NRG ONCOLOGY
Radiation Therapy Oncology Group

RTOG 0815

(ClinicalTrials.gov NCT #:* 00936390*)

A PHASE III PROSPECTIVE RANDOMIZED TRIAL OF DOSE-ESCALATED RADIOTHERAPY WITH OR WITHOUT SHORT-TERM ANDROGEN DEPRIVATION THERAPY FOR PATIENTS WITH INTERMEDIATE-RISK PROSTATE CANCER

Amendment 4: April 21, 2015

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A PHASE III PROSPECTIVE RANDOMIZED TRIAL OF DOSE-ESCALATED RADIOTHERAPY WITH OR WITHOUT SHORT-TERM ANDROGEN DEPRIVATION THERAPY FOR PATIENTS WITH INTERMEDIATE-RISK PROSTATE CANCER

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology, ECOG-ACRIN Medical Research Group, and SWOG.

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Document History

	Version/Update Date	**Broadcast Date**
Closure	**-**	**March 7, 2016**
Amendment 4	April 21, 2015	June 8, 2015
Update	April 29, 2014	April 29, 2014
Update	November 14, 2013	November 14, 2013
Amendment 3	May 23, 2012	August 2, 2012
Update	January 11, 2011	January 11, 2011
Amendment 2	December10, 2010	January 11, 2011
Amendment 1	August 17, 2010	January 11, 2011
Update	September 17, 2009	September 17, 2009
Update	September 14, 2009	September 14, 2009
Activation	September 14, 2009	September 14, 2009

Protocol Agent

Agent	**Supply**	**NSC #**	**IND #**
Bicalutamide	Commercial	N/A	N/A
Flutamide	Commercial	N/A	N/A
Leuprolide	Commercial	N/A	N/A
Goserelin	Commercial	N/A	N/A
Buserelin*	Commercial	N/A	N/A
Triptorelin	Commercial	N/A	N/A
Degarelix	Commercial	N/A	N/A
*Buserelin is not commercially available in the United States.			

Participating Sites

☒ U.S.
☒ Canada
☒ Approved International Member Sites

NRG Oncology
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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION (4/21/15)		
To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone: 1-866-651-CTSU Fax: 215-569-0206 CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)	Please refer to the patient enrollment section (Section 5.0) for instructions on using the OPEN system, which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org..	NRG Oncology 1818 Market Street, Suite 1720 Philadelphia, PA 19103 Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The study protocol and all related forms and documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For patient eligibility: Contact the NRG Oncology Research Associate for Protocol, Data Management section at 215-574-3214. **For treatment-related questions:** Correspond by e-mail (preferred) or by phone with the study chair designated on the protocol cover page.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
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RTOG 0815

A Phase III Prospective Randomized Trial of Dose-Escalated Radiotherapy With or Without Short-Term Androgen Deprivation Therapy for Patients With Intermediate-Risk Prostate Cancer

SCHEMA

STRATIFY	**Number of Risk Factors***	**RANDOMIZE**	**Arm 1**
	1. One risk factor		Dose-escalated RT alone
	2. Two or 3 risk factors		
	Comorbidity Status 1. ACE-27** grade ≥ 2 2. ACE-27 grade < 2		
	RT Modality		**Arm 2**
	1. Dose-escalated EBRT		Dose-escalated RT combined with short-
	2. EBRT + LDR brachytherapy boost		term (6 months) androgen blockade (LHRH
	3. EBRT + HDR brachytherapy boost		agonist + antiandrogen)

Intermediate risk factors: Gleason Score 7; PSA >10 but ≤20; T-Stage T2b-T2c. Patients with all three intermediate risk factors and ≥ 50% of their sampled biopsy cores involved will not be eligible for this study. Note: The percentage of biopsy cores involved will only be considered with respect to eligibility for those patients with all 3 of the above risk factors (i.e., patients with one or two of the above risk factors are eligible irrespective of the percentage of biopsy cores involved).***

****The "untreated malignancy" section of the ACE-27 form is to be disregarded with respect to the patient's newly diagnosed, untreated prostate cancer.***

*****Patients with Gleason score ≥ 8, PSA > 20, or clinical stage > T2c are ineligible for this study.***

See pre-registration requirements in Section 5.0.

Note: To be used on this protocol, low-dose rate brachytherapy sources must be listed on the joint RPC/AAPM source registry at http://rpc.mdanderson.org/rpc. Select "Brachy Sources/Source Registry".

Note: As this protocol allows for treatment with exclusively EBRT or EBRT + brachytherapy (at the discretion of the treating physician), this must be specified at the time of study enrollment. Should a patient who was originally intended to receive brachytherapy be found, post-enrollment, to be a poor brachytherapy candidate based on transrectal ultrasound examination, he will no longer be eligible for participation in this study. **Therefore, it is strongly recommended to obtain ultrasound assessment of prospective brachytherapy patients before enrollment on this study.**

Patient Population: (See Section 3.0 for Eligibility) [11/14/13]
Clinically localized, lymph node negative adenocarcinoma of the prostate diagnosed within 6 months* prior to registration at intermediate risk for recurrence as determined by harboring one or more of the following intermediate-risk features: Gleason Score 7; PSA >10 but ≤20; Clinical Stage T2b-T2c.

*Patients previously diagnosed with low risk (Gleason score ≤ 6, clinical stage < T2a, and PSA < 10) prostate cancer undergoing active surveillance who are re-biopsied and found to have intermediate risk disease according to the protocol criteria are eligible for enrollment within 6 months of the repeat biopsy procedure

Required Sample Size: **1520**

NRG Oncology Institution #
RTOG 0815 **ELIGIBILITY CHECKLIST** (5/23/12)
Case # **(page 1 of 4)**

1. _____ (Y) Is there pathologic (histological) proven diagnosis of intermediate risk prostatic adenocarcinoma within 180 days prior to registration?
2. _____ (Y) Is the patient's prostate cancer considered at intermediate risk for recurrence by presenting with one or more of the following:
    ____ (N/Y) Gleason Score 7
    ____ (N/Y) PSA > 10 but ≤ 20
    ____ (N/Y) T-Stage: T2b-T2c
3. _____ (Y/NA) Does the patient have clinically negative (N0) lymph nodes as defined by pelvic +/- abdominal CT or MRI, nodal sampling, or dissection within 60 days prior to registration?
4. _____ (Y/N/NA) Is there no evidence of bone metastases (M0) on a bone scan performed 60 days prior to registration?
5. _____ (Y) Has the patient had a history/physical examination within 60 days of registration to include the following:
    - digital rectal examination of the prostate
    - formal comorbidity assessment via the ACE-27
6. _____ (Y) Is Zubrod Performance Status 0-1?
7. _____ (Y) Is the patient ≥ 18 years old?
8. _____ (Y) Has the baseline serum PSA value been performed with an FDA-approved assay (e.g., Abbott, Hybritech) within 60 days prior to registration?
9. _____ (Y/NA) For patients undergoing brachytherapy, has the CBC/differential been obtained within 60 days prior to registration with adequate bone marrow function defined as follows:
    - Absolute neutrophil count (ANC) ≥ 1,800 cells/mm^3
    - Platelets ≥ 100,000 cells/mm^3
    - Hemoglobin (HGB) ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve HGB ≥ 8.0 g/dl is acceptable)?
10. _____ (N) Does the patient have any of the following risk factors:
    - Gleason Score ≥ 8
    - PSA > 20
    - T-Stage: ≥T3?
11. _____ (N/NA) If the patient has three intermediate risk factors, are ≥50% of the number of biopsy cores positive for cancer?
12. _____ (N) Does the patient have prior history of invasive (carcinoma in situ is allowed) malignancy (except non-melanomatous skin cancer) or hematological (e.g., leukemia, lymphoma, myeloma) malignancy unless disease free for a minimum of 5 years?

(Continued on the next page)

13. _____ (N) Has the patient had prior radical surgery (prostatectomy), high-intensity focused ultrasound (HIFU), or cryosurgery for prostate cancer?
14. _____ (N) Has the patient received prior hormonal therapy, such as LHRH agonists (e.g. goserelin, leuprolide), antiandrogens (e.g., flutamide, bicalutamide), estrogens (e.g., DES), or bilateral orchiectomy?
15. _____ (N) Has the patient used finasteride within 30 days prior to registration?
16. _____ (N) Has the patient used dutasteride within 90 days prior to registration?
17. _____ (N) Has the patient received prior or concurrent cytotoxic chemotherapy for prostate cancer (prior chemotherapy for a different cancer is permitted)?
18. _____ (N) Has the patient received prior radiotherapy, including brachytherapy, to the region of the study cancer that would result in overlap of radiation therapy fields?
19. _____ (N) Is there prior history of a TURP for patients receiving brachytherapy?
20. _____ (N) Does the patient have any of the following conditions:
    - Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
    - Transmural myocardial infarction within the last 6 months
    - Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
    - Chronic Obstructive Pulmonary Disease (COPD) exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days of registration
    - Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects
    - AIDS (based on current CDC definition)
21. _____ (N) Is the patient sexually active with a woman of childbearing potential and not willing/able to use medically acceptable forms of contraception (e.g., surgical, barrier, medicinal)?

The following questions will be asked at Study Registration:

IMRT/BRACHYTHERAPY CREDENTIALING IS REQUIRED BEFORE REGISTRATION

_____ 1. Institutional person randomizing case

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

_____(Y) 3. In the opinion of the investigator, is the patient eligible?

_____ 4. Date Informed Consent Signed

_____ 5. Patient's Initials

_____ 6. Verifying Physician

_____ 7. Patient's ID Number

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnicity

_____ 11. Gender

_____ 12. Country of Residence

_____ 13. Patient's Zip Code

_____ 14. Method of Payment

_____ 15. Any care at a VA or military hospital?

_____ 16. Calendar Base Date

_____ 17. Randomization Date

_____(Y/N) 18. Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 19. Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 20. Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

(Continued on the next page)

_____(Y/N) 21. Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease)?

_____(Y/N) 22. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?

_____ 23. Number of risk factors:
1. One risk factor
2. Two or 3 risk factors

_____ 24. Comorbidity status:
1. ACE-27 ≥grade 2
2. ACE-27 <grade 2

_____ 25. Radiation Therapy modality:
1. Dose-escalated EBRT
2. EBRT + LDR brachytherapy boost
3. EBRT + HDR brachytherapy boost

_____(N/Y) 26. IMRT

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/NRG Oncology audit.

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Background and Rationale (12/10/10)

Androgen-deprivation therapy (ADT) is a well-recognized treatment for prostate cancer[1,2] and has been shown, as an adjunct to radiotherapy (RT), in multiple prospective randomized trials, to improve clinical outcomes including biochemical, local, and distant disease control as well as disease-free and overall survival.[3-9] The majority of studies in which these benefits have been demonstrated included patients with high-risk, locally advanced, or, in some cases, node-positive disease. The most significant findings produced by these clinical trials for high-risk patients are as follows: (1) patients in this population receiving ADT have improved outcomes over those not receiving ADT, and (2) long-term (2-3 years) ADT is superior to short-term (4 months) ADT.

The mechanism of benefit of ADT in these patients remains unclear, but several potential explanations exist. First, although ADT is not regarded as a curative modality by itself, it may have the potential to eradicate subclinical, microscopic distant disease. Second, there may exist a synergistic relationship between RT and concurrent administration of ADT such that the response of local-regional disease, particularly that in the pelvic lymph nodes that typically receive significantly lower doses than those received by the prostate, is enhanced.[10] Finally, the benefits of ADT in these patients may simply be a manifestation of compensating for what, in a percentage of patients, would be suboptimal definitive local therapy in the form of "standard-dose" (65-70 Gy) RT.

This current RTOG phase III, prospective, randomized trial is designed primarily to define the magnitude of benefit for adding ADT to dose-escalated RT specifically in the treatment of intermediate-risk prostate cancer. The study will allow this to be accomplished on several levels. For purposes of eligibility for this particular study, 3 intermediate-risk features have been identified: T2b-T2c disease, PSA >10 but ≤20, and Gleason score of 7. One or more of these risk features associated with a newly diagnosed prostate cancer connotes clinicopathologic eligibility for this study. Patients with all 3 of these risk factors who additionally present with ≥ 50% of their sampled biopsy cores positive are believed to be at high risk for systemic progression and are excluded from this study.

This study population represents a heterogeneous group, albeit all intermediate-risk by conventional criteria, and bias will be minimized by stratifying patients according to whether they harbor a single vs. multiple intermediate risk factors. While it is acknowledged that potential sources of bias (e.g., Gleason 7, 3+4 vs 4+3[11-14]) are not directly accounted for, this schema is the most optimal and practical method for potentially identifying which patients from this heterogeneous group stand to benefit from the addition of short-term ADT. In addition, by stratifying according to the multiple forms of dose escalation permitted on this study (external beam radiotherapy [EBRT], low dose rate [LDR] brachytherapy boost, and high dose rate [HDR] brachytherapy boost), it is hoped that differences in terms of the interaction of ADT with various radiotherapeutic techniques may be better understood. That is, is the lack of benefit with ADT suggested in prior brachytherapy series[15-17] a patient selection, biologic, or technical phenomenon? Is it simply a dose escalation phenomenon? By allowing both dose-escalated EBRT and brachytherapy in this study and stratifying patients accordingly, a greater understanding of this interplay should be elicited. Finally, a stratification variable will be added to account for patients' pre-existing comorbidity. The Adult Comorbidity Evaluation 27 (ACE-27)[18-20] will be used to describe any such conditions at levels of none, minimal, moderate, or severe with corresponding grades of 0,1,2,3, or 4, respectively, at the time of study entry. Prior prospective data have suggested minimal or no benefit to the addition of ADT to RT for patients with greater than moderate comorbidity on this scale (grade ≥ 2).[21]

The role of ADT in the intermediate-risk population is not well defined, with ADT administration based largely on old practice patterns, physician bias, and extrapolation of data from studies examining patients with different disease characteristics treated with older radiotherapy modalities and lower total doses. No prospective, randomized data exist examining the use of ADT exclusively in an intermediate-risk prostate cancer setting. Likewise, there are no prospective, randomized data to define the role of ADT in the setting of dose-escalated RT for any patient population. The data yielded by this prospective, randomized clinical trial should result in a better understanding of the benefits of ADT in the intermediate risk patient population treated with a range of contemporary radiotherapeutic options. This will allow for physicians to make more informed, objective decisions regarding the use of ADT in this patient population and spare the morbidity of such therapy to patient subgroups in which a benefit is not observed.

Several prospective series have now shown clear benefits in terms of biochemical, local, and distant disease control comparing "dose-escalated" to "standard-dose" RT, illustrating the point that RT techniques used in earlier randomized studies demonstrating the benefits of ADT in these patients were suboptimal by current practice standards. A randomized dose-escalation study from M.D. Anderson has demonstrated, at 8 years of follow-up, improvements in biochemical and clinical disease progression (including distant metastases) for patients treated to an isocenter dose of 78 Gy vs 70 Gy.[22] Massachusetts General Hospital has published a randomized trial that has demonstrated the benefits of delivering doses of 79.2 Gy vs 70.2 Gy while using proton beam therapy as a boost,[23] and a randomized trial from the Netherlands has demonstrated an improvement in freedom from failure for patients receiving 78 Gy vs 68 Gy.[24] Prospective, nonrandomized dose-escalation data from Memorial Sloan Kettering Cancer Center has suggested similar benefits in biochemical and clinical control and, despite the fact that this study was not randomized, suggests an advantage in terms of reduction in the risk of distant failure irrespective of whether or not short-term androgen deprivation therapy was used.[25] These advantages conferred by dose escalation have been a result of more sophisticated imaging and treatment planning techniques that have resulted in the ability to not only increase dose delivery to the prostate, but also to enhance bladder and rectal sparing with a concomitant reduction in the risks of acute and chronic toxicity.[26]

While the benefits of dose escalation are becoming better defined in the setting of EBRT, this has been a relatively recent phenomenon that has yet to be significantly evaluated in the setting of concurrent or adjuvant ADT. Dose escalation, however, has been implemented for a longer period of time using brachytherapy techniques. It is therefore the brachytherapy series that provide the longest available follow-up with respect to the use of ADT in the setting of dose escalation. These series have provided, to this point, only retrospective experiences, but multiple large reviews from different institutions have suggested an equivocal or, in some cases, detrimental effect from the use of adjuvant ADT with brachytherapy (either HDR or LDR).[15-17]

Nonetheless, concurrent long-term ADT with RT remains standard treatment for patients with high-risk disease, and, more recently, published results of a prospective study that included intermediate-risk patients suggest a possible benefit to short-term ADT for this patient subgroup.[7] That is, do patients with organ-confined prostate cancer harboring moderately aggressive features such as a Gleason score of 7 or a pretreatment PSA value of 10-20 ng/mL stand to benefit from the addition of ADT to definitive RT? The trial by D'Amico et al. focused on the role of short-term (6-month) ADT in conjunction with EBRT and suggested benefits in terms of biochemical control, cause-specific survival, and even overall survival. Once again, however, ADT was not administered in the setting of dose-escalated RT, and the trial included both intermediate- and high-risk patients, thereby leaving many questions unanswered with respect to the use of ADT in the setting of intermediate-risk prostate cancer.

The result of the integration of the above data into clinical practice is a situation in which there have evolved two distinct practice "standards" for patients with intermediate risk prostate cancer treated primarily with radiotherapy, and those standards are the two randomization arms of this study. There is currently evidence supporting treatment with either approach, but the fact remains that ADT remains untested in the setting of dose-escalated RT. The question of whether or not the potential implications of ADT with respect to quality of life and potential exacerbation of medical comorbidities are outweighed by increased cure rates of prostate cancer will remain unanswered until this issue is addressed in prospective, randomized fashion.

1.2 The Influence of Short-Term Androgen Deprivation Therapy on Health-Related Quality of Life (HRQOL), Fatigue, and Quality-Adjusted Survival (QAS) in Patients With Intermediate-Risk Prostate Cancer Receiving Dose-Escalated Radiotherapy

1.2.1 Health-Related Quality of Life (HRQOL)

Some of the side effects associated with RT and ADT negatively affect HRQOL, and others may contribute to increased risks for serious health concerns. Urinary, bowel, and erectile dysfunction are well-known side effects of pelvic RT. Sexual side effects are the most well recognized adverse effects from ADT and include loss of libido, erectile dysfunction, and hot flashes. Loss of libido is distressing to many men, and they may not pursue treatments for erectile dysfunction that they may have otherwise pursued after radical prostatectomy or RT. The incidence of hot flashes, which may not abate over the course of ADT, is close to 80%. Physiologic effects, including gynecomastia, changes in body composition (weight gain, reduced muscle mass, increase in body fat), and changes in lipids, are less commonly recognized

as side effects of ADT. These effects may lead to an exacerbation of potentially more serious conditions, such as hypertension, diabetes, and coronary artery disease.[27] Loss of bone mineral density, anemia, and hair changes also may occur. Additionally, both the diagnosis of prostate cancer and the hormonal therapy can cause psychological distress. These side effects need more systematic study in clinical trials. Such studies would provide well-defined side effect profiles for better informing physicians of the far-reaching consequences of ADT and improve the awareness that they should incorporate into routine practice strategies for preventing and managing toxicities.[28]

ADT has been shown to have a negative impact on health-related quality of life (HRQOL) in patients with asymptomatic lymph node positive prostatic carcinoma. One study showed significantly worse sexual, emotional, and physical function, with more hot flashes and worse overall HRQOL (using the Functional Assessment of Cancer Therapy-General [FACT-G] scale) in those patients, compared with patients receiving no therapy.[29] To address HRQOL, RTOG 0815 will compare the treatment arms for differences in prostate cancer HRQOL outcomes (as measured by change over time in the Expanded Prostate Cancer Index Composite [EPIC]) in a subset of patients in each treatment arm. The EPIC is a prostate cancer HRQOL instrument that measures a broad spectrum of urinary, bowel, sexual, and hormonal symptoms related to RT and ADT.[29]

1.2.2 Fatigue

Fatigue has been described as the most frequent and distressing symptom related to cancer and its treatment.[30] RT-associated fatigue is a common early side effect reported by 80% of patients during treatment.[31] There is evidence that cancer-related fatigue (CRF) has profound effects on ability to function in usual roles and activities and can linger for months or years after treatment completion.[32-35] The high prevalence of this symptom in persons treated with RT, as well as its association with poor quality of life, mark it as a significant problem that requires further scientific study.

The etiology of fatigue, its correlates, and prevalence in the context of prostate cancer treatment are poorly understood. Past research suggests that irradiation of larger volumes was associated with more fatigue.[34,36,37] Likewise, ADT has been associated with increased fatigue.[38,39] Only a few studies have examined predictors or correlates of fatigue. In a sample of 28 men receiving EBRT and ADT, Truong[35] found that age, Gleason score, PSA, T-stage, ADT duration, and RT dose and fraction did not predict severity of fatigue at the completion of treatment. In contrast, other investigators[37] found that post-treatment fatigue was associated with baseline fatigue, role limitations, treatment type, and treatment location. Other fatigue correlates have been proposed: depression, poor sleep quality, and lack of regular physical activity.[31,40,41] Thus, we plan to address such confounding factors with brief and focused questions. Of importance, no studies have compared the severity and correlates of fatigue in men receiving RT ± ADT. Also many of the previous studies were secondary analyses or had small subject samples.

Because fatigue is a major problem associated with both RT and ADT, it would be informative to examine this common symptom in the context of a large clinical trial. The large sample would allow for the examination of predictors (demographic and treatment) of fatigue severity as well as the effect of fatigue on quality of life. Secondary hypotheses are that higher fatigue severity will be associated with poorer overall quality of life and that higher baseline fatigue, poorer performance status, and older age will predict higher fatigue severity during, at the end of, and following treatment.

In order to minimize the potential impact of various confounding factors on fatigue, a secondary endpoint of this study, the following key information regarding potential confounds will also be collected at the time of the PROMIS-fatigue short form (using limited questions to minimize patient burden):

- Anxiety/depression item in EQ5D
- Muscle weakness question (scale of 1-5, from none to very much)
- Overall Sleep Quality: Item from Pittsburgh Sleep Quality Index:[42]
- Level of physical activity (per GLTEQ)

Sleep quality will be measured by 1 item (Q3) of the Pittsburgh Sleep Quality Index (PSQI), a self-rated questionnaire which measures sleep quality and disturbances over a 1-week or 1-month time period.[42] The sum of the 19 items yields a global score which has been demonstrated to discriminate good and poor sleepers; also, it has good internal consistency (Cronbach's alpha=0.83), stability (test-retest

reliability=.85, *P*<.001) and discriminant validity. It has been used in patients with cancer and demonstrated sleep problems as expected. [42]

Participants' level of physical activity will be assessed using the Godin Leisure-Time Exercise Questionnaire (GLTEQ),[43,44] which measures time spent per week in each of light, moderate, and vigorous activities. A score can be computed for each level of exercise. A total score is computed by summing the three levels weighted by their respective metabolic (MET) equivalents of 3, 5, and 9. The GLTEQ has good test-retest reliability and has shown convergent validity with both objective and other self-report measures of physical activity.[43,44]

1.2.3 Quality-Adjusted Survival and Failure Free Survival

In this study, the addition of short term ADT is hypothesized to improve overall survival (OS), while having a negative impact on HRQOL. As these are potentially competing advantages and disadvantages of ADT, it is useful to combine these factors into one equation, quality-adjusted life year (QALY). QALYs will be used to determine whether the potential benefits of the ADT, in terms of OS, outweigh the potential disadvantages of this strategy, in terms of a negative effect on HRQOL, compared to the RT only arm. Such a quality adjusted survival (or failure free survival) analysis can be invaluable to future patients faced with these treatment options.

Quality-adjusted survival and freedom from progression can be defined by the weighted sum of different time episodes added up to a total QALY or failure free survival-year [U= sum of quality (q_i) of health states K times the duration (s_i) spent in each health state.[45]

$$\mathbf{U} = \sum_{\mathbf{i=1}}^{\mathbf{K}} \mathbf{q_i s_i}$$

The EQ-5D has been used across numerous disease sites. For example, the EQ-5D mean score for 95 patients with NSCLC (93% male, mean age 62 years) was 0.58 (SD 0.32) [on a scale of "0" death or worst possible health to "1" best possible health].[46] The EQ-5D has been used to assess QALYs and the economic value of prostate cancer screening,[47] and treatment of pain related to prostate cancer metastasis.[48] Further, the EQ-5D was used in a recent study to estimate the economic value of the welfare loss due to prostate cancer pain by estimating the extent to which pain affects HRQOL among patients with prostate cancer. Health status and economic outcomes were modeled among a well-defined population of 200,000 Swedish prostate cancer patients. Health utility ratings (using the EQ-5D) were obtained from a subset of 1,156 of the prostate cancer patients. A descriptive model showed that optimal treatment that would reduce pain to zero during the whole episode of disease would add on average 0.85 QALYs to every man with prostate cancer.[49]

1.3 Correlation of Circulating Proinflammatory Cytokines to Fatigue in Patients Undergoing Radiotherapy for Prostate Cancer (12/10/10)

As described above, fatigue is a major problem for patients treated with RT and ADT. A better understanding of biologic events correlated with fatigue in patients receiving RT and ADT may provide insight into the mechanisms of fatigue in these patients and as a result may provide possible avenues for intervention. Pro-inflammatory cytokines have been found to play a role in cancer-related fatigue (CRF) and fatigue from other chronic illnesses.[50] In this study, we will test the hypothesis that alterations in the circulating levels of the proinflammatory cytokines such as TNF alpha, IL-1, IL-1ra, IL-6 and the marker of inflammation C-reactive protein during RT for prostate cancer predict the likelihood of developing fatigue as measured by the PROMIS instrument.

Pro-inflammatory cytokines have been studied as possible markers of CRF. The most commonly implicated cytokines are IL-1, IL-6, TNF alpha, and IFN alpha.[51] The mechanism by which these cytokines may cause fatigue or be correlated with fatigue is complex; however, IL-1, IL-6, and TNF alpha are known to stimulate the hypothalamic pituitary axis, which is also implicated in CRF. TNF alpha also plays a role in modulating central neurotransmission, another potential central mechanism of CRF.[52]

Because many of the therapies used to treat cancers can induce expression of pro-inflammatory cytokines, it is possible that the cytokine release caused by these therapies also correlate with the occurrence of CRF. Several small studies have addressed the issue of cytokine levels and their correlation with fatigue in patients receiving RT. Ahlberg et al. evaluated 15 patients treated with pelvic RT to a dose of 46 Gy in 2 Gy fractions after hysterectomy.[53] Fatigue was assessed with the

Multidimensional Fatigue Inventory (MFI-20). Cytokine levels were assessed before starting RT, after 30 Gy, and within one week of RT. Fatigue scores were elevated at 30 Gy and at completion of RT. IL-1 remained undetectable at all time points. TNF alpha and IL-6 were increased in several patients at the time points during and at the completion of RT. IL-6 elevated in nearly half of patients, and levels decreased through RT in the remainder with a resultant negative correlation between serum IL-6 and fatigue in this small population. Unfortunately this is a small series of patients in whom surgical therapy was the primary therapy, which is known to alter cytokine levels such as IL-6, CRP, and TNF alpha postoperatively.

Geitnez et al. evaluated cytokine levels in 41 breast cancer patients that had undergone breast conserving therapy. Patients rated fatigue with the Fatigue Assessment Questionnaire and a visual analog scale of fatigue intensity before, during, and 2 months after RT; and at long term follow up.[54,55] Serum IL-1 beta, IL-6, and TNF alpha were also measured at these time points. Fatigue was elevated on the visual analogue scale during RT; however, no change was noted on the Fatigue Assessment Questionnaire. IL-1beta, IL-6, and TNF alpha did not change during therapy and did not correlate with fatigue.

While several of the series that drew negative conclusions above found no increase in inflammatory cytokine levels with RT, several series have found striking elevations. For example, Akmansu et al. found significant elevations in serum IL-6 and TNF alpha after five weeks of RT compared to pretreatment levels in 34 patients receiving RT for head and neck cancer.[56] Greenberg et al. found significant elevations in IL-1 in the early weeks of RT for prostate cancer in 15 patients which correlated with an increase in fatigue.[57] Fatigue was assessed daily on a visual analogue scale. Patients were screened for depression during this study to rule out depression as a confounding factor.

In contrast, the effect of ADT on inflammatory markers is less well known. Small studies have shown altered cytokine expression by prostate tumors after ADT,[58] but levels of systemic cytokines after hormonal therapy for prostate cancer are not well described. Fatigue is a well-known complication of ADT for prostate cancer.[59] The combination of RT and ADT for prostate cancer may result in a more persistent and prolonged fatigue compared to the series evaluating fatigue after RT alone, with as many as 32% of patients experiencing fatigue at the completion of RT and a substantial number experiencing fatigue as late as 6.5 weeks after completion of RT.[35] Correlation of inflammatory cytokines to fatigue may provide mechanistic information regarding the causes of fatigue in these patients and may provide a target for intervention in future studies.

Blood collection is mandatory for patients consenting to the QOL portion of this study and optional for other participants. It will be strongly recommended that patients consent to having a tissue block sent for storage to the NRG Oncology Biospecimen Bank. Paraffin-embedded tissue blocks of diagnostic prostate biopsies will be obtained from participating institutions and banked in the NRG Oncology Biospecimen Bank for future translational analyses. Plasma and whole blood may be collected from patients enrolled on this protocol before and during protocol therapy and banked for future translational research analyses. Specifically, plasma will be collected at baseline and during the last week of RT treatments. Whole blood will be collected at baseline only. The tissue specimens will be collected and processed according to the NRG Oncology specimen processing guidelines and must be clearly labeled with the patient's case number. Anticipated analyses include correlation of whole genome single nucleotide polymorphisms to incidence and severity of toxicity from therapy, and evaluation of circulating markers that may correlate to patient reported outcomes. An example of one anticipated analysis is the evaluation of plasma cytokines for correlation to fatigue as measured by the PROMIS instrument in patients enrolled on this trial. Examples of cytokines that may be tested include CRP, TNF alpha, IL-1, IL-1ra, and IL-6.

2.0 OBJECTIVES

2.1 Primary

To demonstrate an overall survival (OS) advantage for the addition of short-term (6 months) ADT to dose-escalated RT for patients with intermediate-risk prostate cancer. The events for OS will be defined as death due to any cause.

2.2 Secondary (12/10/10)

2.2.1 Determine whether the addition of ADT to dose-escalated RT improves clinical failures (local recurrence, regional recurrence, or distant metastasis), biochemical failure by the "nadir + 2" (Phoenix) definition[60], freedom from failure (the first occurrence of clinical failure or biochemical failure by the Phoenix definition), rate of salvage ADT, and prostate cancer-specific mortality without resulting in increased non-prostate cancer-specific mortality over dose-escalated RT alone

2.2.2 Estimate the magnitude of benefit of ADT with respect to OS for patients treated with different RT modalities (i.e., EBRT alone vs. LDR brachytherapy boost vs. HDR brachytherapy boost)

2.2.3 Compare acute and late treatment adverse events for patients receiving vs. not receiving ADT and correlate this with the presence or absence of pre-existing comorbidity as documented by the Adult Comorbidity Evaluation 27 (ACE-27) assessment.[18-20]

2.2.4 Determine whether HRQOL as measured by the EPIC significantly worsens as a function of treatment assignment (i.e., ADT + RT compared to RT alone)

2.2.5 Demonstrate that the addition of ADT to dose-escalated RT is associated with higher fatigue severity than dose-escalated RT alone by the Patient-Reported Outcome Measurement Information System (PROMIS) fatigue domain

2.2.6 Demonstrate an incremental gain in OS with more aggressive therapy that outweighs the detriments in the primary generic domains of HRQOL (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), reported as QALY.

2.2.7 Determine whether the PROMIS score change is correlated with plasma cytokine change

2.2.8 Collect paraffin-embedded tissue blocks, plasma, and whole blood for future translational research analyses

3.0 PATIENT SELECTION

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

3.1 Conditions for Patient Eligibility (4/21/15)

For questions concerning eligibility, please contact the study data manager.

3.1.1 Pathologically (histologically) proven diagnosis of prostatic adenocarcinoma, at intermediate risk for recurrence, within 180 days prior to registration as determined by having one or more of the following intermediate-risk features: Gleason Score 7; PSA >10 but ≤20; Clinical Stage T2b-T2c.

- Patients previously diagnosed with low risk (Gleason score ≤ 6, clinical stage < T2a, and PSA < 10) prostate cancer undergoing active surveillance who are re-biopsied and found to have intermediate risk disease according to the protocol criteria are eligible for enrollment within 180 days of the repeat biopsy procedure.

3.1.2 Clinically negative lymph nodes as established by imaging (pelvic +/- abdominal CT or MRI), nodal sampling, or dissection within 60 days prior to registration, except as noted immediately below:

- Patients with a single intermediate risk factor only do not require abdominopelvic imaging, but these studies may be obtained at the discretion of the treating physician. Patients with 2 or 3 risk factors are required to undergo pelvic +/- abdominal CT or MRI.
- Patients with lymph nodes equivocal or questionable by imaging are eligible without biopsy if the nodes are ≤1.5 cm; any node larger than this on imaging will require negative biopsy for eligibility.

3.1.3 No evidence of bone metastases (M0) on bone scan within 60 days prior to registration.

- Bone scan is not required for patients enrolled with a single intermediate risk factor only, but this scan may be obtained at the discretion of the treating physician. Patients with 2 or 3 risk factors will require a negative bone scan for eligibility.
- Equivocal bone scan findings are allowed if plain film x-rays are negative for metastasis.

3.1.4 History/physical examination (to include, at a minimum, digital rectal examination of the prostate and examination of the skeletal system and abdomen, and formal comorbidity assessment via the ACE-27 instrument) within 60 days prior to registration. Note: The ACE-27 is posted on the 0815 protocol information page on the NRG Oncology/RTOG web site, http://www.rtog.org. Institutions may access a web-based Comorbidity Calculator at http://oto2.wustl.edu/clinepi/comorbid.html.

3.1.5 Zubrod Performance Status 0-1

3.1.6 Age ≥ 18

3.1.7 Baseline serum PSA value performed with an FDA-approved assay (e.g., Abbott, Hybritech) within 60 days prior to registration

- Study entry PSA must not be obtained during the following time frames: (1) 10-day period following prostate biopsy; (2) following initiation of ADT; (3) within 30 days after discontinuation of finasteride; or (4) within 90 days after discontinuation of dutasteride.

3.1.8 For patients undergoing brachytherapy only: CBC/differential obtained within 60 days prior to registration, with adequate bone marrow function defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,800 cells/mm^3
- Platelets ≥ 100,000 cells/mm^3
- Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.)

3.1.9 Patient must be able to provide study-specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility (12/10/10)

3.2.1 Patients with Gleason Score ≥ 8; PSA > 20; *OR* Clinical Stage ≥ T3 are ineligible for this trial.

- Should findings of extracapsular extension or seminal vesicle invasion be noted on prostate MRI, this study, if used, will not render patients ineligible for accrual to this protocol. Primary tumor staging for eligibility purposes is to be based on palpable or core biopsy evidence only with respect to extracapsular extension or seminal vesicle involvement.

3.2.2 Patients with all three intermediate risk factors who also have ≥ 50% of the number of their biopsy cores positive for cancer are ineligible for this trial.

3.2.3 Prior invasive malignancy (except non-melanomatous skin cancer) or hematological (e.g., leukemia, lymphoma, myeloma) malignancy unless disease free for a minimum of 5 years (prior diagnoses of carcinoma in situ are permitted)

3.2.4 Prior radical surgery (prostatectomy), high-intensity focused ultrasound (HIFU) or cryosurgery for prostate cancer

3.2.5 Prior hormonal therapy, such as LHRH agonists (e.g., goserelin, leuprolide), antiandrogens (e.g., flutamide, bicalutamide), estrogens (e.g., DES), or bilateral orchiectomy

3.2.6 Use of finasteride within 30 days prior to registration

3.2.7 Use of dutasteride within 90 days prior to registration

3.2.8 Prior or concurrent cytotoxic chemotherapy for prostate cancer; prior chemotherapy for a different cancer is permitted.

3.2.9 Prior RT, including brachytherapy, to the region of the study cancer that would result in overlap of RT fields

- Any patient undergoing brachytherapy must have transrectal ultrasound confirmation of prostate volume <60 cc, AUA score ≤15 within 60 days of registration, and no history of prior transurethral resection of the prostate (TURP); prior TURP is permitted for patients who receive EBRT only)

3.2.10 Severe, active co-morbidity, defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
- Transmural myocardial infarction within the last 6 months
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
- Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days before registration
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol.
- Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. While the treatment employed in this study is not significantly immunosuppressive, it is felt that a diagnosis of AIDS associated with prostate cancer is likely to impact this study's primary endpoint of overall survival. Patients who are HIV seropositive but do not meet criteria for diagnosis of AIDS are eligible for study participation.

3.2.11 Men who are sexually active with a woman of child-bearing potential and not willing/able to use medically acceptable forms of contraception (e.g., surgical, barrier, medicinal) during protocol treatment and during the first 3 months after cessation of protocol treatment; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

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 (4/21/15)

4.1.1 AST or ALT <2 x the upper limit of normal

4.1.2 Alkaline phosphatase

4.1.3 Serum total testosterone

4.1.4 Any patient undergoing brachytherapy must have transrectal ultrasound confirmation of prostatic volume <60 cc and American Urologic Association (AUA) symptom index composite score ≤15. This may be performed before or after study enrollment but, ideally, will be performed prior to study enrollment as the RT modality (EBRT alone, EBRT + HDR, EBRT + LDR) must be specified at the time of enrollment. If a patient is thought to be a poor brachytherapy candidate based on anatomy at the time of ultrasound, he may still participate in the study but must receive EBRT only per protocol guidelines. If a patient is deemed an inadequate brachytherapy candidate after he has already been enrolled on the protocol, he may be switched to EBRT administered per protocol guidelines, but this will result in a protocol deviation.

4.2 Highly Recommended Evaluations/Management (5/23/12)

4.2.1 History of non-protocol lipid lowering therapy (statin drug): including drug name, dose, treatment start and end dates (if applicable)

5.0 REGISTRATION PROCEDURES (11/14/13)

Access requirements for OPEN and TRIAD

Site staff will need to be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account. This is the same account (user id and password) used for the CTSU members' web site. To obtain an active CTEP-IAM account, go to https://eapps-ctep.nci.nih.gov/iam.

Institutions that have been previously credentialed for prostate 3DCRT or IMRT on prior RTOG/NRG Oncology protocols and that have successfully irradiated a phantom and been approved by the Imaging and Radiation Oncology Core (IROC) Houston need not perform additional credentialing for RTOG 0815. However, respective institutions may only administer treatment for which they have been previously credentialed (i.e., an institution credentialed for 3DCRT only may not administer IMRT on this study without completing the IMRT credentialing process). Credentialing requirements for IMRT and 3DCRT are specified in Sections 5.1 and 5.2 below.

5.1 Pre-Registration Requirements for IMRT Treatment Approach (11/14/13)

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 IROC Houston web site. Visit http://irhochouston.mdanderson.org and select “Credentialing” and “Credentialing Status Inquiry”.

An IMRT phantom study with IROC Houston 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 IROC Houston web site at http irochouston.mdanderson.org; select “Credentialing” and “RTOG”. Upon review and successful completion of the phantom irradiation, IROC Houston will notify both the registering institution and NRG Oncology that the institution has met the IMRT credentialing requirements.

5.1.2 The institution or investigator must either modify their existing Facility Questionnaire on file at NRG Oncology or complete the online Facility Questionnaire (available on the IROC Houston web site at http://irhochouston.mdanderson.org) and send it to IROC Houston for review prior to entering any cases. IROC Houston will notify the institution and NRG Oncology when all requirements have been met and the institution is RT credentialed to enter patients onto this study.

5.2 Pre-Registration Requirements for 3DCRT Treatment Approach (11/14/13)

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

5.2.2 The online Facility Questionnaire (one per institution, available on the IROC Houston web site at http://irhochouston.mdanderson.org) or a modification to your existing Facility Questionnaire on file is to

be sent to IROC Houston for review prior to entering any cases. IROC Houston will notify the institution and NRG Oncology when all requirements have been met and the institution is RT credentialed to enter patients onto this study.

5.3 Pre-Registration Requirements for Brachytherapy Treatment Approach (4/21/15)
Note: To be used on this protocol, low-dose rate brachytherapy sources must be listed on the joint RPC/AAPM source registry at http://rpc.mdanderson.org/rpc. Select "Brachy Sources/Source Registry".

5.3.1 Institutions must be pre-credentialed by IROC Houston prior to registering any cases to this study. The credentialing materials may be found on the IROC Houston website at http://irochouston.mdanderson.org under the "Credentialing" tab.

If an institution was credentialed for a previous RTOG prostate brachytherapy trial (98-05, P-0019, 0232, or 0526), they do not have to be re-credentialed for RTOG 0815 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 and the Reference Case. A change in either the treatment planning computer or brachytherapy source model will require resubmission of only the Reference Case.

5.3.2 *LDR Brachytherapy Credentialing*
In order to use brachytherapy 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 have already been met, are available at the IROC Houston web site, http://irochouston.mdanderson.org by selecting "Credentialing" and "RTOG".

5.3.3 *HDR Brachytherapy Credentialing*
Only institutions that have completed the Knowledge Assessment Questionnaire, the Facility Inventory, and the Benchmark Cases, as described in the NRG Oncology HDR Prostate Implant Quality Assurance Guidelines (see IROC Houston web site http://irochouston.mdanderson.org) may enter patients onto this study. The sample clinical case with complete post implant data form and other materials are to be sent to IROC Houston. Upon review and successful completion, IROC Houston will notify both the registering institution and NRG Oncology that the institution has successfully completed this requirement. The IROC Houston will then notify the institution and NRG Oncology that all requirements have been met and the institution is eligible to enter subsequent patients onto this study. Institutions previously credentialed for RTOG 0321 do not have to be re-credentialed for RTOG 0815.

The first five cases from any newly-credentialed institution will be reviewed by the study co-chair for each respective RT modality to ensure protocol compliance with respect to target coverage, heterogeneity, and normal critical structure dose constraints. Once an institution has demonstrated protocol compliance, future cases will be selected randomly for review.

5.4 Digital RT Data Submission to NRG Oncology Using TRIAD (11/14/13)
This trial will not utilize the services of the ITC for dosimetry digital treatment data submission. TRIAD, the American College of Radiology's (ACR) image exchange application that is used by NRG Oncology, will be used. TRIAD provides sites participating in NRG Oncology clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to Section 5.0 of the protocol for instructions on how to request a CTEP-IAM account.
- To submit images, the site physics user must have been assigned the 'TRIAD site user' role on the relevant Group or CTSU roster. NRG Oncology users should contact your site Lead RA to be added to your site roster. Users from other cooperative groups should follow their procedures for assignment of roster roles.

- RAs are able to submit standard of care imaging through the same method.

TRIAD Installations:
When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found on the NRG Oncology/RTOG website Core Lab tab.

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

5.5 Regulatory Pre-Registration Requirements (4/21/15)

5.5.1 This study is supported by the NCI Cancer Trials Support Unit (CTSU). Prior to the recruitment of a patient for this study, investigators must be registered members of a lead protocol organization. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch (PMB), CTEP, DCTD, NCI. These forms are available on the CTSU registered member web site: http://ctep.cancer.gov/investigatorResources/investigator_registration.htm . For questions, please contact the CTEP Investigator Registration Help Desk by e-mail at pmbregpend@ctep.nci.nih.gov .

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account. Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' web site. Additional information can be found on the CTEP web site at http://ctep.cancer.gov/branches/pmb/associate_registration.htm. For questions, please contact the CTEP Associate Registration Help Desk by email at ctepreghelp@ctep.nci.nih.gov.

IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

Downloading Site Registration Documents

Site registration forms may be downloaded from the RTOG 0815 protocol page located on the CTSU members' web site. Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password:

- Click on the Protocols tab in the upper left of your screen
- Click on the (state organization type e.g. P2C, CITN, NCTN Groupname) link to expand, then select trial protocol, RTOG-0815
- Click on the Site Registration Documents link

Requirements for RTOG 0815 site registration:

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)
- CTSU RT Facilities Inventory Form (if applicable)

NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Imaging and Radiation Oncology Core (IROC) monitoring program. For non-lead group institutions an RT Facilities Inventory Form must be on file with CTSU. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

- IRB/REB approval letter (for sites not participating via the NCI CIRB);
- IRB/REB approved consent (English and native language versions*)

***Note**: Institutions must provide certification/verification of IRB/REB consent translation to NRG Oncology (See "Non-English Speaking Canadian and Non-North American Institutions" below)

- IRB/REB assurance number renewal information as appropriate

Non-English Speaking Canadian and Non-North American Institutions

Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG Oncology will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

5.5.2 *Pre-Registration Requirements FOR CANADIAN INSTITUTIONS*

Prior to clinical trial commencement, Canadian institutions must complete and fax (215-569-0206) or e-mail (CTSURegulatory@ctsu.coccg.org) the following forms to the CTSU Regulatory Office:

- Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form,
- Qualified Investigator Undertaking Form, and
- Research Ethics Board Attestation Form.

5.5.3 *Pre-Registration Requirements FOR INTERNATIONAL INSTITUTIONS*

For institutions that do not have an approved LOI for this protocol:

International sites must submit an LOI to NRG Oncology to receive approval to participate in this trial. For more details see link below: http://www.rtog.org/Researchers/InternationalMembers/LetterofIntent.aspx .

For institutions that have an approved LOI for this protocol:

All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

5.6 Registration (4/21/15)

5.6.1 OPEN Registration Instructions

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role

on either the LPO or participating organization roster. All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' web site https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPPA authorization form (if applicable).

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In the event that the OPEN system is not accessible, participating sites can contact web support for assistance with web registration: websupport@acr.org or call the Registration Desk at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

6.0 RADIATION THERAPY (4/21/15)

This trial will not utilize the services of the ITC for dosimetry digital treatment data submission. *PRIOR TO ENROLLING PATIENTS*, please see Section 5.4 for information on installing TRIAD for submission of digital RT data.

Protocol treatment must begin within 4 weeks after randomization (administration of either RT alone [Arm 1] or RT + ADT [Arm 2]). Patients randomized to receive short-term ADT should begin RT 8 weeks after the first LHRH agonist injection.

Note: As this protocol allows for treatment with exclusively EBRT or EBRT + brachytherapy (at the discretion of the treating physician) this must be specified at the time of study enrollment. Should a patient who was originally intended to receive brachytherapy be found, post-enrollment, to be a poor brachytherapy candidate based on transrectal ultrasound examination, he may be switched to external beam radiotherapy administered per protocol guidelines, but this will result in a protocol deviation. Therefore, it is strongly recommended to obtain ultrasound assessment of prospective brachytherapy patients before enrollment on this study.

6.1 Dose Specifications: 3D Conformal Radiotherapy (3DCRT) or IMRT

6.1.1 Dose will be normalized such that exactly 98% of the PTV receives the prescription dose and will be scored as per protocol. The maximum allowable dose within the PTV is 107% of the prescribed dose to a volume that is at least 0.03 cc. The minimum allowable dose within the PTV is >95% of the prescribed dose to a volume that is at least 0.03cc.

6.1.2 Patients treated entirely via EBRT shall receive prescription doses to the PTV (with the above constraints) of 79.2 Gy delivered in 1.8 Gy fractions. All attempts should be made to deliver the PTV dose with the above heterogeneity constraints with adherence to the critical structure parameters listed below in Table 1. The PTV prescription dose may be reduced by as many as two fractions (total prescription dose of 75.6 or 77.4 Gy) at the discretion of the treating radiation oncologist only if felt that critical structure dose constraints cannot be met for that particular case at a prescription dose of 79.2 Gy. See Section 6.5 below for specifics regarding when to implement a dose reduction. The final prescription dose will be reported specifically to the study coordinator and recorded on a patient-by-patient basis.

Table 1. Critical Structure Dose Constraints

Normal organ limit†	No more than 15% volume receives dose that exceeds	No more than 25% volume receives dose that exceeds	No more than 35% volume receives dose that exceeds	No more than 50% volume receives dose that exceeds
Bladder Constraint	80 Gy	75 Gy	70 Gy	65 Gy
Rectum Constraint	75 Gy	70 Gy	65 Gy	60 Gy
Penile Bulb	Mean dose less than or equal to 52.5 Gy (See Section 6.5)			

†Normal organ limit refers to the volume of that organ that should not exceed the dose limit.

6.2 Technical Factors

6.2.1 RT will be delivered with megavoltage equipment at energies ≥6 MV.

6.2.2 Patients who receive brachytherapy as a component of their RT will undergo EBRT implementing either 3DCRT or IMRT as described. The prostate and seminal vesicles will be treated to a dose of 45 Gy in 1.8 Gy fractions prescribed to a PTV dose as above.

6.3 EBRT Localization, Simulation, and Immobilization

Simulation will be CT-based in all cases. The use of urethral contrast at the time of simulation is recommended but not required. Patients will be positioned supine on a flat tabletop with a customized thermoplastic immobilization cast or a molded foam cradle for stabilization and setup reproducibility. The degree of bladder fullness should be made to duplicate that which is anticipated for daily treatment, i.e., if the patient is instructed to maintain a full bladder for treatment, he should be simulated as such (especially for cases in which image guidance or adaptive treatments are not implemented). CT images should be acquired at a slice thickness of ≤3 mm from the top of the iliac crests superiorly to the perineum inferiorly. Target volumes (Section 6.4.1) and normal critical structures (Section 6.4.1) will be defined in the slices in which they are visualized. The 3DCRT cases must utilize "beam's eye view" representations to define final beam aperture.

6.4 Treatment Planning/Target Volumes (11/14/13)

6.4.1 The definition of volumes will be in accordance with the ICRU Report #50: Prescribing, Recording, and Reporting Photon Beam Therapy.

The Gross Tumor Volume (GTV) is defined by the physician as all known disease as defined by the planning CT, urethrogram, and clinical information. If a urethrogram is used, the GTV will encompass a volume inferiorly 5 mm superior to the tip of the dye and no less than the entire prostate. Prostate dimensions should be defined as visualized on CT scan.

The Clinical Target Volume (CTV) is the GTV plus areas considered to contain microscopic disease, delineated by the treating physician, and is defined as follows:

CTV is the GTV (prostate) plus areas at risk for microscopic disease extension plus the proximal bilateral seminal vesicles. Only the proximal 1.0 cm of seminal vesicle tissue adjacent to the prostate shall be included in the clinical target volume.[61] This 1.0 cm of seminal vesicles refers to both radial (in plane) and superior (out of plane) extent. If both prostate and seminal vesicle are visualized in the same CT slice, this seminal vesicle tissue will contribute to the 1.0 cm of tissue.

The Planning Target Volume (PTV) will provide a margin around the CTV to compensate for the variability of treatment set up and internal organ motion. A range of 5-10 mm around the CTV is required to define each respective PTV. Superior and inferior margins (capping) should be 5-10 mm depending on the thickness and spacing of the planning CT scan. Careful consideration should be made when defining the 5-10 mm margin in 3 dimensions.

The ICRU Reference Points are to be located in the central part of the PTV and, secondly, on or near the central axis of the beams. Typically these points should be located on the beam axes or at the intersection of the beam axes.

Normal Critical Structures to be defined on the treatment planning CT scan will include the following: bladder, rectum (from its origin at the rectosigmoid flexure superiorly or the bottom of the SI joints, whichever is more inferior to the inferior-most extent of the ischial tuberosities), bilateral femora (to the level of ischial tuberosity), penile bulb, and skin. Any small bowel within the primary beam aperture should

be defined as well. All structures will be contoured in their entirety as solid organs. See the NRG Oncology/RTOG website (**http://www.rtog,org**) to view examples of target and normal tissue contours. The PTV forms the entire target as described. No extension of fields to specifically treat regional lymph nodes is permitted. 3D conformal beams will be shaped to include the entire PTV and minimize dose to surrounding critical structures as described. Intensity modulated radiotherapy (IMRT) using inverse planning is permitted with constraints placed to adhere to critical structure dose limitations as defined above.

The following table summarizes the naming of targets and critical structures for submission of data to NRG Oncology.

Note: All required structures must be labeled as listed in the table below for digital RT data submission. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed.

0815 Standard Name	Description
EBRT	
GTV	Gross Target Volume
CTV	Clinical Target Volume
PTV	Planning Target Volume
Bladder	Bladder
Femur_L	Left Femoral Head
Femur_R	Right Femoral Head
PenileBulb	Penile Bulb
Rectum	Rectum
External	External Patient Contour
SeminalVesicle	Seminal Vesicles
LDR Brachytherapy	
ETV	
Rectum	
Bladder	
HDR Brachytherapy	
CTV	
PTV	
Prostate	
SeminalVesicle	
Urethra	
Bladder	
Rectum	

6.5 Critical Structures (12/10/10)

Critical structure dose constraints shall remain consistent with those represented in prior RTOG 3DCRT/IMRT prostate protocols (see Table 1 above). While every effort should be made to deliver prescription doses to the PTV as specified while adhering to these constraints, it is recognized that certain anatomical factors may prevent this. As mentioned in Section 6.1, a prescription dose reduction to a level of 77.4 Gy or 75.6 Gy is permitted if constraints cannot be met at a prescription dose of 79.2 Gy. For purposes of compliance, up to a 5% absolute increase in the volume of critical structure receiving greater than the specified dose will be considered ”variation acceptable,” e.g. up to 20% of the rectum may receive a dose of > 75.6 Gy without a protocol deviation. Any increase in critical structure volume greater than 5% receiving more than the specified dose will be considered a “deviation unacceptable.” It is at this point that a dose reduction to 77.4 Gy or 75.6 Gy should be implemented. The prescription dose

should be the maximum deliverable up to 79.2 Gy while respecting the critical normal structure constraints. Of note, the penile bulb constraint is to be regarded as a guideline, and adherence to this should not, in any way, result in a reduction of the prescription dose or compromised dose coverage of the target volume.

6.6 Treatment Verification

6.6.1 First day port films or portal images of each field along with orthogonal isocenter verification films (or images) must be obtained. If modifications are made in field shaping or design, a port film of each modified field along with orthogonal isocenter verification films (or images) is required on the first day's treatment of that field. Thereafter, weekly verification films or images of orthogonal isocenter views (anterior to posterior and lateral projection) are required.

For **IMRT** the intensity profiles of each beam must be independently verified and compared to the planned field intensity. Portal films are not required for IMRT but orthogonal verification films are required, just as for 3DCRT. These images are to be archived by the institution for later review if requested by the study chair.

6.6.2 Daily on-line target localization (kV or MV imaging with fiducials, trans-abdominal ultrasound, or other) or off-line adaptive approaches to account for interfraction organ motion and setup variability are permitted on this study but not required. The use of image guidance or daily target localization including the specific type implemented must be documented by the treating physician and submitted to NRG Oncology using the appropriate sections of the Facility Questionnaire.

6.6.3 Management of Radiation Dose to the Patient from Daily Localization

According to the literature, the estimates of patient dose per imaging study for various imaging systems vary considerably. The doses are in the range of 0.1 cGy BrainLab's ExacTrac planar kV-systems and can be considered negligible compared with doses from MV portal imaging and kV and MV CT. The doses from helical MV CT scans on a Tomotherapy unit are estimated to be in range from 1 to 3 cGy, similar to doses reported for kV cone beam CT on Elekta Synergy machine. The doses for MV cone beam CT vary from 1 cGy to 10 cGy depending on the field size. Thus, the doses for 3D imaging systems used one time each day are in the range of 0.1 to 10 cGy and can contribute from 0.06 to 6% to a daily dose of 1.8 Gy. As a technique of controlling patient dose, it is recommended that a QA procedure be established at each institution to verify the accuracy of the image registration software on a daily basis. This QA check should be performed by the therapists operating a particular treatment device and is aimed at reducing the use of repeat imaging to check that the registration software has functioned properly when a shift of patient position is carried out. Additionally, it is not recommended that an institution use a daily imaging technique that delivery greater than 3 cGy/dy to the patient. This limit dictates that repeat imaging on a particular day is held to a minimum when systems that deliver up to 3 cGy per study are used.

6.7 Quality Assurance (5/23/12)

6.7.1 Documentation Requirements

The institution will archive treatment prescription and verification images for later review by the study chair if requested. At least one port film or pretreatment alignment film per field along with the digital reconstructed radiographs (DRRs) from the treatment planning program or, alternatively, a simulation verification radiograph shall be acquired and kept for evaluation if requested except where geometrically impractical.

6.7.2 Compliance Criteria

Cases which meet criteria as stated in Section 6.1.1 will be scored as per protocol. The minimum allowable dose within the PTV is >95% of the prescribed dose to a volume that is at least 0.03cc. Cases in which this small volume of at least 0.03cc receives a minimum dose that is <95% but >93% or a maximum dose that is >107% and <110% of the prescribed dose will be scored as a variation acceptable. Cases in which such a small volume receives less than 93% or >110% of the prescribed dose will be scored as a deviation unacceptable.

- Acceptable dose heterogeneity will be as follows: **This maximum dose volume of the PTV must not be shared by a normal critical structure. (Section 6.4.1).** The maximum point dose to normal critical structures outside the PTV should not exceed the prescription dose. The treating physician must carefully consider the tolerance dose/volume to each critical normal structure and unspecified tissue.

6.8 Dose Specifications/Technical Considerations: LDR Brachytherapy Boost (4/21/15)

Note: As this protocol allows for treatment with exclusively EBRT or EBRT + brachytherapy (at the discretion of the treating physician) this must be specified at the time of study enrollment. Should a patient who was originally intended to receive brachytherapy be found, post-enrollment, to be a poor brachytherapy candidate based on transrectal ultrasound examination, he may be switched to external beam radiotherapy administered per protocol guidelines, but this will result in a protocol deviation. Therefore, it is strongly recommended to obtain ultrasound assessment of prospective brachytherapy patients before enrollment on this study.

6.8.1 LDR, permanent seed, brachytherapy boost is permitted at the discretion of the treating radiation oncologist in conjunction with EBRT as described in Section 6.2.2. Implants will only be offered to patients with a prostate volume documented to be <60 cc by transrectal ultrasound examination, an AUA score ≤15, and no prior history of TURP (Section 3.2.9). The implant may be performed under either general or spinal anesthesia and will be performed following the EBRT portion of treatment no more than 4 weeks following its completion.

6.8.2 Preplanning

This will be carried out prior to the procedure or intraoperatively via transrectal ultrasound examination. The prostate will be defined from base to apex in the axial plane at 5 mm slice intervals. The treatment length and prostate volume will be recorded. The CTV will consist of the prostate only. The PTV may be the same as the CTV or a 2-3 mm margin may be added anteriorly and laterally and up to 5 mm craniocaudally at the discretion of the treating physician.

6.8.3 Isotope Selection

Iodine-125 or Palladium-103 seeds may be used. The sources will be received and inventoried in accordance with state and federal regulations. If nonsterile loose sources or cartridges are used, at least 10% of the sources will be assayed in such a manner that direct traceability to either the National Institute of Standards and Technology (NIST) or an Accredited Dosimetry Calibration Lab (ADCL) is maintained. NIST 1999 standards will be used. If sterile source assemblies or strands are used, alternatively nonstranded loose seeds equal to 5% of the total, or five seeds, whichever is fewer, may be ordered and assayed. Agreement of the average measured source strength shall agree with that indicated in the vendor's calibration certificate to within 5%. No measured source strengths should fall outside 10% of that indicated in the vendor's calibration certificate.

- For I-125, the allowable source strength for each seed is 0.277 U to .650 U (NIST 99 or later). For Pd-103 sources, this range is 1.29 U to 2.61 U (NIST 99 or later).
- The vendor's stated source strength shall be used in all dosimetry calculations. Calculations will be performed in accordance with NIST 1999 calibration standards, the point source formalism described in the report generated by AAPM Task Group 43 and subsequent published AAPM Subcommittee Reports. The AAPM's recommendations for Pd-103 dose specifications and prescription are being followed.

6.8.4 Prescription Doses

The prescription dose for permanent seed interstitial boost will be **110 Gy for I-125 and 100 Gy for Pd-103**. Doses will be prescribed as minimal peripheral dose to the PTV.

6.8.5 Postimplant Imaging

A pelvic x-ray with seed count verification will be obtained immediately postimplant. If the seed count does not match the number of seeds implanted, PA and lateral chest x-rays will be obtained to rule out pulmonary seed migration. CT scan for postimplant dosimetric analysis will be obtained following implant completion. Use of a Foley catheter for this test is encouraged for accurate urethral dosimetry but not required. This may be obtained immediately postoperative on the day of the implant if desired but no later than 5 weeks postimplant. The use of intravesical contrast is encouraged. CT slices should be acquired at ≤3 mm thickness and should encompass the pelvis from, at minimum, the bottom of the sacroiliac joints superiorly to 2 cm caudal to the prostatic apex.

- Structures defined will include the prostate, bladder, and rectum. The rectum will be defined from the bottom of the sacroiliac joints to the ischial tuberosity and will extend to the outer surface of the visualized rectal wall. The postimplant, CT-defined prostate will be defined as the "evaluated target volume" (ETV) and will form the basis for dosimetric analysis.

6.8.6 Dosimetry

Postimplant evaluation will be performed on equipment capable of providing structural and volume-based dosimetric assessment on both the target and critical structures. Volume acquisition will be based on

contiguous axial CT slices as described above. Both target volume and critical structures will be contoured on each applicable axial slice. Isodose line displays and dose-volume histograms for all structures will be generated.

- The calculation grid should be set no larger than (2 mm x 2 mm x axial slice width).
- The planning system shall be capable of transmitting data via DICOM RT to NRG Oncology electronically.
- Guidelines established by the American Brachytherapy Society[62] are to be followed. DVH-based analysis must be used in the postplan evaluation. The following values shall be reported. Vn is the percentage of the ETV that received at least n% of the prescription dose. Dm is the minimum dose received by m% of the ETV.
- Target coverage will be documented in terms of V100, V90, V80, D90.
- Dose uniformity will be expressed in terms of V150.
- The rectum will be defined from the bottom of the SI joints to the ischial tuberosity. The maximum rectal dose as well as the volume and percentage of rectum receiving >100% of the prescription dose will be recorded.

Note: All required **LDR** Brachytherapy Boost structures must be labeled as listed in the table in Section 6.4.1 for digital RT data submission. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed.

6.8.7 Compliance Criteria

- Per protocol: D90 for the ETV is greater than 90% of the prescription dose but less than 130% of the prescription dose.
- Variation acceptable: D90 for the ETV is greater than 80% of the prescription dose, but less than 90% of the prescription dose, or greater than 130% of the prescription dose.
- Deviation unacceptable: D90 for the ETV is less than 80% of the prescription dose.

6.8.8 Dosimetric Data to be Submitted to NRG Oncology

- Copies of preimplant TRUS images with CTV and PTV annotated
- A copy of the implant record generated during the procedure
- A copy of the image taken after the procedure and a copy of the image or scout taken during the post implant CT
- A copy of the postimplant CT scan, ETV and bladder and rectum delineation and dosimetry calculations (must be submitted electronically)
- A copy of the postimplant dosimetry report that contains the information required in Section 6.8.6 above.

6.8.9 Quality Assurance

Individual case review will be performed by Dr. Morton, the LDR brachytherapy study co-chair overseeing this subgroup of patients enrolled on this protocol, as specified below in Section 6.10.

6.9 Dose Specifications/Technical Considerations: HDR Brachytherapy Boost (4/21/15)

Note: As this protocol allows for treatment with exclusively EBRT or EBRT + brachytherapy (at the discretion of the treating physician) this must be specified at the time of study enrollment. Should a patient who was originally intended to receive brachytherapy be found, post-enrollment, to be a poor brachytherapy candidate based on transrectal ultrasound examination, he may be switched to external beam radiotherapy administered per protocol guidelines, but this will result in a protocol deviation. Therefore, it is strongly recommended to obtain ultrasound assessment of prospective brachytherapy patients before enrollment on this study.

6.9.1 HDR brachytherapy boost is permitted at the discretion of the treating radiation oncologist in conjunction with EBRT as described in Section 6.2.2. Implants will only be offered to patients with a prostate volume documented to be <60 cc by transrectal ultrasound examination, AUA symptom index $\leq$15, and no prior history of TURP (Section 3.2.9). HDR treatment will be delivered in 2 fractions separated by a minimum time span of 6 hours. This may be done in a single or multiple implant procedures at the discretion of the treating physician. The implant(s) may be performed during the EBRT portion of the treatment or within 1 week prior to its initiation or following its completion. For patients receiving HDR brachytherapy boost who are randomized to Arm 2, RT should begin, as for other modalities, 8 weeks following the first LHRH administration. The date of HDR brachytherapy implant will constitute the start of RT for those patients receiving implants prior to EBRT.

6.9.2 All implants will be performed under transrectal ultrasound guidance. Epidural, spinal, or general anesthesia may be used. Epidural analgesia may be used for interfraction pain control.

6.9.3 At least 14 treatment catheters should be used to ensure adequate target coverage with acceptable dose heterogeneity.

6.9.4 For patients receiving two fractions in a single implant, fiducial markers identifying the prostatic base and apex should be placed at the time of the implant procedure unless previously placed for guidance of EBRT.

6.9.5 The use of intraoperative cystoscopy is encouraged to ensure the absence of treatment catheters within the urethra or bladder. The cystoscope should be retroflexed within the bladder for visualization of the bladder neck. Light pressure on the treatment catheters should result in mucosal tenting confirming adequate coverage at the prostatic base.

6.9.6 For patients undergoing a single implant, a minimum interval of 6 hours will be allotted between fractions. If there is significant catheter migration or if the treating physician cannot reproduce the same implant geometry, then the implant may be repeated at a later date (without violating Section 6.9.1). Treatment plans for both implants should be submitted to NRG Oncology.

6.9.7 Implant Dosimetry (CT-Based)

The treatment planning CT scan must be performed with the patient in the supine position with the Foley catheter in place. Metallic obturators or non-CT compatible dummy ribbons must be removed prior to the CT scan. The scan must include all of the CTV with at least 9 mm superior and inferior margin, and the scan must include the tips of all the implanted catheters. The scan thickness must be ≤0.3 cm and the slices must be contiguous. The brachytherapy target volume (Section 6.9.7) and normal critical structures (Section 6.9.7) must be outlined on all CT slices.

Dwell Selection and Dwell Time Optimization: Dwell times in positions located outside of the PTV should be turned down or off to minimize normal tissue irradiated. A dwell time optimization program based on implant geometry or an inverse planning algorithm may be used. Manual optimization is also accepted.

Brachytherapy Target Volume: The CTV is the prostate gland plus any visualized tumor. The PTV is equivalent to the CTV.

Brachytherapy Critical Structures: Critical structures to be defined using CT planning include the bladder, rectum, and urethra. The outermost extent of the bladder/rectal wall will define those structures. The urethra is defined by the outer surface of the Foley catheter.

Critical Structure Dose Limits: The volume of bladder and rectum receiving 75% of the prescription dose must be kept to less than 1 cc (V75 <1 cc) and the volume of urethra receiving 125% of the prescription dose must be kept to less than 1 cc (V125 <1 cc). Urethral V150 should be 0%. If the dose to normal critical structures cannot be kept below the specified level, we recommend readjusting the implant or repeating the implant procedure until a more optimal implant is obtained.

Catheter Position Verification: Visual inspection of the catheters prior to delivery of each treatment is required. Fluoroscopy or CT also may be used to verify the position of the catheters in relation to the Foley catheter balloon and fiducial markers. The physician may adjust the catheters if catheter displacement is identified prior to the treatment. If the catheters cannot be satisfactorily repositioned and the PTV and normal critical structure DVH parameters are not met with a new plan, then the treatment should be postponed until a satisfactory implant is done. If the planning process is repeated, then a second set of data should be submitted.

6.9.8 Implant Dosimetry (Ultrasound-Based)

Real-time, transrectal ultrasound-based planning is acceptable. The prostate must be defined from base to apex in axial slices with a maximum slice thickness ≤0.5 cm. A Foley catheter must be in place for definition of the urethra. The slices must include the tips of all the implanted catheters.

Dwell Selection and Dwell Time Optimization: Dwell times in positions located outside of the PTV should be turned down or off to minimize normal tissue irradiated. A dwell time optimization program based on implant geometry or an inverse planning algorithm may be used. Manual optimization is also accepted.

Brachytherapy Target Volume: The CTV is the prostate gland plus any visualized tumor. The PTV is equivalent to the CTV.

Brachytherapy Critical Structures: Critical structures to be defined using ultrasound-based planning include the rectum and urethra. The urethra is defined by the outer surface of the Foley catheter. For ultrasound-based planning, the urethra will be defined by the Foley catheter in slices extending from the base to the prostate apex. The anterior rectal wall must be defined along the length of the prostate.

Critical Structure Dose Limits: Attempts should be made to limit the volume of urethra receiving ≥115% of the prescription dose to ≤5%. Up to 10% will be considered variation acceptable. Dose to > 1 cc of the anterior rectal wall should not exceed 75% of the prescription dose.

Catheter Position Verification: For the ultrasound-based planning system, the treatment should be delivered with the transrectal ultrasound probe in the patient, the same position during the acquisition of

images used for planning. For the second fraction, a repeat ultrasound plan or a CT-based plan must be done prior to delivery of the second fraction. Alternatively, the ultrasound-based implant and treatment may be repeated at a later date (without violating Section 6.9.1). Treatment plans for both implants should be submitted to NRG Oncology.

Note: All required HDR Brachytherapy Boost structures must be labeled as listed in the table in Section 6.4.1 for digital RT data submission. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed.

6.9.9 Compliance Criteria

A prescription dose of 21 Gy will be delivered to the PTV in two equal fractions of 10.5 Gy. Ninety-five percent coverage of the PTV with the prescription dose is considered per protocol, ≥90% but <95% is considered variation acceptable, and <90% coverage is considered deviation unacceptable. The first fraction of 10.5 Gy will be delivered as soon as possible following completion of the implant procedure and treatment planning. Both fractions must be delivered within a single 24-hour period and separated by a minimum of 6 hours. Overnight hospital stay is permitted between fractions if necessary.

6.9.10 Catheter Removal

After completion of the treatment all catheters will be removed.

6.9.11 Data Submission

All data will be digitally submitted to NRG Oncology and include CT data, normal critical structures, all PTV contours, and digital DVH data for all normal critical structures, the PTV for dose plan, a copy of the daily treatment chart for EBRT and Brachytherapy.

6.9.12 Quality Assurance

Individual case review will be overseen by Drs. Martinez and Krauss, the study co-chairs overseeing this subgroup of patients enrolled on this protocol, as specified in Section 6.10.

6.10 Radiation Quality Assurance Reviews (12/10/10)

The study co-chairs for the respective RT modalities offered in this trial will oversee quality assurance reviews for patients treated in those respective fashions. RT quality assurance reviews will be ongoing and performed remotely. RT quality assurance reviews will be facilitated by IROC Philadelphia and IROC Houston.

6.11 Radiation Adverse Events

6.11.1 All patients will be seen weekly by their treating radiation oncologist while undergoing therapy. Any observations with respect to the following symptoms/side effects will be recorded:

- Bowel/rectal irritation manifesting as cramping, diarrhea, urgency, proctitis, or hematochezia
- Urinary frequency, urgency, dysuria, hematuria, urinary tract infection, or incontinence
- Radiation dermatitis

6.11.2 Clinical discretion may be used in managing radiotherapy-related side effects. Diarrhea/rectal frequency/urgency may be managed with diphenoxylate or loperamide. Bladder irritation may be mitigated with phenazopyridine. Urinary frequency/urgency can be managed with anticholinergic agents or alpha-blockers such as tamsulosin. Erectile dysfunction can be managed with phosphodiesterase (PDE) inhibitors such as sildenafil.

6.12 Radiation Adverse Event Reporting

See Section 7.5 for additional Adverse Events information and 7.6 for Adverse Event Reporting Guidelines.

7.0 DRUG THERAPY (5/23/12)

Patients randomized to receive short-term androgen deprivation therapy must begin this treatment within 4 weeks after randomization. Androgen deprivation therapy will consist of "total androgen blockade" consisting of both LHRH agonist and anti-androgen (either Casodex or Eulexin) for a total duration of 6 months. Firmagon (degarelix), an LHRH antagonist with similar androgen suppressive activity is an acceptable alternative to LHRH agonist therapy.

7.1 Anti-Androgen Therapy: Casodex (Bicalutamide)

For further information, consult the package insert.

7.1.1 Timing: Oral anti-androgen therapy will begin within (before, same day as, or after) 10 days of the date of the first administration of LHRH agonist for patients randomized to Arm 2 and continued for a total

duration of 6 months. The total duration of administered anti-androgen therapy must be documented and submitted to NRG Oncology.

7.1.2 Description: Bicalutamide is a nonsteroidal antiandrogen, which has no androgenic or progestational properties. The chemical name is propanamide, N-[4-cyano-3(trifluoromethyl)phenyl]- 3- [(4-fluorophenyl)sulphonyl]- 2- hydroxy- 2- methyl, (+,-). Bicalutamide is a racemic mixture with the antiandrogen activity residing exclusively in the (-) or R-enantiomer. Bicalutamide has a long half-life compatible with once-daily dosing. Bicalutamide is well tolerated and has good response rates in phase II trials.[63,64]

7.1.3 Supply: Commercially available.

7.1.4 Storage: Bicalutamide should be stored in a dry place at room temperature between 68°-77°F.

7.1.5 Administration: Bicalutamide is administered orally at a dose of one 50 mg tablet per day. Bicalutamide will begin within (before, same day as, or after) 10 days of the date of the first LHRH agonist administration, and continue for a total duration of 6 months (i.e. the total duration of planned androgen deprivation). Administration will be suspended only if there is an apparent or suspected reaction to the drug. During RT interruptions, bicalutamide will be continued. Any treatment interruptions or failure of the patient to comply with the prescribed medication schedule must be documented and reported to NRG Oncology.

7.1.6 Toxicity: Consult the package insert for comprehensive toxicity information. In animal experiments, birth defects (abnormal genitalia, hypospadias) were found in male offspring from female animals dosed with bicalutamide during pregnancy. Although offspring from male animals dosed with bicalutamide did not show any birth defects, patients enrolled in this trial are advised not to cause pregnancy nor donate sperm while receiving protocol therapy or during the first 3 months after cessation of therapy. The use of barrier contraceptives is advised. The most frequent adverse events reported among subjects receiving bicalutamide therapy are breast tenderness, breast swelling, and hot flashes. When bicalutamide 50 mg was given in combination with an LHRH analog, the LHRH analog adverse event profile predominated with a high incidence of hot flashes (53%) and relatively low incidences of gynecomastia (4.7%) and breast pain (3.2%). Other side effects include impotence and loss of libido, fatigue, and rarely, photosensitivity and diarrhea.

7.1.7 Dose Modifications: AST and ALT will be measured pretreatment and then monthly during antiandrogen therapy. If the AST or ALT rises to ≥ 2x the institutional upper limit of normal, bicalutamide must be discontinued. Elevated AST/ALT values to < 2x the institutional upper limit of normal are subject to dose modifications or discontinuation of anti-androgen at the discretion of the treating physician.

7.2 Anti-Androgen Therapy: Eulexin (Flutamide)

For further information, consult the package insert.

7.2.1 Timing: See Section 7.1.1.

7.2.2 Description: Flutamide is a substituted anilide. It is a fine, light, yellow powder, insoluble in water but soluble in common organic solvents such as aromatic or halogenated hydrocarbons. Its concentration in plasma can be determined by gas chromatography. Flutamide is a nonsteroidal antiandrogen that is metabolized into a hydroxylated derivative, which effectively competes with the hydrotestosterone for androgen receptor sites.

7.2.3 Supply: Commercially available.

7.2.4 Storage: Flutamide should be stored at temperatures ranging from 20-30°C (68-86°F) and protected from excessive moisture.

7.2.5 Administration: Flutamide is administered orally at a dose of 250 mg (two 125-mg capsules) three times a day for a total daily dose of 750 mg. Flutamide will begin within (before, same day as, or after) 10 days of with the date of the first LHRH agonist administration (and continue for a total duration of 6 months. Administration will be suspended only if there is an apparent or suspected reaction to the drug (See Section 7.1.5). During RT interruptions, flutamide will be continued. Any treatment interruptions or failure of the patient to comply with the prescribed medication schedule must be documented and reported to NRG Oncology.

7.2.6 Toxicity: Consult the package insert for comprehensive toxicity information. The reported side effects of treatment include diarrhea and anemia. A high percentage of patients treated with flutamide alone developed gynecomastia within 2 to 8 months. There have been post-marketing reports of hospitalization, and, rarely, death due to liver failure in patients taking flutamide. Evidence of hepatic injury included elevated serum transaminase levels, jaundice, hepatic encephalopathy, and death related to acute hepatic failure. The hepatic injury was reversible after prompt discontinuation of therapy in some patients.

Approximately half of the reported cases occurred within the initial 3 months of treatment with flutamide. Other side effects include impotence and loss of libido, fatigue, and rarely, photosensitivity.

7.2.7 Dose Modifications: If gastrointestinal disturbances (cramps, diarrhea) occur prior to initiation of radiotherapy, flutamide will be withheld until the side effects subside; the drug will then be reintroduced at a dose of 250 mg/day and increased (at 3-day intervals) to 500 mg/day and then to 750 mg/day as tolerated. If gastrointestinal disturbances occur after administration of radiotherapy, it might be difficult to identify their cause. However, if severity of diarrhea exceeds the level commonly observed during prostate irradiation, the toxicity will be ascribed to flutamide and the drug will be permanently discontinued. AST and ALT will be measured pretreatment, then monthly during oral antiandrogen therapy. If AST or ALT increase ≥ 2x the institutional upper limit of normal, flutamide must be discontinued. Elevated AST/ALT values to < 2x the institutional upper limit of normal are subject to dose modifications or discontinuation of anti-androgen at the discretion of the treating physician.

7.3 LHRH Agonist (Antagonist) Therapy (leuprolide, goserelin, buserelin, triptorelin, degarelix) [5/23/12]

For additional information, consult the package inserts.

7.3.1 Timing: For patients randomized to ADT (Arm 2), the first LHRH administration will occur together with the start of anti-androgen treatment (see Sections 7.1.5 or 7.2.5) 8 weeks prior to the start of RT. The total duration of LHRH therapy will be 6 months. The total administered duration as well as the specific agent used must be documented and submitted to NRG Oncology.

7.3.2 Description: LHRH agonists are long-acting analogs of the native LHRH peptide and are effective at reducing serum testosterone. Analogs approved by the FDA (or by Health Canada for Canadian institutions) can be used in this study.

- Firmagon (degarelix) is an LHRH antagonist with similar testosterone-reducing properties to the LHRH agonists. Initial loading dose of 240 mg subcutaneous followed by monthly maintenance of 80 mg subcutaneous for a total of six months is required.

7.3.3 Supply: Commercially available. (Note: Buserelin is not commercially available in the United States. It is commercially available for use in Canada and other countries.)

7.3.4 Storage: LHRH analogs should be stored as directed by the commercial supplier.

7.3.5 Administration: LHRH analogs are administered with a variety of techniques, including subcutaneous insertion of a solid plug in the abdominal wall (Zoladex), intramuscular injection (Lupron), subcutaneous injection (Eligard), or insertion of a long-acting cylinder that slowly releases the agent (Viadur). The manufacturer's instructions should be followed.

7.3.6 Toxicity: Consult the package inserts for comprehensive toxicity information. Class-related toxicity is generally a manifestation of the mechanism of action and related to low testosterone levels. In the majority of patients testosterone levels increase above normal in the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. The most common side effect of LHRH analogs is vasomotor hot flashes; edema, gynecomastia, bone pain, thrombosis, and gastrointestinal disturbances have occurred. Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction or hematuria which, if aggravated, may lead to neurological problems such as temporary weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms. Other side effects include impotence and loss of libido, weight gain, depression, dizziness, loss of bone density, anemia, increased thirst and urination, unusual taste in the mouth, skin redness or hives, pain at injection site, and muscle mass and strength loss, hair changes, penile length and testicular volume loss, increased cholesterol, hypertension, diabetes exacerbation, emotional lability, nausea, vomiting, and rarely, allergic generalized rash and difficulty breathing.

7.4 Modality Review

All records of ADT administration for patients randomized to Arm 2 should be submitted to NRG Oncology. Protocol compliance will be assessed at the NRG Oncology semi-annual meetings by the study chair/co-chairs. The recommended ADT duration is six months and will be measured from the day of initial LHRH agonist injection until the final day of activity (e.g. 90-day depot injection preparations given on day 1 and 91 equal 6 months of ADT). Likewise, submitted records of anti-androgen therapy should reflect their total duration of administration, which should mirror the duration of LHRH agonist treatment. The review process is contingent on timely submission of hormone therapy treatment data as specified in Section 12.1. The scoring mechanism is: Per Protocol/Acceptable Variation, Not Per Protocol,

and Not Evaluable. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

7.5 Adverse Events (4/29/14)

Beginning October 1, 2010, this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for grading of all adverse events. A copy of the CTCAE version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. **All AE reporting on the study case report forms will continue to use CTCAE version 3.0.**

All adverse events (AEs) as defined in the tables below will be reported via the CTEP-AERS (CTEP Adverse Event Reporting System) application accessed via the CTEP web site (https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613).

Serious adverse events (SAEs) as defined in the tables below will be reported via CTEP-AERS.

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

7.5.1 Adverse Events (AEs)

Definition of an AE: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. February 29, 2012; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm]

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Oncology at 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

7.5.2 Serious Adverse Events (SAEs)

— Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in Section 7.6 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in Section 7.6. **Contact the CTEP-AERS Help Desk if assistance is required.**

Definition of an SAE: Any adverse drug event (experience) occurring at any dose 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.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, any pregnancy, including a male patient's impregnation of his partner, must be reported via CTEP-AERS in an expedited manner.

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

AML or MDS that is diagnosed as a secondary malignancy during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system within 30 days of AML/MDS diagnosis.

Secondary Malignancy
A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy
A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

7.6 CTEP-AERS Expedited Reporting Requirements (4/29/14)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the CTEP Adverse Event Reporting System, accessed via the CTEP web site,
https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613.

Submitting a report via CTEP-AERS serves as notification to NRG Oncology and satisfies NRG Oncology requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to NRG Oncology at 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

- CTEP-AERS-24 Hour Notification requires that a CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a CTEP-AERS 5 Calendar Day Report. Serious adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.
- Supporting source document is not mandatory. However, if the CTEP-AERS report indicates in the *Additional Information* section that source documentation will be provided, then it is expected. If supporting source documentation accompanies an CTEP-AERS report, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation **to the NRG Oncology dedicated SAE FAX, 215-717-0990.**
- A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS System as “expedited reporting NOT required” must still be reported to fulfill NRG Oncology safety reporting obligations. Sites must bypass the “NOT Required” assessment; the CTEP-AERS System allows submission of all reports regardless of the results of the assessment.

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

Phase 2 and 3 Trials Utilizing a Commercially Available Agent: CTEP-AERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days[1] of the Last Dose of the Investigational Agent (Bicalutamide, Flutamide, LHRH Agonists) in this Study

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercially Available Agent:
None

8.0 SURGERY

Not applicable to this study

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

9.1.1 Diarrhea/rectal frequency/urgency may be managed with diphenoxylate or loperamide. Bladder irritation may be mitigated with phenazopyridine. Urinary frequency/urgency can be managed with anticholinergic agents or alpha-blockers such as tamsulosin. Erectile dysfunction can be managed with phosphodiesterase (PDE) inhibitors such as sildenafil.

10.0 TISSUE/SPECIMEN SUBMISSION

Note: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission. If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient's specimens as specified in Section 10.0 of the protocol. Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission

The NRG Oncology Biospecimen Bank- San Francisco, at the University of California San Francisco, acquires and maintains high quality specimens from NRG Oncology trials. Tissue from each block is preserved through careful block storage and processing. The NRG Oncology encourages participants in protocol studies to consent to the banking of their tissue. The NRG Oncology Biospecimen Bank 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 NRG Oncology Biospecimen Bank also collects tissue for Central Review of pathology. Central Review of tissue can be for eligibility and/or analysis.

In this study, tissue will be submitted to the NRG Oncology Biospecimen Bank for the purpose of tissue banking (recommended) and translational research (recommended).

10.2 Specimen Collection for Tissue Banking and Translational Research (Recommended) [5/23/12]

For patients who previously have consented to participate in the tissue/blood component of the study (See Appendix I). Note: Blood collection is mandatory for patients who have provided consent for the QOL portion of this study and optional for other participants.

The following must be provided in order for the case to be evaluable for the Biospecimen Bank:

10.2.1 One H&E stained slide

10.2.2 A corresponding paraffin-embedded tissue block of the tumor core biopsy, or at least ten 5 micron unstained sections on "plus" slides labeled with the surgical pathology number and block ID. Block or unstained slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

10.2.3 A Pathology Report documenting that the submitted block or unstained slides contain(s) tumor. The report must include the NRG Oncology protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

10.2.4 A Specimen Transmittal Form clearly stating that tissue is being submitted for the NRG Oncology Biospecimen Bank; if for translational research, this should be stated on the form. The form must include the NRG Oncology protocol number and patient's case number.

10.2.5 Plasma and whole blood cells

See Appendix IV for the blood collection kit and instructions. **Note**: Kit includes a label for shipping. The following must be provided in order for the case to be evaluable by the Biospecimen Bank: A Specimen Transmittal Form documenting the date of collection of the plasma and whole blood; the NRG Oncology protocol number, the patient's case number, institution name and NRG or NCI ID, time point of study, and method of storage, for example, stored at -80° C, must be included.

10.2.6 Storage Conditions

Store frozen specimens 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).

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).

OR:

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

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

10.2.7 Specimen Collection Summary

Specimens taken from patient:	**Specimens collected when:**	**Submitted as:**	**Shipped:**
Representative H&E stained slides of the primary tumor	Pretreatment	H&E stained slide	Slide shipped ambient
A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or at least 10 unstained 5 micron sections on "plus" slides	Pretreatment	Paraffin-embedded tissue block or unstained slides	Block or unstained slides shipped ambient
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/lavender top) and centrifuge	Pretreatment, during the last week of RT	Frozen plasma samples containing 0.5 mL per aliquot in 1 mL cryovials (five to eight)	Plasma sent frozen on dry ice via overnight carrier
DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix	Pretreatment	Frozen whole blood samples containing 1 ml per aliquot in 1ml cryovials (up to five)	Whole blood sent frozen on dry ice via overnight carrier

10.2.8 Submit materials for Tissue Banking and Translational Research as follows:

U.S. Postal Service Mailing Address: For Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

Questions: 415-476-7864/FAX 415-476-5271; NRGBB@ucsf.edu

10.3 Reimbursement (4/21/15)

Please note that with the start of the new NCI National Clinical Trials Network (NCTN) Program, NCI funds for reimbursement for protocol-specified biospecimen materials will be distributed per the requirements/methods specified by the new NCTN Program. This information will be made available with the other registration materials in the Oncology Patient Enrollment Network (OPEN) portal system. OPEN will serve as the registration system for all patient enrollments onto NCI-sponsored NCTN trials, including this study, which will be transitioned into the new Program from the NCI-sponsored Cooperative Group Clinical Trials Program.

10.4 Confidentiality/Storage

(See the Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx for further details.)

10.4.1 Upon receipt, the specimen is labeled with the NRG Oncology protocol number and the patient's case number only. The NRG Oncology Biospecimen Bank 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 tissue banking will be stored for an indefinite period of time. 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 (12/10/10)

See Appendix I for assessments and timeframes. See Sections 11.1.1 to 11.1.6 for details and/or exceptions to Appendix I.

11.1.1 The pelvic +/- abdominal CT or MRI is required for patients with >1 risk factor (Section 3.1.1) and as described in Section 3.1.2.

11.1.2 Transrectal ultrasound is a one-time test that is required only for patients receiving LDR or HDR brachytherapy boost as a component of their treatment. This should ideally be performed prior to study enrollment as the RT modality (EBRT alone, EBRT + HDR, EBRT + LDR) must be specified at the time of enrollment. In the event that transrectal ultrasound is performed post-enrollment and results in a change in the RT modality being administered (the patient may be switched to EBRT administered per protocol guidelines), this change will result in a protocol deviation. (See last paragraph of Section 11.3)

11.1.3 The CBC/differential is required only for patients who will receive either LDR or HDR brachytherapy boost (must be known at the time of registration).

11.1.4 See Section 3.1.7 for special circumstances regarding PSA. Also, PSA will be obtained prior to each follow-up visit.

11.1.5 Serum testosterone need only be obtained from patients randomized to receive ADT (Arm 2) at the time of study entry (baseline prior to starting ADT), at the start of RT (8 weeks following 1st LHRH agonist

administration)—may be performed in conjunction with timing of AST/ALT/alkaline phosphatase—and every 6 months until rising to baseline levels or for 3 years (whichever is sooner).

11.1.6 Patients receiving anti-androgen therapy (Arm 2) will need monthly liver function testing (AST, ALT, alkaline phosphatase) for the duration of that treatment.

11.2 Measurement of Response

11.2.1 Overall survival is the primary study endpoint and the event date of overall survival will be the date of death due to any cause.

11.2.2 Biochemical failure is defined as the documented rise of 2 ng/ml above its post-treatment nadir value.

11.2.3 Local recurrence is defined as the documented local recurrence as follows: Patients with clinical (palpable) suspicion of local recurrence following treatment completion should undergo biopsy for pathologic confirmation of local recurrence. Once pathologic confirmation is obtained, the event date will be the date at which the palpable progression was first identified. In the event of biochemical failure (nadir + 2 ng/ml), metastatic workup including, at minimum, chest x-ray, bone scan, and abdominopelvic CT should be obtained to exclude the possibility of distant failure. If negative, prostate biopsy should be performed. If positive, biochemical failure will be considered the local recurrence event.

11.2.4 Regional recurrence is defined as the documented progression in pelvic lymph nodes. If discovered on CT of the pelvis prompted by a biochemical failure, then the event date will be the date of documented biochemical failure.

11.2.5 Distant failure is defined as the documented metastatic disease by any method. If diagnosed on diagnostic imaging prompted by biochemical failure, then the event date will be the date of biochemical progression.

11.2.6 Freedom from failure is defined as the first event of biochemical failure, local recurrence, regional recurrence, or distant metastasis, as described above.

11.2.7 Prostate cancer specific mortality is defined as a death due to prostate cancer or a complication from treatment

11.2.8 Non-prostate cancer specific mortality is defined as a death without evidence of prostate cancer or a complication from treatment.

11.2.9 Rate of salvage ADT administration is defined as the first administration of subsequent ADT (either LHRH agonist or anti-androgen) is given.

11.3 Criteria for Discontinuation of Protocol Treatment

Patients who are experiencing excessive adverse events as deemed by their treating physician may be discontinued from the initiated protocol treatment. All attempts should be made to manage adverse events adequately so as to avoid this circumstance. As specified in Sections 7.1 and 7.2, anti-androgen therapy will be withheld if AST/ALT values are elevated to ≥ 2x the institutional upper limit of normal.

Study analysis will be based on “intent to treat.” If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

11.4 Health-Related Quality of Life (HRQOL) (5/23/12)

Note: The Quality of Life component of this study closed to patient accrual on March 22, 2012. If the patient provided consent to participate in the quality of life component of this study prior to closure to new patient accrual, the site is required to administer the QOL assessments as specified in Section 11.0 of the protocol. **Blood collection is mandatory for patients who have provided consent for the QOL portion of this study.**

11.4.1 Prostate Cancer-Specific Health-Related Quality of Life: EPIC

The Expanded Prostate Cancer Index Composite (EPIC) is a prostate cancer health-related quality of life (HRQOL) patient self-administered instrument that measures a broad spectrum of urinary, bowel, sexual, and hormonal symptoms related to RT and ADT.[29] Instrument development was based on advice from an expert panel and prostate cancer patients, which led to expanding the 20-item University of California-Los Angeles Prostate Cancer Index (UCLA-PCI) to the 50-item EPIC. Summary and subscale scores were derived by content and factor analyses. Test-retest reliability and internal consistency were high for EPIC urinary, bowel, sexual, and hormonal domain summary scores (each r ≥0.80 and Cronbach's alpha ≥0.82) and for most domain-specific subscales. Correlations between function and bother subscales within domains were high (r >0.60). Correlations between different primary domains were consistently lower, indicating that these domains assess distinct HRQOL components. EPIC domains had weak to modest correlations with the Medical Outcomes Study 12-item Short-Form Health Survey (SF-12), indicating

rationale for their concurrent use. Moderate agreement was observed between EPIC domains relevant to the Functional Assessment of Cancer Therapy Prostate module (FACT-P) and the American Urological Association Symptom Index (AUA-SI), providing criterion validity without excessive overlap.[65]

EPIC is a robust prostate cancer HRQOL instrument that measures a broad spectrum of symptoms; however, to decrease patient burden we will only use the domains most pertinent to this study: urinary, bowel, sexual, and hormonal. The domains were validated separately, and since each domain will be used intact, there is no threat to validity. Dutch and Japanese translations of the EPIC are available, and a Spanish translation is planned but not yet available.

11.4.2 Patient-Reported Outcome Measurement Information System (PROMIS)-Fatigue Short Form

The PROMIS fatigue measure (7 items) was developed by the Patient-Reported Outcome Measurement Information System (PROMIS), part of the NIH Roadmap Initiative, focused on developing a publicly available resource of standardized, accurate, and efficient PRO measures of symptoms, distress, and functioning. Two content domains of fatigue, experience and impact, were identified by a panel of experts. An item pool of 58 fatigue experience and 54 fatigue impact items were developed. The psychometric properties of these items were evaluated in a sample of 450 individuals from the general US population using classical test theory indices, monotonicity, and scalability. The expert panel selected the 10 best items in each domain. These 20 items were presented to a panel of clinical experts. Only one item was dropped because of redundancy. A preliminary fatigue short-form measure of 7 items was created using items selected for consistency in the response scale, broad coverage across the fatigue continuum (i.e., high to low), and good precision of measurement (discrimination function).

11.4.3 Quality-Adjusted Survival Analysis: EuroQol (EQ-5D)

The EQ-5D is a patient self-administrated questionnaire that takes approximately 5 minutes to complete.[66] The first part consists of 5 items covering 5 dimensions including: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on 3 levels: 1-no problems, 2-moderate problems, and 3-extreme problems. Health states are defined by the combination of the leveled responses to the 5 dimensions, generating 243 (3^5) health states to which unconsciousness and death are added.[67]

The 5-item index score is transformed into a utility score between 0, “Worst health state,” and 1, “Best health state.” The index score can be used in a quality adjusted survival analysis depending on the health state(s) of interest.[68] For this study we plan to report the multidimensional utilities for comparative purposes. The EQ-5D has now been translated into most major languages, with the EuroQol Group closely monitoring the translation process; translations can be accessed at www.euroqol.org.

11.4.4 Pittsburgh Sleep Quality Index (PSQI)

Sleep quality will be measured by 1 item (Q3) of the Pittsburgh Sleep Quality Index (PSQI), a self-rated questionnaire which measures sleep quality and disturbances.[42] The Pittsburgh Sleep Quality Index (PSQI) was developed to discriminate between good and poor sleepers. The PSQI has good internal consistency (Cronbach’s alpha=0.83), stability (test-retest reliability=.85, P<.001) and discriminant validity. It has been used in patients with cancer and demonstrated sleep problems as expected.[42]

11.4.5 Godin Leisure-Time Exercise Questionnaire (GLTEQ)

Participants’ level of physical activity will be assessed using the Godin Leisure-Time Exercise Questionnaire (GLTEQ),[43,44] which measures time spent per week in each of light, moderate, and vigorous activities. A score can be computed for each level of exercise. A total score is computed by summing the three levels weighted by their respective metabolic (MET) equivalents of 3, 5, and 9. The GLTEQ has good test-retest reliability and has shown convergent validity with both objective and other self-report measures of physical activity.[43,44]

12.0 DATA COLLECTION

Data should be submitted to:

NRG Oncology*
1818 Market Street, Suite 1720
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 (12/10/10)

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Pathology Report **(P1)** Pathology Material **(P2)**	**Within 2 weeks of study entry**
EPIC **(FA)** PROMIS **(HP)** EQ-5D **(QF)** PSQI/GLTEQ Form **(QL)**	
Post Treatment Evaluation Form **(F0)**	**ARM 2 only: At the start of RT and 3 months post RT**
Follow-up Form **(F1)**	**ARM 1: At 3 months, 6 months, 9 months, and 12 months after completion of RT, then every 6 months for 4 years, then annually** **ARM 2: At 6 months, 9 months, and 12 months after completion of RT, then every 6 months for 4 years, then annually**
EPIC **(FA)** PROMIS **(HP)** EQ-5D **(QF)** PSQI/GLTEQ Form **(QL)**	**During the last week of RT and at 6 months, 1 year and 5 years after completion of RT**
Autopsy Report **(D3)**	**At the time of death (if available)**

12.2 Summary of Dosimetry Digital Data Submission (Submit to TRIAD; see Section 5 for account access and installation instructions) [11/14/13]

Preliminary Dosimetry Information **Digital data submission includes the following:** • CT dataset with contours for all critical normal structures, GTV, CTV, and PTVs • Digital beam geometry for initial and boost beam sets • Doses for initial, boost and composite sets of concurrently treated beams • Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan • All required structures **MUST** be labeled per the table in Section 6.4.1 **Upon submission of the digital data via TRIAD, complete an online Digital Data Submission Information Form (DDSI) located on the website at http://www.rtog.org/clinicaltrials/protocoltable/studydetails.aspx?study=0815** Note: All simulation and portal films and/or digital film images will be kept by the institution and ONLY submitted if requested.	**Within 1 week of start of RT**
Final Dosimetry Information	

Radiotherapy Form **(T1)** Daily Treatment Record **(T5) [copy to HQ]** Note: T5 submissions for patients receiving brachytherapy must include the Complete Daily Treatment Record for both (EBRT) and brachytherapy boost.	**Within 1 week of RT end**
LDR Brachytherapy Post-implant evaluation CT scan Post-implant structure set Post-implant plan Post-implant dose distribution NRG Oncology/RTOG Prostate Brachytherapy Protocol Compliance Form (BC)-Available on the IROC Houston website, http://rpc.mdanderson.org/rpc Radiotherapy Form **(T1) – 5 weeks post implant** **HDR Brachytherapy** Implant CT scan Implant structure set Implant plan Implant dose distribution NRG Oncology/RTOG Prostate Brachytherapy Protocol Compliance Form (BC)-Available on the IROC Houston website, http://rpc.mdanderson.org/rpc Radiotherapy Form **(T1) – 5 weeks post implant** Note: Copies of simulation and port films/images will be submitted to NRG Oncology ONLY if specifically requested.	**If applicable: 3-5 weeks post implant—Submit listed items to TRIAD.**

12.2.1 Dosimetry Data Submission to IROC Houston (11/14/13)
Submit to TRIAD; see Section 5.0 for account access and installation instructions.
Hardcopies should be sent to:

IROC Houston
ATTN: Dosimetry
8060 El Rio Street
Houston, TX 77054
Phone: 713-745-8989; Fax: 713-794-1364
E-mail: rpc@mdanderson.org

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints (12/10/10)

13.1.1 Primary Endpoint

Overall survival (OS): The failure event for OS will be death due to any cause (See Section 11.2.1).

13.1.2 Secondary Endpoints

- Biochemical failure by the Phoenix (nadir + 2) defintion[60] (See Section 11.2.2)
- Local recurrence (See Section 11.2.3)
- Regional recurrence (See Section 11.2.4)
- Distant metastasis (See Section 11.2.5)
- Freedom from failure (FFF) (See Section 11.2.6)
- Prostate cancer-specific mortality (See Section 11.2.7)
- Non-prostate cancer-specific mortality (See Section 11.2.8)
- Rate of salvage ADT (See Section 11.2.9)
- Rates of OS for patients treated with the 3 different RT modalities in each arm
- Incidence of “acute” adverse events (based on CTCAE, v. 3.0): The acute adverse events will be the first occurrence of worst severity of the adverse event ≤30 days of the completion of RT.
- Time to “late” grade 3+ adverse events (based on CTCAE, v. 3.0): The time of a first late grade 3+ adverse event, defined as >30 days from the completion of RT.
- Comparison of prostate cancer-specific health related quality of life (HRQOL) change as measured by the EPIC (urinary, bowel, sexual, and hormonal domain)

- Comparison of fatigue status as measured by the Patient-Reported Outcome Measurement Information System (PROMIS) fatigue domain
- Assessment and comparison of Quality Adjusted Life Years (QALYs)
- Correlation between the fatigue PROMIS score change and plasma cytokine change
- Collect paraffin-embedded tissue blocks, plasma and whole blood for future translational research analyses

13.2 Sample Size

The sample size calculation addresses the specific primary hypothesis that the OS rate at 5 years in Arm 2 will be better than in Arm 1. Assume an exponential survival distribution for each arm and define λ_1 is the hazard rate for Arm 1 and λ_2 is the hazard rate for Arm 2. (H_A: $\lambda_1 > \lambda_2$).

$$H_0: \lambda_1 \leq \lambda_2 \text{ vs. } H_A: \lambda_1 > \lambda_2$$

Based on the prior results from multiple dose-escalation trials in which patients were treated without androgen deprivation, we project that the rate of 5-year OS of Arm 1 is 90% (a yearly hazard rate of 0.0211). The study is designed to show an absolute improvement of 3.3% in the 5-year overall survival rate (i.e., a 5-year overall survival rate of 93.3%), which translates to a yearly hazard rate of 0.0139 in Arm 2. An exponential distribution for overall survival distribution was assumed for each arm. Three interim analyses and a final analysis are planned for early stopping for the efficacy and futility. The efficacy testing is based on the power family of test[69] with Δ=0 and the futility testing is based on the Freidlin and Korn[70] method at a nominal significance level of 0.005. Two hundred twenty deaths are required to detect a 34% relative reduction in the yearly death rate with 85% statistical power using a one-sided log-rank test at the 0.025 significance level. After adjusting the sample size for these interim analyses, the sample size per arm for the hypotheses is 684. Guarding against an ineligibility or lack-of-data rate of up to 10%, **the final targeted accrual for this study will be 1520 patients.**

13.3 Accrual and Duration (12/10/10)

The proposed trial, RTOG 0815, builds on the experience obtained in RTOG 0126. RTOG 0126 involved a similar group of patients treated with dose-escalated radiotherapy and accrued 1431 patients over 6 years at an average rate of 20 cases per month. We are estimating an average of 20 cases per month in the new trial. We expect RTOG 0815 to complete accrual in 6.3 years. Based on patient accrual in previous NRG Oncology/RTOG randomized prostate studies, there will be relatively few entries during the initial 6 months while institutions are obtaining IRB approval. The total duration of the study is expected to be 11.3 years from the time the first patient is entered to the final analysis under the null hypothesis, the hazard rate of Arm 2 will not be better than that of Arm 1, and a uniform accrual rate of 20 patients per month.

The NRG Oncology Data Monitoring Committee (DMC) will begin evaluating patient accrual semiannually following the anticipated quiet period. In accordance with CTEP policies for slowly accruing trials, 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 4 patients per month), the study will close to further accrual. If the average monthly accrual rate is greater than 20% but less than 50% of projected (i.e., fewer than 10 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, the study will close to future accrual. The participation of non-NRG Oncology/RTOG institutions through CTSU is expected to follow a similar pattern as seen in NRG Oncology/RTOG.

13.4 Analysis Plan (5/23/12)

13.4.1 Analysis of the Primary Endpoint

The primary endpoint is overall survival (OS). The time to failure for overall survival will be measured from the date of randomization to the date of documented death due to any cause. The overall survival function will be estimated by the Kaplan-Meier method.[71] We want to test whether or not the overall survival rate in Arm 2 is higher than that of Arm 1. The null and alternative hypotheses are:

$$H_0: \lambda_1 \leq \lambda_2 \text{ vs. } H_A: \lambda_1 > \lambda_2$$

where, λ_1 and λ_2 are yearly death rate for Arm 1 and Arm 2, respectively. We will use the log-rank test[72,73] with a significance level of 0.025 at the final analysis to test this hypothesis. In addition, the Cox

proportional hazard regression model[74] will be used to compare the treatment differences. Both adjusted and unadjusted hazard ratios and the respective 95% confidence interval will be computed. The number of risk factors (1 vs. 2 or 3), comorbidity status (ACE-27 grade ≥ 2 vs, < 2), and RT modality (EBRT vs. EBRT+LDR brachytherapy boost vs. EBRT+HDR brachytherapy boost), age, and race (as appropriate) will be adjusted for in this analysis.

13.4.2 Biochemical Failure by Phoenix Definition and Freedom From Failure

The freedom from failure (FFF) rate by 5 years is defined as the proportion of patients without events of FFF failure by 5 years from randomization among all eligible patients at baseline. The failure events for FFF will be the first occurrence of clinical failure (local recurrence, regional recurrence, or distant metastasis), biochemical failure by the Phoenix definition (PSA ≥2 ng/ml over the nadir PSA).[60] Patients who are event free with less than 5 years of follow-up, die due to any cause, or who receive any salvage therapy (e.g., salvage androgen deprivation, vaccine therapy, biologic/small molecule therapy, or chemotherapy) will be censored. The biochemical failure (BF) rate by 5 years is defined in a similar way; the proportion of patients with biochemical failure by 5 years (PSA ≥2 ng/ml over the nadir PSA)[60] from randomization among all eligible patients at baseline. The salvage ADT is defined as the first administration of subsequent ADT (either LHRH agonist or anti-androgen). The rate of salvage ADT is defined as the proportion of patients who have salvage ADT by 5 years among all eligible patients at baseline. The endpoint FFF rate by 5 years will be estimated by the Kaplan-Meier method[71] and the BF rate by 5 years will be estimated by cumulative incidence method.[75]

The Z-test statistic for the difference between the 2 rates with the standard errors estimated by Greenwood's method will be used, with a significance level of 0.025. The following test statistics (T.S.) will be used for testing between the 2 arms:

$$T.S. = \frac{(1-\hat{p}_1)-(1-\hat{p}_2)}{\sqrt{\hat{p}_1^2\sum_{i=1}^{n_1}\frac{f_i}{r_i(r_i-f_i)}+\hat{p}_2^2\sum_{j=1}^{n_2}\frac{f_j}{r_j(r_j-f_j)}}} = \frac{\hat{p}_2-\hat{p}_1}{\sqrt{\hat{p}_1^2\sum_{i=1}^{n_1}\frac{f_i}{r_i(r_i-f_i)}+\hat{p}_2^2\sum_{j=1}^{n_2}\frac{f_j}{r_j(r_j-f_j)}}} \quad (1)$$

where $\hat{p}_1$ and $\hat{p}_2$ are the FFF, BF, or the salvage ADT rate of Arm 1 and Arm 2, respectively, estimated by the Kaplan-Meier method or cumulative incidence method, r_i is the number of patients who are at risk and f_i is the number of patients who have FFF, BF, or the salvage ADT failure events (i=1,2). If H_0 is rejected, then we conclude that Arm 2 is better than Arm 1. If H_0 is not rejected, then we conclude that Arm 2 is not better than Arm 1.

In addition, logistic regression[76] will be used to compare the treatment differences in the hypothesis with and without adjustment for at least the following covariates; the number of risk factors (1 vs. 2 or 3), comorbidity status (ACE-27 grade ≥ 2 vs, < 2), and RT modality (EBRT vs. EBRT+LDR brachytherapy boost vs. EBRT+HDR brachytherapy boost), age, and race (as appropriate). Odds ratios and the respective 95% confidence intervals will be computed.

13.4.3 Time to Failure of Secondary Survival Endpoints

The time to failure for secondary endpoints (local recurrence, regional recurrence, distant metastasis, prostate cancer-specific mortality, non-prostate cancer specific mortality) will be measured from the date of randomization to the date of the event of interest. The failure events for the secondary endpoints are defined as follows—local recurrence: biopsy-proven failure within the prostate/seminal vesicles; distant metastasis: clinical and/or radiographic appearance of disseminated disease; prostate cancer-specific mortality: death due to prostate cancer; non-prostate cancer-specific mortality: death in a patient with disease clinically controlled.

The treatment effect on these failures may impact the observable measures of outcomes (local recurrence, regional recurrence, distant metastasis, prostate cancer-specific mortality, non-prostate cancer-specific mortality) and other competing risks may dilute the sensitivity. We will use the cause-specific hazard rate[77,78] (the instantaneous rate of cause-specific mortality in the presence of competing failure types as a function of time) approach to consider the competing events. Freidlin and Korn[70] showed that the cause-specific hazard rate approach is better than other approaches, for example, the

cumulative incidence method,[75] in most cases. The log-rank test on the times to the specific type of failure, which considers the presence of competing events, will be used to test whether the survival rates of these secondary endpoints in one arm are higher than that of the other arm for each hypothesis at a significance level of 0.025. In this approach, patients who experience other failure first are censored. In addition, Fine and Gray's regression[79] will be used for these secondary survival outcomes. Both unadjusted and adjusted hazard ratios and the respective 95% confidence interval will be computed. At least the treatment arm, the stratification variables (the number of risk factors, comorbidity status, and RT modality), age, and race (as appropriate) will be adjusted for in this analysis.

13.4.4 Estimation of Rates of OS of Patients Treated with the Different RT Modalities

Three different RT modalities are allowed for this trial: EBRT, EBRT+LDR brachytherapy boost, and EBRT+HDR brachytherapy boost. The rate of OS for patients treated with an RT modality among three modalities is defined as the proportion of patients who are treated with an RT modality and alive at 5 years from the randomization among all eligible patients treated with the RT modality at baseline. This rate will be estimated in each arm separately.

13.4.5 Comparison of the Incidence of Acute Adverse Events and Time to Late Grade 3+ Adverse Events and Correlation with Pre-Existing Comorbidity with Adverse Events

Adverse events are scored according to CTCAE, v. 3.0. An acute adverse event will be defined as the first occurrence of worst severity of the adverse event occurring less than or equal to 30 days after the completion of RT. Univariate logistic regression[76] will be used to model the distribution of acute adverse events. Multiple logistic regression[76] will be used to model the distribution of acute adverse events adjusted for covariates. Both unadjusted and adjusted odds ratios and the respective 95% confidence interval will be computed and tested using a one-sided Chi-Square test statistic with the significance level of 0.025. Late grade 3+ adverse events will be defined as grade 3+ adverse events occurring more than 30 days after the completion of RT. The time to late grade 3+ adverse events will be measured from the time protocol treatment started to the time of the earliest occurrence of a late grade 3+ adverse event. If no such late adverse event is observed until the time of the analysis, the patient will be censored at the time of the analysis. Death without late adverse event will be considered as the competing risk for late adverse events and the distribution of time to late grade 3+ adverse events will be estimated using the cumulative incidence method[75] and tested using a one-sided Gray's test statistic[75] with the significance level of 0.025. A Fine and Gray's regression model[79] will be used to compare the treatment differences of time to late adverse event with and without adjusting for other covariates. Both unadjusted and adjusted hazard ratios and the respective 95% confidence interval will be computed. At least the treatment arm, the stratification variables (the number of risk factors and RT modality), age, and race (as appropriate) will be considered when it is adjusted in the analysis.

The correlation of acute adverse events and the ACE-27 grade (≤ 2 vs. 2) will be calculated by Chi-square test statistics at the significance level of 0.05. The acute toxicity will be considered in two ways: 1) absent or present or 2) ≥ grade 3 or < grade 3. The correlation of late adverse events (≥ grade 3 vs. < grade 3) and the ACE-27 grade (≤ 2 vs. 2) will be calculated by Chi-square test statistics at the significance level of 0.05.

13.4.6 Analysis for Endpoints Related to Quality of Life (QOL)

Patient accrual for the QOL measurements will be limited to 200 cases in each arm.

Quality of life will be assessed via the following instruments: the Expanded Prostate Cancer Index (EPIC), the Patient-Reported Outcome Measurement Information System (PROMIS) fatigue domain, and the EuroQol (EQ-5D).

Information regarding potential confounds will also be collected in a short form (QL) using limited questions to minimize patient burden. This information can be used to evaluate the potential impact of these confounding factors on fatigue. Patient responses to the following will be collected in the QL form: muscle weakness (one item), overall sleep quality as measured by one item from the Pittsburgh Sleep Quality Index (PSQI),[42] and level of physical activity as measured by the Godin Leisure-Time Exercise Questionnaire (GLTEQ).[43,44] Anxiety/depression is also a potential confound with fatigue and patient responses to the anxiety/depression item in the EQ-5D can be used.

Protocol-eligible patients will be included in the QOL analysis only if they agree to participate in the QOL portion of this study. All the QOL instruments (EPIC, PROMIS fatigue domain, EQ-5D) will be collected on all cases participating in this portion of the trial. Patients will complete the EPIC, PROMIS fatigue domain, and the EQ-5D at pretreatment (baseline), week 3 of RT, at the last week of RT, and at 6 months, 1 year,

and 5 years after the end of RT. At the same time points, the QL form (i.e., one item from the PSQI, 3 items from the GLTEQ, and one question regarding general muscle weakness) will be collected. To minimize missing QOL data, we have included detailed instructions for collection of QOL and what to do if the patient misses a scheduled assessment, and RTOG provides individualized patient calendars available to Investigators and Research Associates 24/7 on the NRG Oncology/RTOG web site.

We will describe the distributions of QOL data collection patterns over all collection points in each treatment arm. Longitudinal data analysis, specifically the general linear mixed-effect model[80] will be performed to describe the change trend of the EPIC, PROMIS fatigue domain, and the EQ-5D across the 2 treatments. The primary objective in HRQOL analysis is to determine the QOL differences. The response will be the change of measurement from baseline for each measurement. The model will include the baseline and stratification variables (the number of risk factors, comorbidity score, and RT modality).

Patient self-assessment of symptoms will be performed using 4 primary EPIC domains: urinary, bowel, sexual, and hormonal symptoms. The PROMIS fatigue domain consists of 7 questions to quantify the fatigue continuum (i.e., high to low), and good precision of measurement (discrimination function). Each question has a 5-point Likert scale (1-never, 2-rarely, 3-sometimes, 4-often, 5-always). The EQ-5D is a 2-part self-assessment questionnaire and only the first part will be used. This consists of 5 items covering 5 dimensions (mobility, self care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a 3-point Likert scale (1-no problems, 2-moderate problems, and 3-extreme problems). There are 243 ($=3^5$) health states. We will transform the 5-item index score into a utility score between 0 (worst health state) and 1 (best health state) for comparative purposes. We hypothesize that the measurements from the EPIC will be worse in Arm 2 than Arm 1 because of the aggressiveness of treatment. We also hypothesize that measurements from the PROMIS fatigue domain will be higher in Arm 2 than in Arm 1.

To address the non-ignorable missing data caused by censoring survival time, the data analysis also will include patients who have not died. To examine trade-offs between survival time and QOL, we will combine them for each patient into a single measurement: Quality Adjusted Life Year (QALY). If (and only if) the primary endpoint hypothesis is substantiated, we will conduct a cost-utility analysis. The cost-utility analysis will not be done until after the primary endpoint results are published. QALY is defined by the weighted sum of different time episodes added up to a total quality-adjusted survival time. These health state-based methods of quality-adjusted survival analysis are known as the quality-adjusted time without symptoms and toxicity method (Q-TwiST).[45]

$$\text{Q-TwiST} = \sum_{i=1}^{k} q_i \, s_i$$

where q_i is the quality (the utility coefficient) of health state i, s_i is the duration spent in each health state, and k is the number of health states. We will use Glasziou's multiple health-state (Q-TwiST) models to use the repeated measures of EQ-5D. Because Glasziou's method incorporates longitudinal QOL data into an analysis of quality-adjusted survival, the health-stated model must be constructed on the following assumptions:

A1) QOL is independent from treatment.
A2) A health state is independent from previous states.
A3) Proportionality of quality-adjusted duration and duration of the actual state of health

Assumption A1 can be checked by plotting QOL over time according to treatment, and the *t* test can be used to compare the mean QOL scores of each treatment arm. Assumption A2 can be checked by comparing the QOL for patient groups in a given health state where the groups are defined by duration of previous health state experience using a regression model. Suitable checks for assumption A3 at minimum would be a simple plot. If data does not support these assumptions, we will use a method which uses the longitudinal QOL data directly. Cost-utility will be analyzed at 2 time points: at 1 year and 5 years posttherapy. We will use the 5-item utility score in EQ-5D for the cost-utility analysis. We will use the Z-test to test the hypothesis that the cost-utility in the 2 treatment arms is the same with a significance level of 0.05 and a 2-sided test.

To inspect the missing data mechanism, we will use at least a graphical method. A missing completely at random (MCAR) mechanism exists when missing values are randomly distributed across all observations. A missing at random (MAR) mechanism exists when values are not randomly distributed across all observations, rather than one or more sub-samples. If the cause of missing data is MCAR, listwise deletion (complete case analysis) will be done. If the MAR assumption is supported by the data, then an imputation method such as multiple imputation will be applied to impute missing data. If the MAR assumption is not supported by the data, then adjusting for covariates (such as the baseline QOL score) might reduce the conditional association between outcomes and missing values. If missing data patterns look similar when stratified by such covariate(s), then an analysis that adjusts for such covariate(s) will be conducted and an imputation method such as multiple imputation will be applied. If approximate conditional independence cannot be obtained with any set of covariates, then MNAR (missing not at random) must be addressed by an explicit model for the missing data mechanism and then an imputation method such as multiple imputation will be applied. All results from the imputed analysis using the multiple imputation will be compared to the complete case analysis results to assess any potential biases. We will conduct a sensitivity analysis using various assumptions on the missing data to determine what impact missing data and imputation methods have on the study conclusions. Imputation methods when prescribed by validated instrument developers will be employed first. Additional methods or methods used when none are described for a given instrument may include linear mixed-effects models to obtain separate estimates for the QOL outcome within strata based on missing data patterns.[81,82] NRG Oncology recognizes that all options are subject to bias and analysis with more than one method for consistency across methods is prudent.

13.4.7 Correlation Between the Fatigue PROMIS Score Change and Plasma Cytokine Change

Four hundred patients participating in the QOL portion of this trial will be used for this analysis. The analysis will be done in each arm separately to test the prognostic vales of biomarkers. At least the following plasma cytokines will be evaluated: CRP, TNF alpha, IL-1, IL-1ra, and IL-6. The highest fatigue is typically reported and plasma cytokine levels are known to be altered in the third to fourth week of radiation therapy (RT). Therefore, the evaluation time point will be 3 weeks after the start of RT. The fatigue PROMIS score change for each item will be calculated by subtracting the fatigue PROMIS score at 3 weeks following the start of RT from the baseline score. Similarly, the cytokine change will be calculated by subtracting the plasma cytokines measurement at 3 weeks following the start of RT from the baseline measurement. The fatigue PROMIS score change ranges from -4 to 4 (1-5 for each item). This will be categorized in a meaningful group at the time of analysis. The measure of each cytokine change will be a continuous variable. At the least, an Analysis of Variance (ANOVA) will be conducted to see if there is a correlation between the fatigue PROMIS score change and plasma cytokine change. Additional methods, such as linear mixed-effects, will be used. Additional time points will be tested in a similar way**.**

13.4.8 Collect paraffin-embedded tissue blocks, plasma, and whole blood for future translational research analyses

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 propose specific details of the markers to be investigated. We will address the assays that will be used and a list of specific correlative aims with appropriate statistical considerations.

13.4.9 Group Sequential Testing for Early Termination and Reporting of Efficacy and Futility

A group sequential test with 3 planned interim analyses and a final analysis will be performed. The interim analysis will be carried out when the cumulative deaths are met. At each planned interim analysis, the p-value from the log-rank test statistic assessing treatment efficacy and futility with respect to the primary endpoint, OS, will be compared to the nominal significance level. The efficacy testing is based on the power family of test[69] with Δ=0 (see Table 2 for nominal significance level for efficacy testing) and for the futility testing boundary we will use a less aggressive boundary, Rule C (at a nominal significance level of 0.005) in Freidlin and Korn.[70] The following hypotheses are tested:

$$H_0: \lambda_1 \leq \lambda_2 \text{vs. } H_A: \lambda_1 > \lambda_2$$

where λ_1 and λ_2 are the hazard rate for Arm 1 and Arm 2, respectively. If the H_0 is rejected, then we conclude that the OS rate of Arm 2 will be better than Arm 1 and stop accrual if applicable.

Table 2: Schedule for the Planned Interim Analysis

Information	Estimated Analysis	Cumulative Number of	Nominal Significance

Time	Time*	Deaths in the Two Arms	Level for Efficacy (Z-value)
0.25	4.7 years	55	0.0001 (4.049)
0.50	6.8 years	109	0.0018 (2.863)
0.75	8.9 years	163	0.015 (2.338)
1.00	11.1 years	218	0.025 (2.024)

*Time to the interim analysis from the first patient entry without considering ineligibility or lack-of-data rate and under the null hypothesis

For futility testing, the alternative hypotheses, H_A ($\lambda_1 = \lambda_2 + 0.0072$) will be tested at 0.005 level (the futility nominal significance level). If the computed p-value is less than 0.005 then we will consider stopping the trial in favor of the H_0 and conclude that the overall survival rate of Arm 1 will be better than Arm 2. Otherwise, we will continue the trial.

Based on the results of each interim analysis, the following action will be taken and the responsible statistician will recommend to the NRG Oncology Data Monitoring Committee (DMC) that the randomization be discontinued, if applicable, and the study be considered for early publication. Before making such a recommendation, the accrual rate, treatment compliance, safety of the treatments, and the importance of the study are taken into consideration along with the p-value. The DMC will then make a recommendation about the trial to the appropriate NRG Oncology Leadership as needed.

13.4.10 Interim Report to Monitor the Study Progress

Interim reports with descriptive statistics will be prepared twice per year until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase, compliance rate of treatment delivery with the distributions of important prognostic baseline variables, and the frequencies and severity of the adverse event by treatment arm. The interim reports will not contain the results of the treatment comparisons with respect to the primary endpoint and secondary endpoints.

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.4.11 Reporting the Initial Treatment Analysis

The analysis reporting the treatment results will be carried out after the criteria for early stopping/reporting are met. Five interim analyses and one final analysis will be performed for efficacy and futility of the addition of ADT and will be carried out as described in Section 13.4.9. It will include tabulation of all cases entered and those excluded from the analyses; the distribution of the important prognostic baseline variables; safety treatments; treatment compliance; and observed results with respect to the primary and secondary endpoints will be shown. All eligible patients randomized will be included in the comparison and will be grouped by assigned treatment in the analysis (intent-to-treat analysis). In addition, exploratory analyses of treatment comparisons of the primary and secondary survival endpoints will be tested using the Cox or Fine and Gray's proportional hazard model that includes treatment arms, the stratification factors (the number of risk factors and RT modality), age, and race (as appropriate).

13.5 Gender and Minorities

In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, participation rates of men will be examined in the interim analyses. Based on the accrual statistics from RTOG 94-08, we project that 81% of the men in the study will be White, 15% will be Black or African American, 3% will be Hispanic, 0.5% will be Asian, 0.3% will be Pacific Islander and 0.2% will be American Indian or Alaskan Native. The following table lists the projected accrual by race/ethnicity.

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	**Females**	**Males**	**Total**

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	N/A	46	46
Not Hispanic or Latino	N/A	1474	1474
Ethnic Category: Total of all subjects	N/A	1520	1520
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	N/A	49	49
Asian	N/A	7	7
Black or African American	N/A	228	228
Native Hawaiian or other Pacific Islander	N/A	5	5
White	N/A	1231	1231
Racial Category: Total of all subjects	N/A	1520	1520

13.5.1 In the setting of prostate cancer, African American ethnicity has been associated with both increased incidence and inferior clinical outcomes. The etiology of this phenomenon remains unclear. As such, no specific differences in outcome are hypothesized based on race/ethnicity in this study. Data will be collected and available for retrospective outcomes analysis at the time of study conclusion.

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APPENDIX I (4/21/15)

STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENTS *(may be required for eligibility)*		
	≤ 6 months prior to registration	≤ 60 days prior to registration
Elig-related tissue collection	x	
History/physical		x
CT or MRI abd/pelvis & bone scan		x
Transrectal ultrasound		For brachy patients only
Performance status		x
AUA		For brachy patients only (AUA) symptom index composite score ≤15
PSA		x
CBC w/ diff & ANC		For brachy patients only
AST, ALT, alk phosphatase	Pre-treatment	
Serum testosterone		x
Statin	x	
QOL Assess. (if patient consents): EPIC, PROMIS, EQ-5D, PSQI/ GLTEQ	Pretreatment	
Tissue for banking (if patient consents)		
Blood for banking (if patient consents)*		
***Blood collection is mandatory for patients who have provided consent for the QOL portion of the study.**		

APPENDIX I (continued) **STUDY PARAMETER TABLE: ASSESSMENTS DURING TREATMENT**					
	Weekly during RT	Weeks 1 and 5 of RT	Week 3 of RT; last week of RT	Monthly (Arm 2 only)	6-8 weeks post RT
Performance status			x		
PSA					x
CBC w/ diff & ANC		x			
AST, ALT, alk phosphatase				See 11.1.5	
Serum testosterone		See 11.1.5			
Statin				x	
QOL Assess. (if patient consents): EPIC, PROMIS, EQ-5D, PSQI/ GLTEQ			Last week of RT		
Blood for banking (if patient consents)*			Last week of RT		
AE evaluation	x				
***Blood collection is mandatory for patients who have provided consent for the QOL portion of the study.**					

APPENDIX I (continued) **STUDY PARAMETER TABLE: FOLLOW UP ASSESSMENTS**					
	ARM 1 3, 6, 9, and 12 months post RT	**ARM 2** 6, 9, and 12 months post RT	6 mos, 1 yr, 5 yrs post RT	Every 6 months for 4 years	Annually
Performance status	x	x		x	x
Serum testosterone	See 11.1.5				
Statin	x				
Tumor response eval: physical, DRE, PSA	x	x		x	x
QOL Assess. (if patient consents): EPIC, PROMIS, EQ-5D, PSQI/ GLTEQ			x		
AE evaluation	x	x		x	x

APPENDIX II

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 III

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)

(continued on next page)

Primary Tumor, Pathologic (pT)

pT2* Organ confined
- pT2a Unilateral, involving one-half of one lobe or less
- pT2b Unilateral, involving more than one-half of one lobe but not both lobes
- pT2c Bilateral disease

pT3 Extraprostatic extension
- pT3a Extraprostatic extension**
- pT3b Seminal vesicle invasion

pT4 Invasion of bladder, rectum

*Note: There is no pathologic T1 classification

**Note: Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).

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])

(continued on next page)

APPENDIX III (continued)
AJCC STAGING SYSTEM
PROSTATE, 6th Edition

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	M0	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 IV (4/21/15)

APPENDIX FOR NRG ONCOLOGY BIOSPECIMEN COLLECTION: BLOOD COLLECTION KIT INSTRUCTIONS

Shipping Instructions:

US Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen or Trackable Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

- ❑ Include all NRG Oncology paperwork in pocket of biohazard bag.
- ❑ Check that the Specimen Transmittal Form (STF) has the consent boxes checked off.
- ❑ Check that all samples are labeled with the NRG Oncology study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

- ❑ **FFPE Specimens:**
  - o Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
  - o FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear the slides shaking it is likely that they will break during shipping.
  - o Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). **Do NOT ship on Dry Ice**.

- ❑ **Frozen Specimens:**
  - o Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
  - o Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - o Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - o Send frozen specimens via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80° C until ready to ship.

- ❑ **For Questions regarding collection/shipping please contact the NRG Oncology Biospecimen Bank by e-mail: NRGBB@ucsf.edu or phone: 415-476-7864 or Fax: 415-476-5271.**

(continued on next page)

APPENDIX IV

NRG ONCOLOGY BLOOD COLLECTION KIT INSTRUCTIONS (continued)

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

Kit contents:

- One Purple Top EDTA tube for plasma pre-tx (A)
- One Purple Top EDTA tube for Whole Blood (B)
- Twenty-one (21) 1 ml cryovials
- Biohazard bags (3) and Absorbent shipping material (3)
- Styrofoam container (inner) and Cardboard shipping (outer) box
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form (STF) and Kit Instructions

PREPARATION AND PROCESSING OF PLASMA AND WHOLE BLOOD:

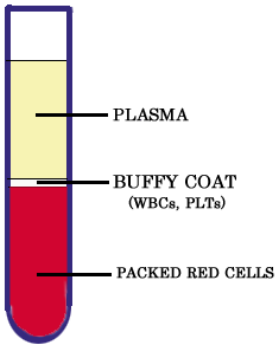
(A) Plasma (If requested): Purple Top EDTA tube #1

- ❑ Label as many 1ml cryovials (5 to 8) as necessary for the plasma collected. Label them with the NRG Oncology study and case number, collection date, time, and time point, 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 if done within 2 hours of draw but must be noted on the STF..
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot 0.5 ml plasma into as many cryovials as are necessary for the plasma collected (5 to 8) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as "plasma". Avoid pipetting up the buffy coat layer.
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 and include collection time point on the STF.



(C) <u>Whole Blood for DNA (if requested): Purple Top EDTA tube #2</u>

- ❑ Label as many 1ml cryovials (up to 5) as necessary for the whole blood collected..Label them with the NRG Oncology study and case number, collection date/time, and time point, and clearly mark cryovials "blood".

<u>Process</u>:

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 as are necessary for the blood collected (up to 5) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as "blood".
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.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on STF.

<u>Freezing and Storage</u>:

- ☐ Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- ❑ 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).

  <u>OR</u>:
  - 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).

  <u>OR</u>:
  - 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.

<u>Shipping/Mailing</u>:

- ❑ 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 NRG Oncology paperwork in a sealed plastic bag 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 NRGBB@ucsf.edu or call (415)476-7864.**

Shipping Address:

Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call 415-476-7864 or e-mail: NRGBB@ucsf.edu