is recommended. An isocentric multiple (≥4) field arrangement with customized blocking material of ≤5% primary beam transmission (≥4.3 HVL), multileaf collimation, or IMRT methods will be used.

6.1.3 Localization, Simulation, and Immobilization: Treatment planning computed tomography (CT) is required and will be performed with the patient in the same position (immobilization strongly recommended) and conditions (full bladder and empty rectum are strongly recommended) that will be used for treatment. CT images should be acquired at a slice thickness of ≤0.3 cm from the top of the iliac crests superiorly to the perineum inferiorly.

6.1.4 Treatment Planning/Treatment Volumes: Definitions are based on ICRU Report #50. The gross tumor volume (GTV) is the prostate gland. The clinical target volume (CTV) is an expansion of the GTV with margins to account for subclinical extraprostatic tumor extension (typically ≤0.3 cm, except at the prostate – anorectum interface where no margin is added) ± seminal vesicle invasion (typically the inferior-most 1.0-1.5 cm). The PTV is a 3-dimensional expansion of the CTV with margins (typically 0.5-1.0 cm) to account for variations in treatment set up and internal organ motion. Blocking or collimator margins are set to account for the field edge effect of dose build-up (i.e., penumbra). **NOTE: Treatment of the pelvic and/or para-aortic lymph nodes is not allowed (Section 3.2.17).**

6.1.5 Treatment Parameters: It is recommended that instructions be given to assure that the patient is treated with a full bladder in order to displace the small bowel and more bladder out of the treatment volume. Daily target localization with implanted markers, beacons, CT, or transabdominal ultrasound is highly recommended.

6.1.6 Critical Normal Structures: 3-dimensional conformal or intensity modulated planning is required to restrict the volume of critical normal structures (i.e., organs at risk) that receive dose, which is evaluated by dose-volume histogram (DVH) analysis. The treatment plan should deliver the PTV dose with adherence to the critical structure parameters listed in the Table below.

6.1.6.1 Critical normal structures will be defined on the treatment planning CT and will include the bladder, rectum (from the rectosigmoid flexure to the inferior-most portion of the ischial tuberosities), bilateral femora (to the level of ischial tuberosity), penile bulb, and skin. The penile bulb constraint is a guideline that must not result in reduced PTV coverage. All structures will be contoured as solid organs.

Critical Normal Structure Dose Constraint*				
Structure†	≤15% volume receives	≤25% volume receives	≤35% volume receives	≤50% volume receives
Bladder	>80Gy	>75Gy	>70Gy	>65Gy
Rectum	>75Gy	>70Gy	>65Gy	>60Gy
Femora	≤10% volume receives >52Gy			
Penile bulb	≤50% volume receives >52.5Gy			

* Every attempt will be made to keep the volume as small as possible.
† Refers to the volume of that structure that should not exceed the dose limit.

6.1.7 Treatment Verification: Portal images of each 3DCRT field should be obtained on the first treatment day and should be obtained of each modified field also on its first treatment day. Thereafter, weekly images should be obtained. For IMRT the intensity profiles of each beam should be verified independently and compared to the planned field intensity; orthogonal isocenter images should be obtained on the first treatment day, with any modification, and weekly thereafter.

6.2 Low Dose Rate Permanent Brachytherapy

Note: Use of brachytherapy must be specified at registration. If a patient was registered to receive brachytherapy, but is found subsequently to be a poor brachytherapy candidate, the patient will no longer be eligible for study participation. Therefore, it is strongly recommended to obtain all assessments for brachytherapy patients before enrollment.

6.2.1 Dose Specification: The prescribed dose will be 145 Gy (TG-43 dosimetry; point source approximation) to the PTV for I-125, and the prescribed dose will be 125 Gy to the PTV for Pd-103. The prescription dose minimum peripheral dose (mPD) is intended to be delivered to the CTV and is the reference dose.

6.2.2 Technical Factors: Preimplantation or intraoperative planning with transrectal ultrasound and/or CT for source location is required. The prostate will be defined from base to apex in the axial plane at 0.5 cm slice intervals. Transperineal needle placement should be done through a template manufactured exclusively for this purpose. Transrectal ultrasound±fluoroscopic guidance is typically used to direct needle placement. All needles will be removed at completion of the procedure, and cystoscopy may be performed to retrieve any errant seeds in bladder or urethra as clinically indicated.

6.2.3 Isotope Selection: Resorbable suture-impregnated or free I-125 or Pd-103 sources may be used. Sources will be received and inventoried according to state and federal regulations. At least 10% of the sources will be assayed and directly traceable to either National Institute of Standards and Technology (NIST) 1999 or an Accredited Dosimetry Calibration Lab (ADCL). The average measured source strength will agree with the vendor's calibration certificate to within 5%; no measured source strength should be >10% of the calibration certificate.

6.2.3.1 For I-125, the allowable source strength for each seed is 0.277 U to 0.650 U (NIST 99 or later). For Pd-103, it is 1.29 U to 2.61 U (NIST 99 or later).

6.2.4 Treatment Volumes: The clinical tumor volume (CTV) is the preimplantation ultrasound or CT defined prostate volume. The planning target volume (PTV) may be the same as the CTV or a 0.2 – 0.3 cm margin may be added anteriorly and laterally, and up to 0.5 cm craniocaudally; the PTV posteriorly is the CTV.

6.2.5 Post-Implant Dosimetry: A CT scan with ≤0.3 cm axial image spacing will be performed with the patient in supine position ≤5 weeks after the implant. All seeds used in the implant should be encompassed in the scan. The CT scan will be used to create a post-implant treatment plan (post plan), and a DVH analysis that includes prostate (also referred to as the evaluation target volume), rectum, bladder and penile bulb will be performed.

6.3 Radiation Adverse Event Reporting

See Section 7.6 for Adverse Event Reporting.

7.0 DRUG THERAPY

7.1 Treatment

Tadalafil or placebo must be started within 7 days after the initiation of RT. "Day 1", the start of "Week 1", corresponds to the date of initiation of external RT for patients receiving external RT or the date of brachytherapy implantation for patients receiving brachytherapy.

7.1.1 Arm 1 (Tadalafil) and Arm 2 (Placebo)

Administration of tadalafil 5 mg or placebo (1 pill per day) begins within 7 days after initiation of RT. The date of initiation of RT is "day 1." Tadalafil or placebo will be continued daily for 24 weeks (168 days). At 2 weeks and 13 weeks after starting tadalafil or placebo, patients must bring their pill bottles and pill diaries to clinic for a compliance check and to receive a renewed prescription for tadalafil or placebo.

7.2 Tadalafil

7.2.1 Description

Tadalafil works by enhancing the effect of nitric oxide by inhibiting phosphodiesterase type 5 (PDE5), which causes increased levels of cyclic guanosine monophosphate (cGMP) in the corpus cavernosum and results in smooth muscle relaxation and inflow of blood. This occurs in conjunction with sexual stimulation. Tadalafil is rapidly absorbed following oral administration. The maximum observed plasma concentration C_{max} of tadalafil is achieved within 30 minutes and 6 hours (median 2 h). The absolute bioavailability of tadalafil following oral administration has not been determined. The rate and absorption of tadalafil are not influenced by the consumption of food; tadalafil can be taken with or without food.

Pharmacokinetics are dose-proportional over the recommended dose range. Tadalafil is primarily eliminated by the hepatic metabolism, specifically, cytochrome P450 3A4 (CYP3A4). The use of concomitant potent CYP3A4 inhibitors (e.g., ritonavir, ketoconazole) will cause an increase in plasma concentrations of tadalafil (see Section 3.2.9). Tadalafil is primarily metabolized to a catechol metabolite. The mean oral clearance is 2.5 L/h and the mean terminal half-life in a healthy subject is 17.5 hours. Tadalafil is primarily excreted as metabolites in the feces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36%) of the dose.

7.2.2 Storage

Tadalafil should be stored in a dry place at room temperature, 59°-86° F.

7.2.3 Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7.4.

7.2.4 Compliance

Pill counts will be assessed and pill diaries collected 2 weeks and 13 weeks after the start of tadalafil/placebo and during weeks 28-30. Patients must bring their pill bottles and pill diaries to clinic 2 weeks and 13 weeks after the start of tadalafil/placebo in order to get a renewed prescription for tadalafil/placebo for the duration of the 24 weeks. In addition, site staff will mail a compliance letter to patients during months 2, 4, 5, and 6 after the start of tadalafil or placebo.

7.2.5 Supply and Distribution

The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

Lilly USA, LLC will supply tadalafil and placebo free of charge to patients on study. The drug will be distributed by a vendor, Biologics, Inc., under contract to RTOG.

Institutions must meet all pre-registration requirements before calling to register the first case. Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the RTOG web site, www.rtog.org (next to the protocol). U.S. and Canadian institutions must fax the SASF to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified.

Biologics will ship a patient-specific supply of tadalafil/placebo with enough quantity to complete protocol treatment once the site has registered the patient. Sites can obtain additional per-patient supply for individuals by contacting Biologics. It is possible that sites will have more than one tadalafil clinical study ongoing at the same time. **It is imperative that only product designated for RTOG 0831 be utilized for this study.** RTOG 0831 product must be segregated from other investigational or marketed product.

Upon notification of a new patient enrollment, Biologics will place an outbound call to the site contact to confirm that the site's shipment is being processed. Biologics' distribution team will monitor packages throughout the duration of transit via the FedEx web site and FedEx One Call Solution (live support). Real time monitoring enables Biologics to mitigate potential delivery delays.

Questions about supply and delivery should be directed to:

Karl Buer, Clinical Trial Project Manager

Biologics, Inc.
120 Weston Oaks Court
Cary, NC 27513
Phone (Clinical Trial Services): 800-693-4906
Phone (direct): 919-459-4991
FAX (919) 256-0794
kbuer@biologicstoday.com

Unused supplies at the sites should be returned directly to Biologics.

7.2.6 Accountability
Drug accountability records must be maintained at all sites according to good clinical practices and NCI guidelines.

7.2.7 Drug Interactions
Because there is a potential for interaction of tadalafil with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. In particular, there is an increased risk of orthostatic hypotension when tadalafil is used in conjunction with alpha-blocker medications. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect this agent.

7.2.7.1 Many of the patients in tadalafil clinical trials were taking other medications concomitantly to treat such diseases as hypertension, depression, ulcers, diabetes, and arthritis. Analysis of the safety database showed no difference in the side effect profile in patients taking tadalafil with any other medication, excluding nitrates. Patients with either renal or hepatic insufficiencies should be treated cautiously, because data on tadalafil clearance in the renal and hepatic systems are scarce.[18] Patients with known hepatic or moderate to severe renal insufficiency will be ineligible for this trial.

7.2.7.2 Tadalafil metabolism is principally mediated by the CYP3A4 pathway. Studies have shown that tadalafil does not interfere with drugs metabolized by cytochrome P450 (CYP isoforms) (e.g., midazolam, lovastatin, theophylline, warfarin).[18] However, in the case of the CYP3A4 inhibitors (e.g., ritonavir, ketonazome, itraconazole), the dose of tadalafil should be limited to 10 mg every 72 hours. For this trial, patients on these medications will be ineligible. Other cytochrome inhibitors have not been studied, but it is postulated that erythromycin, itraconazole, and grapefruit juice may increase tadalafil exposure. Conversely, studies have shown that drugs that induce CYP3A4 can decrease tadalafil exposure. For example, rifampin can reduce tadalafil (10 mg single dose) exposure by 88% and C_{max} by 46% relative to the values for tadalafil 10 mg alone. Gastrointestinal drugs such as antacids appear to reduce the rate of absorption of tadalafil without altering exposure to tadalafil.

7.2.8 Dose Modifications
No treatment delays will be permitted on this study.

7.2.9 Code Breaks
The decision to break the code must be based on a life-threatening event or extraordinary clinical circumstance for which knowledge of drug assignment will affect clinical judgment.

During business hours (8:30 AM to 4 PM ET), call RTOG Headquarters at 215-574-3150 and ask to speak to the Study Statistician. For after hours, weekends, and holidays, call (215) 459-3576.

7.3 Modality Review
None

7.4 Adverse Events
7.4.1 Tadalafil Adverse Events
Tadalafil was administered to 5,700 men (mean age 59 years, range 19-87 years) in clinical trials worldwide. Over 1,300 patients were treated for 6 months or more and more than 1,000 patients were treated for 1 year or longer. In placebo-controlled Phase III clinical trials, the discontinuation rate due to adverse events in patients treated with 10 or 20 mg tadalafil was 3.1% compared to 1.4% in placebo-treated patients.

Across the 8 primary placebo-controlled Phase III studies, treatment emergent adverse events were reported by ≥2% of patients treated with tadalafil (5 mg, 10 mg, and 20 mg). Adverse events were reported at higher proportions as the dosage increased to 20 mg. Side effects included headache, dyspepsia, back pain, myalgia, nasal congestion, flushing (includes facial) and limb pain. The most commonly reported side effect was headache (11% at 5 and 10 mg; 15% at 20 mg). Back pain (3% at 5 mg; 5% at 10 mg; 6% at 20 mg), myalgia (4% at 10 mg; 3% at 20 mg), were reported less frequently. Nasal congestion (2% at 5 mg; 3% at 10 and 20 mg), flushing (includes facial flushing) (2% at 5 mg; 3% at 10 and 20 mg), limb pain (3% at 10 mg and 20 mg) and myalgia (4% at 10mg) were the least reported side effects.

In general, myalgia was reported as mild or moderate in severity and did not require medical treatment. Severe pain occurred infrequently (<5% of all reports). Overall, only 0.5% of all tadalafil-treated subjects discontinued treatment as a consequence of back pain or myalgia. There was no evidence of significant underlying pathology, as evidenced through diagnostic testing, for inflammation, muscle injury, or renal damage. However, myalgia (including back pain) was reported at incidence rates ranging from 1% (5 mg) to 3-4% (10 and 20 mg) and occurred within 12 to 24 hours after dosing and resolved within 48 hours. The back pain/myalgia associated with tadalafil treatment was localized to the lower lumbar, the gluteal, and the thigh region with diffuse bilateral discomfort.

Other adverse events (<2%) reported in controlled clinical trials include pain in the body as a whole (asthenia, face edema, fatigue), cardiovascular (angina pectoris, hypertension), digestive (diarrhea, dry mouth), musculoskeletal (neck pain), respiratory (dyspnea), dermatological (rash), ophthalmologic (blurred vision) and urogenital (spontaneous penile erection). (Eli Lilly package insert)

7.4.2 Adverse Events in the Elderly

Approximately 25% of the participants in the primary efficacy and safety studies of tadalafil were >65 years of age. There were no overall differences in efficacy and safety observed between older and younger patients. Participant age alone did not warrant dose adjustment, but investigators should carefully consider older participants' use of other medications when prescribing tadalafil (Eli Lilly package insert).

7.4.3 Visual Abnormalities

Anterior ischemic optic neuropathy (AION) is a vascular event presumed to occur due to a decrease in blood flow to the small arteries that supply the optic nerve. There are 2 types of AION: arteritic AION, an inflammatory vasculitis, and nonarteritic AION (NAION), a diagnosis of exclusion (i.e., AION in the absence of provable arteritis). It is the most common acute optic nerve disease in men older than 50 years. Although the etiology is unknown, it shares many risk factors with ED (ischemic heart disease, hypertension, hypercholesterolemia, diabetes, and increased age). It is difficult to determine whether NAION is related to the use of PDE5 inhibitors such as Viagra® and Cialis®, or to the underlying participant vascular risk factors or anatomical defects, or to a combination of these factors, or to some unknown factor. (Eli Lilly package insert)

In a press release with comments from the FDA, spokeswoman Susan Cruzan said, "The Food and Drug Administration still is investigating, but has no evidence yet that the drug is to blame [for the rare reports of blindness among some men using impotence drugs]."[50] (Eli Lilly package insert).

7.4.4 Daily Dosing of PDE5 Inhibitors: The VeCaPSED Trial

To assess safety of nightly dosing of maximum permissible daily dosage with a PDE5 inhibitor in a similar prostate cancer population, colleagues from Australia were kind enough to share preliminary data. In a similar but smaller ongoing Australian trial, "A randomized double-blind controlled trial of the use of daily sildenafil (Viagra) in men with early cancer of the prostate treated with radiation for the prevention of subsequent erectile dysfunction" (VeCaPSED), subjects start on the PDE5 inhibitor sildenafil or placebo 4 weeks after RT is completed (in the current proposal, patients start on drug or placebo at the start of RT) and continue daily for 6 months. Dosing is started at 50 mg with dose-escalate to 100 mg after 4 weeks. Preliminary toxicity data on the first 23 men accrued with 12-month data was provided. Seven men who took the active agent and 16 men who were on the placebo arm and completed 6 months of active agent or placebo were evaluated. All had tolerated 50 mg and had gone to 100 mg every

night. None had been withdrawn. Per CTCAE v3.0 adverse events criteria, 2 toxicities (in 1 patient) >Grade 2 (hematemsis and obstruction requiring catheter, both not thought to be drug-related) were documented. The most common adverse events noted were dyspepsia (in 9 patients) and mild nasal congestion (in 11 men).[51] These data, as in studies in other populations with ED using daily dosing of PDE5 inhibitors, show these drugs are well tolerated with minimal toxicity profiles (Eli Lilly package insert).

7.4.5 Other Trials of Long-Term Use of Tadalafil

Although there is little daily long-term data on the use of PDE 5 inhibitors in addition to that above, there is mounting long-term preliminary evidence of the safety of these drugs in patients treated for pulmonary arterial hypertension (PAH)[52-54] and recurrent priapism.[55] In studies of sildenafil (50 mg orally every 8 hours) administered for 3 to 12 months as adjuvant therapy to standard treatments for PAH, sildenafil was well tolerated with minimal side effects. This suggests that PDE5 inhibitors are safe and effective over long-term use.[52,53] Further, long-term use of PDE5 inhibitors is being tested in children as well as adults and all studies to date have found acceptable toxicity.[54]

7.5 Adverse Events (8/20/10)

The NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4 will be utilized for adverse event (AE) reporting. The CTCAE Version 4 is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE Version 4.

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup).

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (http://www.rtog.org/members/toxicity/main.html) for this information.

In order to ensure consistent data capture, serious adverse events reported on AdEERS reports also must be reported on an RTOG case report form (CRF). In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

7.5.1 Adverse Events (AEs)

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. January 2005; http://ctep.cancer.gov/reporting/adeers.html]

The following guidelines for reporting adverse events (AEs) apply to **all** NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1). **Note: AEs indicated in the AdEERS Expedited Reporting Requirements in text and/or table in Section 7.6 also must be reported via AdEERS.**

NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.

7.5.2 Serious Adverse Events (SAEs) — All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS. Contact the AdEERS Help Desk if assistance is required.

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:

- **Phase II & III Studies: All unexpected potentially related SAEs**
- **Phase I Studies: All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship**

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via AdEERS.

All supporting source documentation indicated as being provided in the Additional Information Section of the AdEERS Report must be properly labeled with the study/case numbers and the date of the event and must be faxed to both the NCI at 301-230-0159 and the RTOG dedicated SAE FAX, 215-717-0990, before the 5 or 10-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. The RTOG Case Number without any leading zeros should be used as the Patient ID when reporting via AdEERS. Non-RTOG intergroup study and case numbers must also be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient's case number as the patient ID when reporting via AdEERS.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. **Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as "expedited reporting NOT required" must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the "NOT Required" assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note:** Sites must select the option in AdEERS to send a copy of the report to the FDA or print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

7.5.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at http://ctep.cancer.gov/forms/index.html. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via the AdEERS system and must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.

RTOG Headquarters
AML/MDS Report
1818 Market Street, Suite 1600
Philadelphia, PA 19103

7.6 AdEERS Expedited Reporting Requirements

CTEP defines routine AE reporting requirements for phase 2 and 3 trials as described in the table below. **Important:** All AEs reported via AdEERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

Phase 2 and 3 Trials Utilizing an Agent Under a Non-CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent Tadalafil in this Study (Arm 1)

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a non-CTEP IND require reporting as follows:**

AdEERS 24-hour notification followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see exceptions below under section entitled "Additional Instructions or Exceptions."

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Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. "On study" is defined as during or within 30 days of completing protocol treatment.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a Non-CTEP IND:

None

8.0 SURGERY

Not applicable to this study

9.0 OTHER THERAPY

Not applicable to this study

10.0 TISSUE/SPECIMEN SUBMISSION (8/20/10)

NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission or quality of life assessment.

If the patient consents to participate in the specimen collection component of the study, the site is required to submit the patient's specimens as specified in Section 10.0 of the protocol. **Note**: Sites are not permitted to delete the specimen collection component from the protocol or from the sample consent.

10.1 Specimen Submission

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Biospecimen Resource provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. The RTOG Biospecimen Resource also collects tissue for Central Review of pathology. Central Review of tissue can be for eligibility and/or analysis.

In this study, serum, plasma, and whole blood will be submitted to the RTOG Biospecimen Resource for translational research (recommended). Single nucleotide polymorphisms (SNPs) and/or copy number variants (CNVs) in certain genes are associated with the development of erectile dysfunction (ED) resulting from RT for prostate cancer. The goal of this study will be to identify SNPs and CNVs associated with the development of erectile dysfunction in prostate cancer patients following RT.

10.2 Specimen Collection for Translational Research (Strongly Recommended)

For patients who have consented to participate in the blood collection component of the study (See Appendix I).

The following must be provided in order for the case to be evaluable for the Biospecimen Resource (See Appendix V for detailed instructions):

10.2.1 A Specimen Transmittal Form clearly stating that serum, plasma, or whole blood is being submitted for the RTOG Biospecimen Resource. It should be stated on the form that the specimen is being banked for translational research. The form must include the RTOG protocol number and patient's case number.

10.2.2 Storage Conditions

Store at -80° C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

OR:

- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

OR:

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

10.2.3 Specimen Collection Summary

Specimens taken from patient:	Collected when:	Submitted as:	Shipped:
5-10 mL of whole blood in red-top tube and centrifuge for serum	Once during treatment or during 1st follow-up visit	Frozen serum samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials	Serum sent frozen on dry ice via overnight carrier
5-10 mL of anticoagulated whole blood in EDTA tubes (purple/lavender top) and centrifuge for plasma	Once during treatment or during 1st follow-up visit	Frozen plasma samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials	Plasma sent frozen on dry ice via overnight carrier
5-10 mL of anticoagulated	Once during treatment or	Frozen whole blood samples	Whole blood sent frozen on

whole blood in purple/lavender EDTA tube for DNA	during 1st follow-up visit	containing a minimum of 0.5 ml per aliquot in 1 ml cryovials	dry ice via overnight carrier

10.2.4 Submit materials for Translational Research as follows:

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

10.3 Reimbursement (8/20/10)

RTOG will reimburse institutions for submission of protocol-specified biospecimen materials sent to the RTOG Biospecimen Resource at the University of California San Francisco and other protocol-specified collection repositories/laboratories. After confirmation from the RTOG Biospecimen Resource or other designated repository/laboratory that appropriate materials have been received, RTOG Clinical Trials Administration will authorize payment according to the schedule posted with the Reimbursement and Case Credit Schedule found on the RTOG web site (http://www.rtog.org/pdf_document/RTOG_STUDY_LIST.pdf). Biospecimen payments will be processed quarterly and will appear on the institution's summary report with the institution's regular case reimbursement.

10.4 Confidentiality/Storage

(See the RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/biospecimen/tissuefaq.html for further details.)

10.4.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The RTOG Biospecimen Resource database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.4.2 Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix II for a summary of patient assessments and time frames. See Section 11.2 below for details and/or exceptions to Appendix II.

11.2 Evaluation During Treatment

11.2.1 Married patients and their spouses or patients living as married with a partner (female or male partner is permitted) will also complete the Locke's Marital Adjustment Test (LMAT). Unmarried patients or married patients whose spouse refuses to participate will not complete the LMAT.

- Patients will be asked if they have a spouse or sole partner and if they will permit contact to recruit the spouse/partner to the study. The partner or spouse will be asked to complete the Sexual Adjustment Questionnaire, Partner version (SAQ-P) at the same time points.
- The schedule for Quality of Life (QOL) questionnaires is to be reviewed with the patient and partner/spouse before study entry.
- Patient and partner/spouse are to be reassured that these questionnaires will be kept separately and confidentially in their research charts at the site and at RTOG.

11.2.2 Assessments at week 28-30 will occur between 28-31 days after tadalafil ended.

11.2.3 Pill diary collection and pill counts: In addition to the time points in Appendix II (when compliance checks will occur in person), site staff will mail a compliance letter to patients during months 2, 4, 5, and 6 after the start of tadalafil or placebo.

11.2.4 The patient's use of erectile aids will be assessed with the Expanded Prostate Cancer Index Composite (EPIC) Sexual Medications and Devices Evaluations Supplement question regarding the "desire for sexual medications or devices if not currently using them."

11.2.5 See Section 11.4 for QOL measures. Additional instructions:

11.2.5.1 The QOL questionnaires are to be mailed by member site staff 1 week prior to the patient's scheduled visit when possible or given to the patients and their partner at their scheduled visits and should be completed before leaving the clinic.

11.2.5.2 Patients who fail to return for a scheduled appointment will receive follow-up phone calls from member site staff and the appointment should be rescheduled as close to the original date as possible.

11.2.5.3 Patients or partners who cannot or refuse to come in for an appointment must be asked if they will accept a telephone interview. The telephone interview will be conducted as follows: Research staff at the participating site will contact the participant by telephone to set up an appointment for a telephone interview at a time that is convenient for the participant. The date the interview was conducted, the name of the interviewer, and the name of the interviewee must be documented in writing.

11.2.5.4 Questionnaires must be reviewed after the patient/partner completes the form to be sure all items are answered and that each item has only 1 response. Patients/partners must sign and date each questionnaire upon completion.

11.2.5.5 It is permissible to send the questionnaire home with the patient or partner in a sealed envelope and a return addressed stamped envelope if he/she refuses to complete them at the time of their appointment.

11.2.5.6 Completed questionnaires should be sent by member site staff to RTOG within 14 days after study time point.

11.3 Criteria for Discontinuation of Protocol Treatment

11.3.1 In the absence of treatment delays due to adverse event(s), treatment may continue for the duration of each randomization period (168 days) or until any of the following criteria apply:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Concurrent use of any organic nitrates
- Concurrent use of cimetidine, ketoconazole, itraconazole, erythromycin or ritonavir
- Concurrent use of mechanical (vacuum) devices, intracorporeal, intraurethral, topical, or oral agents as therapy for ED
- General or specific changes in the patient's condition rendering the patient unacceptable for further treatment in the judgment of the investigator

11.3.2 If treatment is discontinued early, the patient will remain enrolled in the study and will undergo all remaining assessments and procedures per Section 11, unless any of the following criteria apply:

- Use of LHRH agonist androgen suppression (Lupron, Zoladex), antiandrogen (Casodex, Eulexin, Nilandron), or estrogenic (diethylstilbestrol) agents
- Request for withdrawal from patient or partner or spouse; if a partner or spouse withdraws from the study, the patient may continue on the study
- Discontinuation of external RT prior to completion of total treatment course or inability to perform brachytherapy
- Progression of disease requiring additional therapy (surgery or hormones) after initiation of study drug

The reason for and date of discontinuation for all patients who exit the study will be documented. Each partner or spouse will be asked to continue with follow-up until 2 years after the patient started radiation therapy or until the patient dies, if death occurs prior to completion of study requirements.

If protocol treatment is discontinued, follow-up and data collection will continue as specified in Sections 11 and 12.

11.4 Background and Description of Assessment Instruments

11.4.1 International Index of Erectile Function Questionnaire (IIEF)[56]

The IIEF was developed as a measure of erectile function and is mandatory for completion as the primary inclusion and outcome measure. Relevant cross-cultural domains of sexual function were identified via the literature and were reviewed and endorsed by an international panel of experts. The resulting 15-item questionnaire underwent linguistic validation in 10 languages. Psychometric testing was conducted, and a principal components analysis identified 5 factors with eigenvalues greater than 1.0: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. Internal consistency was high with Cronbach alphas for the 5 domains ranging from .73 to .92 with an overall alpha of .91. Scale reliability was determined with high test-retest correlation coefficients ranging from r=0.64 to r=0.84 depending on the domain. Discriminant validity was demonstrated by the scales' ability to differentiate between patients with ED and age-matched controls. IIEF was positively correlated with clinical interviews of sexual function but not with measures of marital adjustment and social desirability, exhibiting acceptable convergent and divergent validity. Sensitivity and specificity were demonstrated with those patients responding to ED treatment over time showing significant change while patients who did not respond to treatment showed no change in IIEF scores.[56] In addition, the 2-item partner questions developed as a companion to the IIEF will be given to patients' partners and include: "Has the quality of your partner's erections changed since your partner started treatment?"; "Has the quality of your sex life changed since your partner started treatment?" scored on a 1 to 5, (1=much worse to 5=much better) scale.[57]For partner convenience, these 2 items appear on the SAQ-P form.

11.4.2 Sexual Adjustment Questionnaire (SAQ)[58]

Patient Version: The SAQ is a 16-item patient self-assessment questionnaire modified from the 30-item version developed by Metcalfe and Waterhouse. The original psychometric testing was conducted on 84 healthy and 8 head and neck cancer patients. SAQ rates most responses on a 5-point Likert-type scale, with a higher score indicating a higher level of sexual adjustment. Combined data from 2 RTOG prostate cancer studies was used to assess the psychometric properties of the RTOG modified SAQ. Seven hundred and thirty-three patients were accrued on 2 RTOG studies as of March 1997. All patients were treated with external beam radiation therapy (RT) + neoadjuvant androgen suppression. SAQ was given to the patients pre-treatment and at follow up. If there were more than 5 missing answers, the questionnaire was rejected as incomplete. The RTOG modified SAQ retained 5 of the original 8 subscales, including: desire, activity, arousal, orgasm, and satisfaction, and dropped relationship, technique, and miscellaneous, due to concern for patient burden in large clinical trials.[59]

An exploratory factor analysis with oblique rotation was performed to discern the underlying structure. With the factors identified, a confirmatory factor analysis was performed to test construct validity. A total of 471 patients completed the pre-treatment SAQ. The factor analysis yielded a 5-factor solution and on the basis of content, was labeled as follows: 1. Dysfunction, 2. Satisfaction, 3. Desire, 4. Activity, and 5. Fatigue. Reliability was demonstrated with Cronbach alpha for the new subscales ranging from 0.66 to 0.86 with an overall alpha of 0.77. Construct validity was demonstrated with empirical testing of similar and dissimilar clinical measures. Specificity was exhibited by SAQ's ability to discriminate among younger patients (≤60) and older patients (>70). All 5 domains demonstrated a high degree of sensitivity to changes over time. There was a clear relationship among certain pre-treatment demographic and prognostic variables and SAQ scores, including age, ejaculation and erection. Patients who were younger (≤60), able to have erections, and were not having problems with ejaculation at the time of study enrollment had superior scores compared to patients who were older (60-69 or >70), or having difficulties with erection or ejaculation pre-treatment. There was no difference in scores by race. Of additional interest, physician and patient assessment of the patient's ability to have an erection differed in up to 47% of cases. The RTOG modified SAQ appears to provide more accurate assessment of patient sexual function compared to physician assessment in the same study, reinforcing the value of QOL patient self-assessments in clinical trials.[59] This instrument should be completed by the patient (if they consent) even if they do not currently have a spouse/partner or if their spouse/partner refuses participation.

11.4.3 Sexual Adjustment Questionnaire, Partner Version (SAQ-P)

The RTOG modified SAQ has been adapted for partner (either female or male partner) participation in this study. The same questions as in the patient version are asked of partners, with the modification that partners are to fill out the questionnaire from their own perspective.

The Partner Version was used in the previous RTOG sildenafil trial conducted by the Principal Investigator, RTOG 0215. This instrument will be used for spouses/partners but if the partner refuses to participate, the patient should still complete the patient version of the SAQ.

11.4.4 Locke's Marital Adjustment Test (LMAT)[60]

The LMAT is a well-established 23-item self-administered instrument that measures marital adjustment. The same instrument is completed by married patients and their spouses, with weighted scoring allowing for a possible range for men of 48 to 138 and for women of 50 to 138. A principal components factor analysis with varimax rotation identified a 3-factor solution labeled sexual congeniality, compatibility, and closeness. Criteria for factor loading included a minimum of 2 items with loadings greater than .50. Two to 4 year test-retest correlations were remarkably stable at .76 for wives and .78 for husbands. This instrument will be used for husbands and wives or for patients living with a partner as married whether the partner is female or male. Unmarried or unpartnered patients or patients whose spouse/partner refuses participation will not have to complete this questionnaire.

11.4.5 Expanded Prostate Cancer Index Composite (EPIC) Sexual Medications and Devices Evaluation Supplement[61]

The Utilization of Sexual Medications and Devices Supplement, developed as a companion questionnaire to the EPIC, will be administered to assess patient utilization of medications and devices for erectile dysfunction and the effectiveness of such interventions. The patient-completed Utilization of Sexual Medications/Devices will be collected to provide a context for interpreting the sexual domain score of the EPIC questionnaire.

12.0 DATA COLLECTION

Data should be submitted to:

RTOG Headquarters*
1818 Market Street, Suite 1600
Philadelphia, PA 19103

***If a data form is available for web entry, it must be submitted electronically.**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission (8/20/10)

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)**	Within 2 weeks of registration
IIEF [patient] **(QF)**	
SAQ [patient] **(SA)** SAQ-P [spouse/partner] **(SB)** LMAT [patient] **(PF)** LMAT [spouse/partner] **(PQ)** EPIC **(FA)**	
Pill Diary **(DP)**	2, 13, and 30 weeks after the start of tadalafil or placebo
Treatment Form **(TF)**	2, 13, and 30 weeks after the start of tadalafil or placebo
IIEF [patient] **(QF)**	2, 4, 24, 30 weeks and 1 and 2 years after start of tadalafil or placebo
SAQ [patient] **(SA)** SAQ-P [spouse/partner] **(SB)**	24, 30 weeks and 1 and 2 years after start of tadalafil or placebo

LMAT [patient] **(PF)** LMAT [spouse/partner] **(PQ)**	
EPIC **(FA)**	30 weeks, 1 and 2 years after start of tadalafil or placebo
Follow-Up Form **(F1)**	1 and 2 years after start of tadalafil or placebo
Compliance Letter **(FC)**	2, 4, 5, and 6 months after start of tadalafil or placebo
Final Dosimetry Data	
Radiotherapy Form **(T1)**	Within 1 week of the completion of RT

NOTE: All digital RT data will be archived at the site. RTOG Headquarters will request digital data to be submitted in the event that the Principal Investigator would like to review due to toxicities or other issues with the case.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints (8/20/10)

13.1.1 Primary Endpoint

Spontaneous (off-drug) erectile function, as measured by the International Index of Erectile Function (IIEF)-Question 1 at weeks 28-30 after initiation of radiation therapy (RT) for prostate cancer

13.1.2 Secondary Endpoints

13.1.2.1 Spontaneous (off-drug) erectile function at years 1 and 2 after initiation of RT

13.1.2.2 Overall sexual function, as measured by the total IIEF, at weeks 28-30 and years 1 and 2 after initiation of RT

13.1.2.3 Overall sexual satisfaction, patient and partner, as measured by the SAQ, at weeks 28-30 and years 1 and 2 after initiation of radiation treatment

13.1.2.4 Marital adjustment, patient and partner, as measured by the LMAT, at weeks 28-30 and years 1 and 2 after initiation of RT

13.1.2.5 Patient-related predictors of erectile function—age, pretreatment response, tobacco use, comorbidities—at weeks 28-30 and years 1 and 2 after initiation of RT

13.1.2.6 Adverse events according to CTCAE criteria (CTCAE Version 4)

13.1.2.7 Collection of patient specimens for future translational research analyses, specifically predictive and prognostic biomarkers of erectile dysfunction

13.1.3 Tertiary Endpoints (Exploratory Aims)

13.1.3.1 Patient follow-up treatment for erectile dysfunction—tadalafil, a PDE5 inhibitor other than tadalafil, a non-PDE5 inhibitor, or no erectile aide at weeks 28-30 and years 1 and 2

13.1.3.2 RT factors, including modality, prescribed total dose, planning target volume margin, penile bulb DVH parameters, associated with spontaneous (off-drug) erectile function at weeks 28-30 and years 1 and 2 after initiation of RT

13.1.3.3 Evaluation of number of patients screened for inclusion, the number that are presented the protocol, the number who refuse, and the number accrued

13.2 Sample Size (8/20/10)

13.2.1 Stratification and Randomization

Patients will be stratified before randomization with respect to RT modality (external RT vs. brachytherapy) and age (≤65 years vs. >65 years) because there may be differences in erectile response based on RT dose and distribution within the PTV and to critical normal structures (e.g., penile bulb), and because there are highly significant individual variations in erectile response associated with the aging process. The treatment allocation scheme described by Zelen[62] will be used because it balances patient factors other than institution. Within each stratum, patients will be randomized in a 1:1 ratio to either tadalafil or placebo after RT.

13.2.2 Sample Size Derivations

The sample size calculations will address the specific primary hypothesis that the use of tadalafil (Arm 1) will result in a statistically significant change in the proportion of patients maintaining spontaneous erectile function as compared to the use of placebo (Arm 2). No adjustments will be made for addressing the secondary hypotheses. All eligible patients will have responded to Question 1 of the IIEF form with a 3, 4, or 5 response at baseline (pre-treatment). Maintenance of spontaneous erectile function will be defined as patient response at 28-30 weeks that is at least the same as their response at pre-treatment. Patients maintaining erectile function are considered responders. Patients that have a lower week 28-30 score (IIEF Q1) than the baseline score will have less erectile function and are considered non-responders.

Moyad[63] documents a placebo response rate of 25% (range 23-41%) in PDE5 inhibitor trials across a variety of erectile dysfunction etiologies. Currently, the only double-blind placebo controlled tadalafil trial[37] reports a placebo response rate of 20%. Based on these results, we expect patients receiving placebo to experience a similar response rate. We expect patients receiving tadalafil to experience an increased response rate of 40%. Based on a 2-sided Fisher exact test with alpha=0.05, 91 patients per arm would be required to have 80% statistical power to detect an increase from 20% to 40% in spontaneous erectile response at weeks 28-30. Assuming an attrition rate of 15%,[64] the **target sample size will be 218 patients**.

13.3 Patient Accrual

Based on patient accrual to RTOG 9910, a prostate treatment trial, there will be negligible accrual (10 patients) during the initial 6 months while institutions are obtaining IRB approval. After this initial period, it is projected that this study will accrue approximately 10 patients per month and that it will take 27 months to accrue the sample size of 218 patients. The RTOG Data Monitoring Committee (DMC) will begin evaluating patient accrual semi-annually. If the average monthly accrual rate for the trial in the fifth and sixth quarters after study activation (i.e., in months 13-18) is less than 20% of the rate projected in the paragraph above (i.e., less than 2 patients per month), the study will be re-evaluated for feasibility. If the average monthly accrual rate is greater than 20% but less than 50% of projected (i.e., between 2-5 patients per month), the trial will be placed on probation for 6 months. If the average monthly accrual rate at the end of the probationary period is less than 50% of projected (5 patients per month), the study statistician will recommend to the RTOG DMC that the trial close to future accrual.

13.4 Analysis Plan

All randomized patients that are eligible for the study will be included in the comparison of treatment arms, regardless of treatment compliance (intent-to-treat analysis).

13.4.1 Primary Endpoint

The primary endpoint is maintenance of spontaneous (off-drug) erectile function at weeks 28-30 after initiation of RT, as measured by the IIEF Q1. All patients have erectile function prior to initiation of RT, indicated by a score of 3, 4, or 5 on IIEF Q1. Patients with a lower IIEF Q1 score at weeks 28-30 than at baseline will have less erectile function and be categorized as nonresponders. Patients with similar or improved erectile function will be categorized as responders. We hypothesize that the proportion of patients maintaining erectile function while receiving tadalafil (Arm 1) will be significantly higher than for patients receiving placebo treatment (Arm 2).

$H_0: p_1 = p_2$ vs. $H_A: p_1 \neq p_2$
where p_i is the proportion of patients maintaining spontaneous erectile function in arm i.

Treatment differences will be tested at the 0.05 significance level using the Fisher exact test. Point estimates and 95% confidence intervals will also be provided. Subgroup analyses based on the stratification variables, RT modality and age, will also be conducted.

Patients who die prior to the week 28-30 assessment will be analyzed separately. If these patients are not equally distributed between the 2 treatment arms, a sensitivity analysis will be conducted to determine the impact of the exclusion.

Imputation methods will be used to determine values for all live patients missing the week 28-30 assessment. Multiple imputation procedure provides a valid strategy for dealing with missing data sets, properly reflecting the uncertainty due to missing values and will be used for estimating the missing data. Other imputation methods will be used to assess the sensitivity of imputation. In the propensity score method, a logistic regression model will be used to generate a propensity score for each live patient indicating the probability of that observation being missing given patient baseline IIEF Q1 score and treatment group. The observations are then grouped based on these propensity scores, and an approximate Bayesian bootstrap imputation is applied to each group.[65]

13.4.2 Secondary Endpoints

13.4.2.1 *Spontaneous Erectile Response*

Erectile function will be assessed at years 1 and 2 in addition to the primary endpoint of weeks 28-30. Treatment differences will be tested at the 0.05 significance level using the Fisher exact test. Point estimates and 95% confidence intervals will also be provided. In addition to comparing response at specific time points, trends in response will be modeled using the generalized estimation equation (GEE).[66] The model allows for adjustments using baseline erectile function, stratification variables, and other covariates of interest.

13.4.2.2 *Overall Sexual Function (International Index of Erectile Function)*

The IIEF is a 15-item questionnaire in which scores range from 0 to 75 and higher scores indicate improved sexual function. Patients must answer all 15 items to have a composite score. Changes in sexual function from baseline (pretreatment) to weeks 28-30 and years 1 and 2 will be of interest. Treatment differences will be tested at the 0.05 significance level using the *t* test. Point estimates and 95% confidence intervals will also be provided.

In addition to comparing change in sexual function at specific time points (weeks 28-30, year 1 and year 2) trends in sexual function will be modeled using the general linear mixed model.[67] The model allows for adjustments using stratification variables and other covariates of interest.

13.4.2.3 *Overall Sexual Satisfaction, Patient and Partner (Sexual Adjustment Questionnaire)*

The SAQ is a 20-item questionnaire in which scores range from 0 to 100 and higher scores indicate improved sexual well-being. Patients must answer at least 15 items to have a composite score. Missing item values are imputed using the average value of the completed items. The SAQ comprises 5 domains: desire (Q1,Q3,Q5-6,Q8,Q14), dysfunction (Q10-13,Q17), activity (Q7,Q9), satisfaction (Q15-16), and fatigue (Q4).

The SAQ-Partner is an 18-item questionnaire in which scores range from 0 to 90 and higher scores indicate improved sexual well-being. Partners must answer at least 14 items to have a composite score. Missing item values are imputed using the average value of the completed items. The SAQ comprises 5 domains—desire (Q1-2,Q4-6,Q9), dysfunction (Q8,Q12,Q14-16), activity (Q7), satisfaction (Q10-11), and fatigue (Q3).

Changes in both partner and patient sexual satisfaction from baseline (pretreatment) to weeks 28-30 and years 1 and 2 will be of interest. Treatment differences will be tested at the 0.05 significance level using the *t* test. Point estimates and 95% confidence intervals will also be provided.

In addition to comparing changes in patient (partner) sexual satisfaction at specific time points (weeks 28-30, year 1 and year 2) trends in sexual satisfaction will be modeled using the general linear mixed model. The model allows for adjustments using stratification variables and other covariates of interest.

In addition to comparing treatment differences in patient (partner) sexual satisfaction, Spearman's correlations, computed using the bootstrap method to adjust for multiple assessments per patient, will be used to determine the association between patient and partner sexual satisfaction within and across treatment arms.[68] Associations between both patient and partner sexual satisfaction and marital adjustment will be evaluated in a similar manner.

13.4.2.4 *Marital Adjustment, Patient and Partner (Locke's Marital Adjustment Test)*

Locke's Marital Adjustment Test (LMAT) is a 23-item questionnaire in which scores range from 48 to 138 for male partners and from 50 to 138 for female partners and higher scores indicate improved marital adjustment. Respondents must answer all 23 items to have a composite score.

Changes in both partner and patient marital adjustment from baseline (pretreatment) to weeks 28-30 and years 1 and 2 will be of interest. Treatment differences will be tested at the 0.05 significance level using the *t* test. Point estimates and 95% confidence intervals will also be provided.

In addition to comparing changes in patient (partner) marital adjustment at specific time points (weeks 28-30, year 1 and year 2) trends in marital adjustment will be modeled using the general linear mixed model. The model allows for adjustments using stratification variables and other covariates of interest.

In addition to comparing treatment differences in patient (partner) marital adjustment, Spearman's correlations, computed using the bootstrap method to adjust for multiple assessments per patient, will be used to determine the association between patient and partner marital adjustment within and across treatment arms.[68] Associations between both patient and partner sexual satisfaction and marital adjustment will be evaluated in a similar manner. If feasible, further subgroup analyses will be conducted if substantial numbers of same sex partners participate.

13.4.2.5 *Predictors of Erectile Response*

Multivariate logistic regression will be used to model the distribution of spontaneous response at weeks 28-30, adjusting for covariates, including, but not limited to treatment arm, age, pretreatment erectile response, tobacco use, and comorbidities. Both unadjusted and adjusted odds ratios and their respective 95% confidence interval will be computed.[69] Additionally, GEEs will be used to model the distribution of spontaneous response at weeks 28-30 and years 1 and 2, adjusting for covariates, including, but not limited to treatment arm, age, pretreatment erectile response, tobacco use, and comorbidities.

13.4.2.6 *Incidence of Adverse Events*

Adverse events are reported according to CTCAE criteria (CTCAE Version 4). Differences in incidence rates at weeks 28-30 between the two treatment arms will be tested at the 0.05 significance level using the χ^2 test.

13.4.2.7 *Collection of patient specimens for future translational research analyses, specifically predictive and prognostic biomarkers of erectile dysfunction*

The feasibility of proposed translational studies will be assessed following completion of accrual and sample collection. At the time of data maturity of this study, we will address the assays that will be used and develop a list of specific correlative aims with identified markers of interest and appropriate statistical considerations. The following is a general guideline for the statistical consideration for this analysis. In determining the prognostic value of single nucleotide polymorphisms (SNPs) or copy number variants (CNVs), case subjects will be men that represent the 20% of patients in this study that exhibit the largest pre-treatment to post-treatment decrease in their IIEF scores, i.e., the worst development of ED. The control subjects will be the 20% of patients that exhibited the largest increase (or smallest decrease) in their post-treatment IIEF scores, i.e., the patients who maintained erectile function. In determining the predictive value of SNPs or CNVs the cases and controls will be determined within each treatment arm, placebo or tadalafil. The null hypothesis of no association between case/control status (ED/erectile function) and SNP genotype will be tested using at least Fisher's exact test and other methods such as the Cochran-Armitage test and haplotype-based methods.[70] The false discovery rate (FDR) approach will be used to correct for multiple testing.[71] Odds ratios for ED and corresponding 95% confidence intervals will be estimated using conditional multivariable logistic regression models. A two-step analysis of the SNP/CNV data will be performed. First, approximately 150 genes (100 SNPs) known to be associated with response to radiation will be examined for associations with ED. Second, all available SNPs (approximately 1 million) will be tested for association with ED. Because the number of case subjects will be modest (see Section 10.0), SNPs that are identified may require further validation using a larger number of patient samples in a replication set.

13.4.3 Tertiary Endpoints

13.4.3.1 *Follow-up Treatment for Erectile Dysfunction, Patient Preference*

The proportion of patients who decide to (1) continue on tadalafil; (2) continue on another PDE5 inhibitor; (3) continue with a non-PDE5 inhibitor erectile aid; or (4) continue without any erectile aids will be compared at weeks 28-30 and years 1-2. Treatment differences will be tested at the 0.05 significance level using the χ^2 test. In addition to comparing the response at specific time points, trends in patient preference will be modeled using GEEs. The model allows for adjustments using stratification variables and other covariates of interest.

13.4.3.2 *Radiotherapy Factors Associated with Spontaneous Erectile Response*

Logistic regression will be used to evaluate predictive factors of erectile response such as RT modality, prescribed total dose, PTV margin, and penile bulb DVH parameters.

13.4.3.3 *Evaluation of Screening and Eligibility*

Descriptive statistics will be provided detailing the number of patients screened for eligibility, the number of eligible patients presented the protocol, and the number of eligible patients that enroll on the protocol.

13.5 Interim Reports to Monitor Study Progress

The RTOG Data Monitoring Committee (DMC) will monitor the trial for safety. Interim reports with descriptive statistics will be prepared twice a year until the initial paper reporting the treatment results has been accepted for publication. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase; data quality; compliance rate of treatment delivery with the distributions of important prognostic baseline variables; and the frequencies and severity of adverse events. The interim reports will not contain results from the treatment comparisons with respect to the primary or secondary endpoints.

This study will also be monitored by the Clinical Data Update System (CDUS) version 3.0. Quarterly CDUS reports are submitted electronically.

13.6 Reporting the Initial Treatment Results

The purpose of this study is to determine whether the use of tadalafil will significantly change the proportion of patients maintaining spontaneous erectile function at weeks 28-30 as compared to placebo. The final analysis will occur after each patient has been potentially followed for at least 30 weeks from randomization. It will include tabulation of all cases entered and those excluded from the analyses with the reasons for such given; the distribution of the important prognostic baseline variables; and observed results with respect to the primary and secondary endpoints. The primary hypothesis of tadalafil treatment benefit will be compared using the Fisher exact test after imputing for missing values as specified in the analysis plan. Also, where feasible, treatment comparisons with respect to all endpoints will be compared within each racial and ethnic category.

13.7 Gender and Minorities

In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, participation rates of women and minorities will be examined during the interim reports. Based on accrual statistics from RTOG 0215, the sildenafil trial, the projected accrual by gender, race, and ethnicity is shown below:

Projected Distribution of Gender & Minorities

	Gender
	Males
Ethnic Category	
Hispanic or Latino	9
Not Hispanic or Latino	209
Ethnic Category: Total of all subjects	**218**

	Gender
	Males
Racial Category	
Native American or Alaskan Native	0
Asian	2
Black or African American	57
Native Hawaiian or other Pacific Islander	0
White	159
Racial Category: Total of all subjects	**218**

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APPENDIX I
RTOG 0831

Informed Consent Template for Cancer Treatment Trials
(English Language)

A Randomized, Double-Blinded, Placebo-Controlled Phase III Trial to Evaluate the Effectiveness of a Phosphodiesterase 5 Inhibitor, Tadalafil, in Prevention of Erectile Dysfunction in Patients Treated With Radiotherapy for Prostate Cancer

[Prevention of Erectile Dysfunction Study (PEDS)]

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have prostate cancer and as part of your treatment, you are receiving radiation therapy with either external beam or with a brachytherapy implant.

Why is this study being done?

The purpose of this study is to compare the effects, good and/or bad, of a drug, tadalafil, with a placebo (an inactive drug). Tadalafil is given as a treatment for erectile dysfunction (inability to maintain an erection long enough to engage in sexual intercourse). This study is being done to find out if tadalafil prevents erectile dysfunction in men with prostate cancer who are undergoing radiation therapy (that is, if the drug helps the participants taking it to maintain an erection following sexual stimulation). In this study, you will get tadalafil or placebo. You will not get both.

How many people will take part in the study?

About 218 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study**,** you will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- History and physical exam, including a digital rectal examination and an assessment of your ability to carry out activities of daily living (which will include questions such as whether you are able to feed, bathe, and dress yourself)
- Blood tests to measure testosterone and PSA (a value that helps determine the aggressiveness of your prostate cancer)

- You will be asked to complete one questionnaire: International Index of Erectile Function Questionnaire (IIEF). The IIEF assesses erectile function and takes about 5-10 minutes to complete.
- You will be asked to give information about any medications that you may be taking.

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part, you will be "randomized" into one of the study groups described below.

Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your study doctor can choose the group you will be in. You will have an equal chance of being placed in either group.

If you are in group 1 (often called "Arm A"), you will take tadalafil (1 pill) by mouth every day for 168 days (24 weeks), beginning within 7 days after starting radiation therapy (either external beam or brachytherapy).

If you are in group 2 (often called "Arm B"), you will take a placebo (1 “inactive” pill that looks and tastes like tadalafil but does not have an effect on the body) by mouth every day for 168 days (24 weeks), beginning within 7 days after starting radiation therapy (either external beam or brachytherapy).

After randomization, you will need the following tests and procedures:
<u>2 weeks after starting tadalafil or placebo</u>

- Completion of one questionnaire: IIEF
- You will be asked to turn in your pill diary and pill counts. You will use the pill diary to keep track of when you take pills and how many.
- You will be asked to give information about any medications that you may be taking

<u>4 weeks after starting tadalafil or placebo</u>

- Completion of one questionnaire: IIEF

<u>13 weeks after starting tadalafil or placebo</u>

- You will be asked to turn in your pill diary and pill counts.

<u>20-24 weeks after starting tadalafil or placebo</u>

- Completion of one questionnaire: IIEF

Both Groups
For the duration of this study (24 weeks), you must agree to take only the study pills and not use any other medication or devices to get an erection. In addition, although you can take your usual medications, you must agree not to take any organic nitrate (such as nitroglycerin) or drugs such as cimetidine, ketoconazole, itraconazole, erythromycin, or ritonavir while taking part in this study (for 24 weeks). If you are not sure if you are taking any of these drugs, you can talk to your doctor. If your doctor tells you that you need to take one of these drugs, you must stop taking tadalafil/placebo, and tell us immediately by calling *[doctor/institution]*.

When you are finished taking tadalafil or placebo, you will need these tests or procedures**:**
28-30 weeks after starting tadalafil or placebo

- Blood test to measure testosterone level
- Completion of one questionnaire: IIEF
- You will need to turn in your pill diary and pill counts at this time
- You will be asked to give information about any medications that you may be taking

1 year (52-54 weeks) after starting tadalafil or placebo

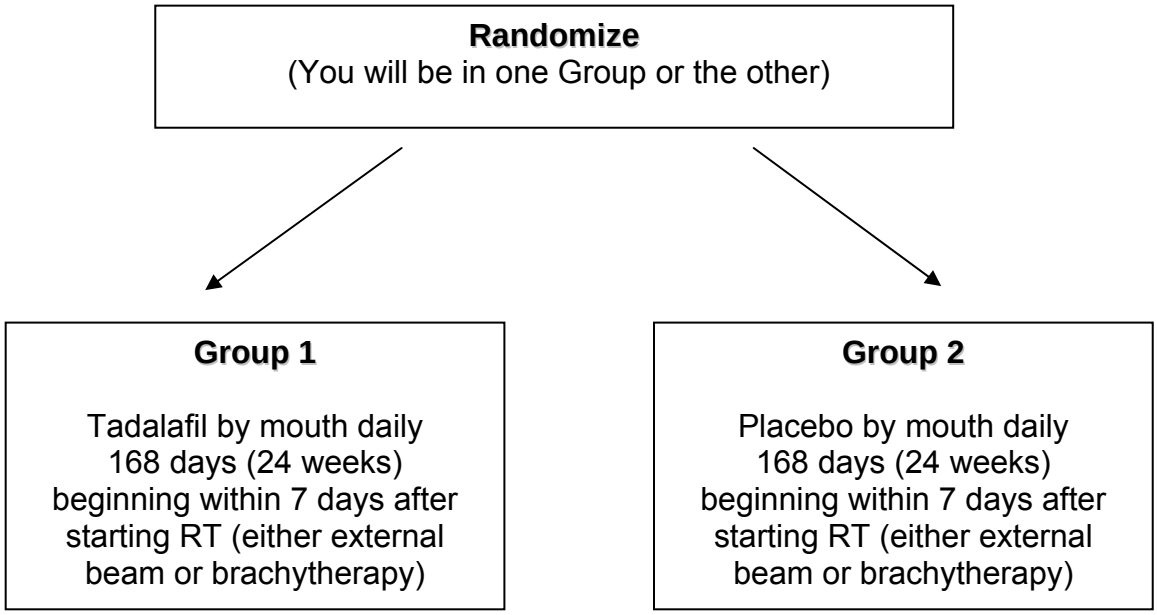
- Blood test to measure testosterone level
- Completion of one questionnaire: IIEF
- You will be asked to give information about any medications that you may be taking

2 years after starting tadalafil or placebo

- Blood test to measure testosterone level
- Completion of one questionnaire: IIEF
- You will be asked to give information about any medications that you may be taking

Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.



How long will I be in the study?

You will be asked to take tadalafil or placebo for 168 days (24 weeks). After you are finished taking tadalafil or placebo, the study doctor will ask you to visit the office for follow-up examination and to complete the study questionnaires at 28-30 weeks and again at 1 year and 2 years after the start of tadalafil or placebo.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the tadalafil can be evaluated by him/her. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study? (8/20/10)

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the tadalafil. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Other than headache, which was reported by only 11% of patients, risks and side effects related to the tadalafil are rare (reported by 5% or less of the patients who took the medication) and include:

- Upset stomach
- Back pain
- Muscle ache
- Nasal congestion
- Flushing
- Limb pain

Rare, but serious (reported by less than 2% of patients who took the medication)

- Chest pain
- Myocardial infarction (heart attack)
- Abnormal heart beat
- High blood pressure
- Changes in the optic nerve leading to vision abnormalities
- Decreased hearing, hearing loss (in rare cases, may become permanent)
- Severe rash resulting in skin breakdown (Stevens-Johnson Syndrome)
- Painful erection that won't go away (priapism)

When taking alpha-blocker medications, your risk increases for

- Orthostatic hypotension (sudden decrease in blood pressure when you stand up, resulting in dizziness, faintness or lightheadedness)

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While researchers hope tadalafil will prevent erectile dysfunction in men undergoing radiation therapy for prostate cancer, there is no proof of this yet. We do know that the information from this study will help researchers learn more about tadalafil as a form of treatment for preventing erectile dysfunction in men undergoing radiation therapy for prostate cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for erectile dysfunction without being in a study
- Taking part in another study
- Getting no treatment for erectile dysfunction

Talk to your study doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

Data are housed at RTOG Headquarters in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The Radiation Therapy Oncology Group (RTOG)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Lilly USA, LLC, the manufacturer of tadalafil and the placebo

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Eli Lilly and Company will supply the tadalafil or placebo at no charge while you take part in this study. Eli Lilly and Company does not cover the cost of getting the tadalafil or placebo ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the tadalafil or placebo for some reason. If this occurs the study would likely close or be redesigned as a study without placebo. If a problem with getting tadalafil or placebo occurs, your study doctor will talk to you about these options.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

A Data Monitoring Committee (DMC) will be regularly meeting to monitor safety and other data related to this study. The Committee members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). *[*Only applies to sites using the CIRB.]*

Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say 'no' to taking part in this additional research.

You can say "yes" or "no" to the following study. Please mark your choice below.

Quality of Life Study (8/20/10)

We want to know your view of how your life has been affected by cancer and its treatment. This "Quality of Life" study looks at how you are feeling physically and emotionally during your cancer treatment. It also looks at how you are able to carry out your day-to-day activities.

This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer.

<u>You and your spouse/partner</u> (if your spouse/partner agrees to participate) will be asked to complete the *Sexual Adjustment Questionnaire (SAQ)* or the *SAQ-Partner version* at five different times: before you begin taking tadalafil or placebo, at 20-24 weeks and at 28-30 weeks after you begin taking tadalafil or placebo, and 1 year and 2 years after you begin taking tadalafil or placebo.

<u>Married patients and their spouses</u> (if your spouse agrees to participate) will be asked to complete another questionnaire, *Locke's Marital Adjustment Test (LMAT)*, at the same times as the above questionnaires are completed: before you begin taking tadalafil or placebo, at 20-

24 weeks and at 28-30 weeks after you begin taking tadalafil or placebo, and 1 year and 2 years after you begin taking tadalafil or placebo.

In addition, you will be asked to complete one questionnaire [the Expanded Prostate Cancer Index Composite (EPIC)] about the use of erectile aids, such as medications or devices, at four different times: before you begin taking tadalafil or placebo, at 28-30 weeks after you begin taking tadalafil or placebo, and at 1 year and 2 years after you begin taking tadalafil or placebo.

It will take about 30 to 45 minutes to fill out the questionnaires each time you and your spouse/partner are asked to complete them. If any questions make you and your spouse/partner feel uncomfortable, you and your spouse/partner may skip those questions and not give an answer.

If you and your spouse/partner decide to take part in this "Quality of Life" study, the only thing you and your spouse/partner will be asked to do is fill out the questionnaires. You and your spouse/partner may change your mind about completing the questionnaires at any time.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please circle your answer.

I choose to take part in the Quality of Life Study. I agree to fill out the Quality of Life Questionnaires.

YES NO

Consent Form for Use of Blood for Research

About Using Blood for Research

You are going to have blood tests before you begin taking tadalafil or placebo, at 28-30 weeks after you begin taking tadalafil or placebo, and at 1 year and 2 years after you begin taking tadalafil or placebo as part of your cancer care. We would like to keep about four teaspoons of blood (from either your pre-treatment visit blood draw or from your first follow-up visit after you start treatment) for future research as well. If you agree, this blood will be kept and may be used in research to learn more about cancer and other diseases. One specific test will analyze whether your blood contains certain genes and if the side effects you had from radiation therapy (such as erectile dysfunction) are related to these genes. We will then try to see if these genes can help us learn about why some people get worse side effects than others.

Your blood may be helpful for research. The research that may be done with your blood is not designed specifically to help you. It might help people who have cancer and other diseases in the future. Reports about research done with your blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About
The choice to let us keep the left over blood for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

If you decide now that your blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your blood. Then any blood that remains will no longer be used for research and will be returned to the institution that submitted it.

In the future, people who do research may need to know more about your health. While the *[Institution: insert relevant information]* may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes blood is used for genetic research (about diseases that are passed on in families). Even if your blood is used for this kind of research, the results will not be put in your health records. Your blood will be used only for research and will not be sold. The research done with your blood may help to develop new treatments for cancer and other diseases in the future.

Benefits

The benefits of research using blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at _____ *[IRB's phone number]*.

No matter what you decide to do, it will not affect your care.

1. My blood may be kept for use in research to learn about, prevent, or treat cancer.

Yes No

2. My blood may be kept for use in research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No

3. Someone may contact me in the future to ask me to take part in more research.

Yes No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

APPENDIX IA
RTOG 0831

Informed Consent Template for Spouses/Partners of RTOG 0831 Trial Participants: Quality of Life Study
(English Language)

A Randomized, Double-Blinded, Placebo-Controlled Phase III Trial to Evaluate the Effectiveness of a Phosphodiesterase 5 Inhibitor, Tadalafil, in Prevention of Erectile Dysfunction in Patients Treated With Radiotherapy for Prostate Cancer

[Prevention of Erectile Dysfunction Study (PEDS)]

Why is this study being done?

Your spouse or partner has agreed to participate in RTOG 0831, a clinical trial (research study) for men being treated with radiation therapy for prostate cancer. In addition to the main RTOG 0831 study, we are conducting a "Quality of Life" study. We want to know your spouse or partner's view of how their life has been affected by cancer and its treatment. This "Quality of Life" study looks at how your spouse or partner is feeling physically and emotionally during their cancer treatment. It also looks at how they are able to carry out their day-to-day activities.

In addition to your spouse or partner's participation, we also want to know your view of how your spouse or partner's life has been affected, physically and/or emotionally, by cancer and its treatment.

How many people will take part in the study?

The spouses or partners of about 218 men participating in RTOG 0831 will take part in this study.

What will happen if I take part in this research study and how long will I be in the study? **(8/20/10)**

If you agree to participate, you will be asked to complete the *Sexual Adjustment Questionnaire–Partner version (SAQ-P)* at five different times: before your spouse or partner begins taking tadalafil (RTOG 0831 study drug) or placebo (inactive pill that looks like tadalafil), at 20-24 weeks and at 28-30 weeks after your spouse or partner begins taking tadalafil or placebo, and 1 year and 2 years after your spouse or partner begins taking tadalafil or placebo.

Spouses or partners living as married with an RTOG 0831 participant will be asked to complete another questionnaire, *Locke's Marital Adjustment Test (LMAT)*, at the same times as the SAQ-P is completed: before your spouse or partner begins taking tadalafil or placebo, at 20-24 weeks and at 28-30 weeks after your spouse or partner begins taking tadalafil or placebo, and 1 year and 2 years after your spouse or partner begins taking tadalafil or placebo. The SAQ assesses sexual adjustment and the LMAT assesses marital adjustment.

It will take about 30 to 45 minutes to fill out the questionnaires each time you are asked to complete them. If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

If you decide to take part in this "Quality of Life" study, the only thing you will be asked to do is fill out the questionnaires. You may change your mind about completing the questionnaires at any time.

What side effects or risks can I expect from being in the study?
None. If any questions in the questionnaires make you feel uncomfortable, you may skip those questions and not give an answer.

Will my personal information be kept private?

We will do our best to make sure that your personal information will be kept private.
Data are housed at RTOG Headquarters in a password-protected database. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your responses to the questionnaires for research, quality assurance, and data analysis include:

- The Radiation Therapy Oncology Group (RTOG)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Lilly USA, LLC, the manufacturer of tadalafil and the placebo

What are the costs of taking part in this study?

There will be no costs to you for participating in this study. You will not be paid for taking part in this study.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may change your mind about completing the questionnaires at any time. No matter what decision you make, there will be no penalty to you.

Who can answer my questions about the study?

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). *[*Only applies to sites using the CIRB.]*

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your spouse or partner's study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant_____
(Spouse/Partner of RTOG 0831 Participant)

Date _____

APPENDIX II: STUDY PARAMETERS [*See Sections 3.0, 4.0, or 11.2 for details and/or exceptions.]

Assessment	**Pre-Treatment (may be required for eligibility)**	**During Treatment**				**Follow-Up**		
	Pre-RT	**2 Wks After Drug/Placebo Start**	**4 Wks After Drug/Placebo Start**	**13 Wks After Drug/Placebo Start**	**20-24 Wks After Drug/Placebo Start**	**28-30* Wks After Drug/Placebo Start**	**1 Year (52-54 Wks) After Drug/Placebo Start**	**2 Years After Drug/Placebo Start**
History/physical with DRE	X							
Zubrod	X							
Testosterone	X					X	X	X
PSA	X							
IIEF* (patient)	X	X	X		X	X	X	X
SAQ* (patient)	If patient consents				If patient consents	If patient consents	If patient consents	If patient consents
LMAT* (married patients)	If patient consents				If patient consents	If patient consents	If patient consents	If patient consents
SAQ-P* (spouse/partner)	If spouse/partner consents				If spouse/partner consents	If spouse/partner consents	If spouse/partner consents	If spouse/partner consents
LMAT* (spouses)	If spouse consents				If spouse consents	If spouse consents	If spouse consents	If spouse consents
EPIC-Use of erectile aids*	If patient consents					If patient consents	If patient consents	If patient consents
Pill diary collection & pill counts*		X		X		X		
Concurrent medications	X	X				X	X	X
Adverse events	X	X				X	X	X

APPENDIX III

ZUBROD PERFORMANCE SCALE

0	**Fully active, able to carry on all predisease activities without restriction**
1	**Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work**
2	**Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours**
3	**Capable of only limited self-care, confined to bed or chair 50% or more of waking hours**
4	**Completely disabled. Cannot carry on self-care. Totally confined to bed**
5	**Death**

APPENDIX IV

AJCC STAGING SYSTEM
PROSTATE, 6th Edition

DEFINITION OF TNM

Primary Tumor, Clinical (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor

T1 Clinically inapparent tumor neither palpable or visible by imaging
- T1a Tumor incidental histologic finding in 5% or less of tissue resected
- T1b Tumor incidental histologic finding in more than 5% of tissue resected
- T1c Tumor identified by needle biopsy (e.g., because of elevated PSA)

T2 Tumor confined with prostate*
- T2a Tumor involves one-half of one lobe or less
- T2b Tumor involves more than one-half of one lobe but not both lobes
- T2c Tumor involves both lobes

T3 Tumor extends through prostate capsule**
- T3a Extracapsular extension (unilateral or bilateral)
- T3b Tumor involves the seminal vesicle(s)

T4 Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles and/or pelvic wall

*Note: Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c

**Note: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3, but as T2.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in regional lymph node(s)

Distant Metastasis (M)*

MX Presence of distant metastasis cannot be assessed (not evaluated by any modality)
M0 No distant metastasis
M1 Distant metastasis
- M1a Nonregional lymph node(s)
- M1b Bone(s)
- M1c Other site(s) with or without bone disease

*Note: When more than one site of metastasis is present, the most advanced category is used; pM1c is most advanced.

Histopathologic Grade (G)

GX	Grade cannot be assessed
G1	Well-differentiated (slight anaplasia [Gleason 2-4])
G2	Moderately differentiated (moderate anaplasia [Gleason 5-6])
G3-4	Poorly undifferentiated or undifferentiated (marked anaplasia [Gleason 7-10])

Stage Grouping

Stage I	T1a	N0	M0	G1
Stage II	T1a	N0	M0	G2, G3-4
	T1b	N0	M0	Any G
	T1c	N0	M0	Any G
	T1	N0	N0	Any G
	T2	N0	M0	Any G
Stage III	T3	N0	M0	Any G
Stage IV	T4	N0	M0	Any G
	Any T	N1	M0	Any G
	Any T	Any N	M1	Any G

APPENDIX V (8/20/10)
RTOG BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of serum, plasma, or whole blood (as specified by protocol):

Kit contents:

- One Red Top tube for serum
- One Purple Top EDTA tube for plasma
- One Purple Top EDTA tube for Whole Blood
- Twenty (20) 1 ml cryovials
- Biohazard bags (3)
- Absorbent shipping material (3)
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Pre-paid shipping label(s)
- UN1845 DRY Ice and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form
- Kit Instructions

Serum (if requested): Red Top Tube

- ❑ Label as many 1ml cryovials (up to 10) as serum collected. Label them with the RTOG study and case number, collection date and time, and clearly mark cryovials "serum".

Process:

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable but must be noted on the Specimen Transmittal Form.
3. Aliquot 0.5 ml serum into as many cryovials as serum collected (up to 10) labeled with RTOG study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as "serum".
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90° C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90° C until ready to ship on dry ice. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Plasma (If requested): Purple Top EDTA tube #1

- ❑ Using four (4) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials "plasma".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable within one hour but must be noted on the Specimen Transmittal Form.
3. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot 0.5 ml plasma into each cryovial labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as "plasma".
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

(continued on next page)

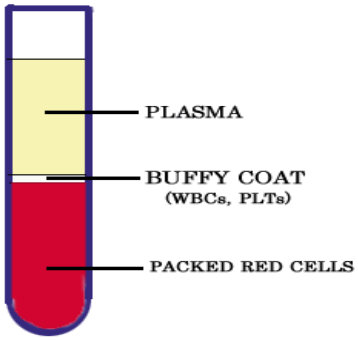
Whole Blood for DNA (if requested): Purple Top EDTA tube #2

- ❑ Using four (4) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovial(s) "blood".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials labeled "blood" as possible. Clearly mark the tubes with date/time of collection and time point collected.
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
4. Store blood samples frozen until ready to ship on dry ice. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.



PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Freezing:

- ☐ Freeze Blood samples in a -80C Freezer or on dry ice or snap freeze in liquid nitrogen.

Storage:

- ❑ Store at -80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- ❑ Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

*RTOG labels are obtained at the time of patient registration. **PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.**

(continued on next page)

APPENDIX V (8/20/10)
RTOG BLOOD COLLECTION KIT INSTRUCTIONS (continued)

Shipping/Mailing:

- Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- Include all RTOG paperwork in sealed plastic and tape to the outside top of the Styrofoam box.
- Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice. Add padding to avoid the dry ice from breaking the tubes.*
- For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail RTOG@ucsf.edu or call (415) 476-7864.

Ship specimens and all paperwork as follows:

Courier Address (FedEx, UPS, etc.): For Frozen Specimens (and all courier packages)
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

For questions, call 415-476-RTOG (7864) or e-mail: RTOG@ucsf.edu