NRG ONCOLOGY

RTOG 0534

A PHASE III TRIAL OF SHORT TERM ANDROGEN DEPRIVATION WITH PELVIC LYMPH NODE OR PROSTATE BED ONLY RADIOTHERAPY (SPPORT) IN PROSTATE CANCER PATIENTS WITH A RISING PSA AFTER RADICAL PROSTATECTOMY

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

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CONTACT INFORMATION (15-Jan-2019)		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	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 most current version of the **study protocol and all supporting 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 ProgramIdentity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For patient eligibility or treatment-related questions Contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical 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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NRG ONCOLOGY

RTOG 0534

A Phase III Trial of Short Term Androgen Deprivation with Pelvic Lymph Node or Prostate Bed Only Radiotherapy (SPPORT) in Prostate Cancer Patients with a Rising PSA After Radical Prostatectomy

SCHEMA (1/8/09) (3/24/10)

	SV Involvement		
	1. No		
S	2. Yes	**R**	**Arm 1: PBRT Alone**
T		**A**	PBRT 64.8-70.2 Gy
R	**Prostatectomy Gleason Score**	**N**	
A	1. Gleason ≤ 7	**D**	
T	2. Gleason 8-9	**O**	**Arm 2: PBRT + NC-STAD**
I		**M**	PBRT 64.8-70.2 Gy + NC-STAD for 4-6 months,
F	**Pre-Radiotherapy PSA**	**I**	beginning 2 months before RT
Y	1. PSA ≥ 0.1 and ≤ 1.0 ng/mL	**Z**	
	2. PSA > 1.0 and < 2.0ng/mL	**E**	
			Arm 3: PLNRT + PBRT + NC-STAD
	Pathology Stage		PLNRT to 45 Gy and PBRT to 64.8-70.2 Gy,
	1. pT2 and margin negative		NC-STAD for 4-6 months,
	2. All others		beginning 2 months before RT

SV = seminal vesicle; RT = radiotherapy; PBRT = prostate bed RT; PLNRT = pelvic lymph node RT; NC-STAD = neoadjuvant and concurrent short term androgen deprivation

NOTE: It is mandatory the treating physician determine the radiation therapy technique (3D-CRT vs. IMRT) to be used prior to the site registering the patient. See pre-registration requirements in Section 5.1. See details of radiation therapy and hormone therapy in Sections 6.0 and 7.0.

Patient Population: (See Section 3.0 for Eligibility) (3/31/09) (3/24/10)
Lymph node negative adenocarcinoma of the prostate treated with radical prostatectomy
Post-radical prostatectomy PSA of ≥ 0.1 - < 2.0 ng/mL; pathologic T3N0/Nx disease or pathologic T2N0/Nx disease, with or without a positive prostatectomy surgical margin; Gleason ≤ 9

Required Sample Size: 1764

NRG Oncology Institution # __
RTOG 0534 **ELIGIBILITY CHECKLIST (11/23/11)**

Case # _____ (page 1 of 4)

_____(Y) 1. Is there adenocarcinoma of the prostate treated primarily with radical prostatectomy, pathologically proven to be lymph node negative by pelvic lymphadenectomy (pN0) or lymph node status pathologically unknown (undissected pelvic lymph nodes [pNx]?

_____(Y) 2. Is the post-radical prostatectomy entry PSA ≥ 0.1 and < 2.0 ng/mL at least 6 weeks (45 days) after prostatectomy and within 30 days of registration?

_____(Y) 3. Does the patient meet one of the following pathologic classifications:
T3N0/Nx disease; or
T2N0/Nx disease…….Margin Negative_____ Margin Positive_____?

_____(Y) 4. Is the prostatectomy Gleason score 9 or less?

_____(Y) 5. Is the Zubrod Performance Status 0-1?

_____(Y) 6. Is the age ≥ 18?

_____(Y) 7. Was there a digital rectal exam within 8 weeks (60 days) prior to registration?

_____(Y) 8. Was a history/physical examination done within 8 weeks (60 days) prior to registration?

_____(N) 9. Are there distant metastases, based upon the following minimum diagnostic work up?
- A CT scan of the pelvis (with contrast if renal function is acceptable; a noncontrast CT is permitted if the patient is not a candidate for contrast) or MRI of the pelvis within 120 days prior to registration;
- Bone scan within 120 days prior to registration and plain films and/or MRI if the bone scan is suspicious

_____(Y) 10. Is there adequate bone marrow function, within 90 days prior to registration, defined as follows?
- Platelets ≥ 100,000 cells/mm^3 based upon CBC;
- Hemoglobin ≥ 10.0 g/dl based upon CBC

_____(Y) 11. Is the AST or ALT < 2 x the upper limit of normal within 90 days prior to registration?

_____(Y) 12. Was serum total testosterone obtained within 90 days prior to registration and ≥40% of the lower limit of normal of the assay used? Assay Lower Limit _____, Value_____?

_____(Y) 13. Did the patient sign a study-specific informed consent prior to study entry?

(Continued on the next page)

_____(N/Y) 14. Was there a palpable prostatic fossa abnormality/mass suggestive of recurrence?
_____(Y) If yes, was the abnormality/mass shown by biopsy under ultrasound guidance not to contain cancer?

_____(N) 15. Does the patient have N1 disease?

_____ (N/Y) 16. Does the patient have pelvic lymph node enlargement ≥ 1.5 cm in greatest dimension by CT scan or MRI of the pelvis?
(Y) If yes, was the enlarged lymph node sampled and found to be negative?

_____(N) 17. Did the patient receive androgen deprivation therapy that was started prior to prostatectomy for > 6 months (180 days) duration (Note: The use of finasteride or dutasteride (±tamsulosin) for longer periods is acceptable prior to prostatectomy)?

_____(N) 18. Did the patient receive androgen deprivation therapy that was started after prostatectomy and prior to registration (Note: The use of finasteride or dutasteride (±tamsulosin) is not acceptable after prostatectomy - must be stopped within 3 months after prostatectomy. Androgen deprivation therapy must be stopped within 3 months after prostatectomy)?

_____ (N) 19. Did the patient have neoadjuvant chemotherapy before or after prostatectomy?

_____ (N) 20. Did the patient have prior chemotherapy for any other disease site if given within 5 years prior to registration?

_____ (N) 21. Did the patient have prior cryosurgery or brachytherapy of the prostate?

_____(N) 22. Did the patient have prior pelvic radiotherapy?

_____(N) 23. Did the patient have a prior invasive malignancy (except non-melanomatous skin cancer) or superficial bladder cancer within the past 5 years?

_____(N) 24. Does the patient have any of the following severe, active comorbidities?

- History of inflammatory bowel disease;
- History of hepatitis B or C;
- 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 at the time of registration;
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects;
- Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition?

(Continued on next page)

_____(N) 25. Did the patient have any prior allergic reaction to the study drug(s) involved in this protocol?

The following questions will be asked at Study Registration:

3D-CRT or IMRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION

_____(N/Y) Specify use of IMRT

_____ 1. Institutional person registering this case

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

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

_____ 4. Date Informed Consent signed

_____ 5. Participant 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 VA or military hospital?

_____ 16. Calendar Base Date

_____ 17. Randomization Date

_____(Y/N) 18. Have you obtained the patient's consent for his specimens to be used for research to learn about, prevent or treat cancer?

_____(Y/N) 19. Have you obtained the patient's consent for his specimens to be used for research to learn about, prevent or treat cancer?

(Continued on next page)

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_____(Y/N) 20. Did the patient consent to having someone contact them in the future for new research not included in this consent?

_____ 21. Specify SV involvement

_____ 22. Specify Prostatectomy Gleason score

_____ 23. Specify Pre-radiotherapy PSA

_____ 24. Specify Pathology Stage

_____ 25. Specify LHRH agonist planned duration

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 Rationale for a Salvage Postoperative Radiotherapy (RT) Trial (1/8/09)

As the use of prostatectomy has increased substantially over the last 10 years, so has the application of post-prostatectomy radiotherapy (RT). RT is the mainstay of salvage treatment for men with a persistently detectable PSA (PD-PSA) or a delayed rise in PSA (DR-PSA) without evidence of metastasis.[1-13] Because there are no published salvage RT randomized trials, the rationale for this treatment is derived mostly from small retrospective series. The largest retrospective analysis was a multi-institutional effort reported by Stephenson et al.[13] They examined predictors of response to salvage RT and found that high Gleason score, high pre-radiotherapy PSA, negative prostatectomy surgical margins, short PSA doubling time (PSADT), and seminal vesicle involvement were independently associated with adverse outcome. Similar factors have been reported in many of the other retrospective series as well.[14] Despite gains in understanding how to select patients for salvage treatment, level I evidence on the outcome of patients receiving well-delineated treatment (e.g., RT technique and use of androgen deprivation) is lacking.

Level I evidence supporting the application of RT to patients treated postoperatively has been reported for adjuvant RT, and the results are encouraging. The findings of a European Organization for Research and Treatment of Cancer trial (EORTC 22911)[15] showed that adjuvant RT resulted in a significant delay in biochemical and clinical failure. The results from a Southwest Oncology Group trial, SWOG 8794,[16] were similar, as were those from a preliminary report of a German Cancer Society trial, ARO 96-02,[17] reported at the 2005 American Society of Clinical Oncology meeting. Adjuvant RT is effective at reducing progression.

Although, there are no published phase III clinical trials examining the efficacy of salvage radiotherapy for a rising PSA after radical prostatectomy, one study has completed accrual. RTOG 96-01 compares salvage RT alone to salvage RT plus 2 years of androgen deprivation (AD), accomplished using 150 mg/day of Casodex. The trial described here differs from RTOG 96-01 in several ways. First, the eligibility criteria are stricter; more favorable patients have been selected for RTOG 0534. Second, short-term AD is being tested, while in RTOG 96-01 long-term AD was examined. Third, pelvic lymph node radiotherapy was not allowed in RTOG 96-01 and has never been studied in a randomized trial in post-prostatectomy patients. There is no consensus on how to apply these treatment methods in the postoperative setting, yet AD and pelvic lymph node irradiation (PLNRT) are being used.[18-26] The proposed three-arm trial is designed to address the following key questions: 1) Is neoadjuvant and concurrent short-term AD (NC-STAD) plus prostate bed radiotherapy (PBRT) superior to PBRT alone? and 2) Is NC-STAD plus pelvic lymph node RT (PLNRT) superior to NC-STAD+PBRT? In the context of this study description, reference to PLNRT is made with the understanding that the prostate bed will receive the same total dose in all three treatment arms.

RTOG 0534 is not intended to address the efficacy of RT alone over observation. The complete response rate (a drop in PSA to undetectable levels) after salvage RT is 70%-80% and durable responses are observed in 30%-40% of patients. For these reasons, it is likely not feasible or appropriate to randomize men between observation and salvage RT. The more important issue is whether the proportion of durable responses is increased by altering the therapeutic approach, such as the use of NC-STAD with or without extended RT fields.

The pre-salvage radiotherapy PSA doubling time has been reported in several series to be an important determinant of outcome after radical prostatectomy. Until recently, the consensus was that men with short PSADTs of ≤6 mo would respond unfavorably to salvage PBRT because of an increased risk of distant metastasis. Thus, the initial stratification criteria for RTOG protocol 0534 excluded patients with a PSADT of ≤6 mo from eligibility. However, Trock et al,[27] in a recent series from Johns Hopkins reported just the opposite. Those men with a post-prostatectomy PSADT of ≤6 mo experienced the greatest cause-specific survival benefit from salvage radiotherapy, when compared to men who did not receive salvage PBRT. There are no other comparable data available. As a consequence, the eligibility and stratification criteria based on PSADT have been removed from RTOG 0534. We plan to collect all PSA data so that any information pertinent to calculating PSADT will be recorded for secondary analyses later.

The eligibility criterion of a PSA ≥0.2 ng/mL has been relaxed to a PSA ≥0.1 ng/mL because many patients have a documented rise in PSA using hypersensitive assays and are pathologically high risk by virtue of having pT3 disease and/or a positive margin. These patients should be treated as early as possible.

1.2 Rationale for Using NC-STAD and PLNRT Treatment Postoperatively

No postoperative randomized trials investigating AD plus RT have been published, but three prior phase III studies of men treated primarily for prostate cancer, one by the RTOG (86-10),[28] one by investigators at Harvard,[29] and one by the Trans-Tasman Radiation Oncology Group,[30] concluded that neoadjuvant and concurrent short-term NC-STAD plus RT reduces cause-specific mortality compared with RT alone. The results of RTOG protocol 94-13[31] extend these observations. RTOG 94-13 compared PLNRT to prostate-only RT and NC-STAD to adjuvant STAD plus RT in men with newly diagnosed prostate cancer using a 2x2 design. PLNRT significantly delayed progression, while the timing of STAD did not. When the four treatment groups were examined individually, the men who received PLNRT plus NC-STAD had significantly fewer failures (including biochemical) than those in the other three groups. The findings from RTOG 94-13 suggest that there was an interaction between PLNRT and NC-STAD, resulting in a reduction in progression by more effectively eradicating microscopic pelvic lymph nodal disease. RTOG 0534 builds on the observations of 94-13 and the other randomized trials of men treated primarily with NC-STAD plus RT in a population of patients who were initially treated with prostatectomy.

RTOG 0534 is a three-arm trial that does not include a PLNRT alone arm. The rationale for a three-, as opposed to a four-, arm trial is based on two primary considerations. First, a control arm of PLNRT alone was not included because in RTOG 94-13, it was the NC-STAD plus PLNRT arm that was superior to all other arms. No difference was seen for PLNRT plus adjuvant STAD, prostate-only RT plus adjuvant STAD, or NC-STAD plus prostate-only RT, and all were inferior to NC-STAD plus PLNRT. The hypothesis here is that the combination of NC-STAD plus PLNRT is necessary to significantly improve outcome when PLNRT is used. Second, a four-arm study that includes a PLNRT alone arm is prohibitive in terms of patient numbers. As described below, the three-arm trial design requires 1764 patients, a target that the RTOG is capable of completing within 9.2 years.

1.3 Rationale for Using the PSA Nadir+2 Definition of Biochemical Failure as the Primary Endpoint

The primary endpoint is freedom from progression (FFP), including a biochemical parameter that is highly related to clinical progression (CP; includes local, regional, or distant progression). After radical prostatectomy, a detectable PSA of ≥ 0.2 ng/mL has been associated with a median time to distant metastasis from prostate cancer of 7-8 years.[32-33] There has been debate about the absolute biochemical cut-point that best correlates with eventual disease relapse (mainly in the range from 0.1-0.5 ng/mL). In a detailed analysis by Amling, et al[34] a biochemical failure cut-point of 0.4 or greater was found to be more significantly related to eventual CP than lower cut-point values and was nearly the same as higher cut-point values.

Since the goal here is to use an endpoint that is strongly related to clinical progression and, ultimately, death due to prostate cancer, we compared a number of PSA-based definitions in a large cohort of men treated with RT post-prostatectomy.[35-36]This IRB-approved analysis included more than 1200 men with lymph node negative disease who were treated with either adjuvant (23%) or salvage (77%) RT. Median follow-up after RT was 61 months, and there were 147 patients who manifested clinical failure: 13% and 22% at 5 and 10 years, respectively.

Table 1 (below) displays the relationships of different biochemical estimates of CP (BECPs) to CP for men treated with salvage RT. There are four categories of biochemical parameters displayed: a) PSA of x ng/mL; b) PSA of x ng/mL plus 2 consecutive rises with the second rise above the cut-point being tested; c) Three consecutive PSA rises with backdating to between the nadir and first rise per the ASTRO consensus definition,[37] and d) PSA ≥ 2 ng/mL above the nadir PSA per the “RTOG Phoenix” definition.[38-42] The RTOG Phoenix definition was the favored biochemical failure (BF) definition for men treated primarily for prostate cancer with RT at a consensus conference organized by the RTOG and ASTRO in January 2005.[43] The Phoenix definition has also been previously referred to as the “Houston” definition[40] or simply as nadir +2 ng/mL.[38-42] The reports examining the sensitivity, specificity, positive predictive value (PPV), and accuracy have

consistently pointed to the RTOG Phoenix definition as being nearly ideal. Not only does the RTOG Phoenix definition have high specificity, sensitivity, PPV, and accuracy, the definition also addresses the pitfalls of the ASTRO definition. The ASTRO definition involves backdating, which alters the shape of Kaplan-Meier curves (causes an artificial flattening at the tail end), results in inaccurate estimates of BF when follow-up is short,[40,42,44] and overestimates BF after release from androgen deprivation.[42,44,45] Moreover, during the first two years of follow up after radiotherapy, the RTOG Phoenix definition identifies patients with BF in greater numbers than the ASTRO definition, indicating that the classification of BF by the RTOG Phoenix definition is not delayed in patients treated primarily for prostate cancer.[42]

Table 1 confirms that the RTOG Phoenix definition is useful for men treated with salvage RT post-prostatectomy. The highest sensitivity, specificity, and PPVs were obtained for the definitions that incorporated a 2-ng/mL cut-point. Three definitions were similar: ≥ 2 ng/mL, ≥ 2 ng/mL + two rises, and nadir + 2 ng/mL or higher. Since the RTOG Phoenix definition has emerged as the BF definition of choice after definitive RT for prostate cancer, and the findings in Table 1 show that it is likewise a very appropriate BECP definition in the postoperative setting, the RTOG Phoenix definition will be the primary endpoint in the proposed trial. Biochemical criteria have previously been included as the primary endpoint in an RTOG randomized trial examining NC-STAD (RTOG 94-13),[31] which supports the rationale for the Phoenix definition as the primary endpoint in the proposed trial. The initiation of further "salvage" therapy in any form (e.g., androgen deprivation therapy, vaccine therapy, or chemotherapy) after completion of protocol treatment and prior to nadir + 2 ng/mL failure will not be counted as a failure and is strongly discouraged. The success of the trial depends upon allowing the nadir + 2 ng/mL failure criteria to be met before any other therapeutic intervention. The use of this BECP endpoint facilitates a trial sample size of 1764 patients (see below), a sample size that is feasible for the RTOG to accrue in this patient population.

Table 1: Endpoint Considerations from A Pooled Multi-Institutional Analysis Salvage Only Patients, No AD (n=533)

BECF Definition	%5 / 8 yr. Failure	Specificity	Sensitivity	PPV
1. ≥ 0.2	59% / 72%	56%	95%	23%
2. ≥ 0.4	47% / 64%	66%	94%	27%
3. ≥ 1.0	35% / 52%	77%	92%	35%
4. ≥ 2.0	29% / 41%	84%	90%	43%
5. ≥ 0.2+2 rises	42% / 59%	72%	93%	31%
6. ≥ 0.4+2 rises	39% / 57%	74%	93%	32%
7. ≥ 1.0+2 rises	32% / 46%	80%	90%	39%
8. ≥ 2.0+2 rises	29% / 39%	85%	90%	45%
9. ASTRO	33% / 36%	82%	90%	40%
10. Phoenix (nadir+2)	31% / 40%	83%	91%	43%

BECF = biochemical estimate of clinical failure; PPV = positive predictive value

Other PSA-related measures will be examined as secondary endpoints. A more conventional early estimate of biochemical failure after radical prostatectomy is a PSA of ≥ 0.4 ng/mL and rising (two consecutive rises with one being at or above 0.4 ng/mL) at a given time point. A two-year time point was chosen to reduce the effect of potential delays from short-term AD. In the analysis shown in Table 1, this endpoint had slightly lower specificity as a BECP. Our plan is to compare the primary and secondary PSA-related endpoints to the other secondary endpoints of time to development of hormone refractory disease based on biochemical criteria (three consecutive rises in PSA modeled after the ASTRO criteria, but without backdating), distant metastasis, cause-specific mortality, and overall mortality. Local failure is not included as a separate endpoint because palpable evidence of local recurrence is rare after radiotherapy, and patients are typically

started on salvage AD without prostate bed biopsy. However, local failure will be recorded and is part of the primary endpoint of biochemical and clinical failure.

1.4 Rationale for Biomarker Studies (11/16/15)

The RTOG has been collecting pretreatment diagnostic tissue from all prostate cancer protocols for over 10 years. A number of histologic, cell kinetic/proliferation, and molecular markers of apoptosis and angiogenesis are under investigation, with several showing promise for the stratification of patients in future trials. A focus of prior biomarker studies from the principal investigators and genitourinary committee has been DNA-ploidy, Ki-67, p53, MDM2, bcl-2, bax, p16 and Cox-2.[46-51] These markers have shown promise in complementing the standard clinical parameters of PSA, Gleason score, and stage in prior RTOG (or other) analyses of men with high-risk features treated primarily with RT, with or without AD. With the exception of DNA-ploidy, the protein expression of these markers was measured using immunohistochemical methods. While these markers have been selected based on prior analyses, it is likely that some other markers and/or methods will be investigated when the proposed trial matures. The quantification of gene expression based on the RNA level in formalin fixed archival tissue is now possible after laser capture microdissection and the initial studies on proteomics in archival tissue are encouraging. Approximately 7 years will be required for this protocol to mature; by that time, a clearer definition of the markers to be studied will be evident. The plan is to collect and store tissue from the prostatectomy specimens. The findings are expected to contribute to better risk group classification, enhance our understanding of radiation response and distant spread, and lead to therapeutic strategies based on correcting or counterbalancing the abnormalities detected.

The collection of blood and urine before and after treatment for proteomic and genomic studies is also proposed. Preliminary findings of other studies indicate that serum protein patterns defined through patterns of ion signatures generated from high-dimensional mass spectrometry data may be of value in determining the presence of prostate cancer.[52-53] Likewise, the presence of prostate cancer has been accurately determined through the identification of hypermethylation of the glutathione S transferase p1 (GSTP1) gene locus in urine.[54] Both of these methods have potential for predicting outcome in pretreatment samples and the presence of recurrence in specimens obtained during follow-up. Blood (serum, plasma, and whole blood) and urine will be collected prior to treatment and during the 6th week of RT. Some blood (serum and plasma) and urine will continue to be collected after completion of RT per Section 10 and Appendix IV.

1.5 Health-Related Quality of Life and Neurocognitive Assessment

Some of the side effects associated with RT and AD are deleterious and affect quality of life, and others may contribute to increased risks for serious health concerns associated with aging. Urinary, bowel, and erectile dysfunction are well-known side effects of pelvic RT. Sexual side effects are the most well recognized adverse effects from AD 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 AD, 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 AD. These effects may lead to an exacerbation of potentially more serious conditions, such as hypertension, diabetes, and coronary artery disease.[55] 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 AD therapy and improve the awareness that they should incorporate into routine practice strategies for preventing and managing toxicities.[56]

AD 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 flushes and worse overall HRQOL (using the Functional Assessment of Cancer Therapy-General [FACT-G] scale) in those patients, compared with patients receiving no therapy.[57] To address HRQOL, RTOG 0534 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 radiotherapy and hormonal therapy.[57]

Studies also suggest selective associations with decline in testosterone and estradiol, including cognitive performance. The cognitive domains of verbal fluency, visual recognition, and visual memory were associated with decline in estradiol. Visual-motor slowing and slowed reaction times in some attentional domains including working memory, impaired delayed recall, and recognition speed of letters were associated with decline in testosterone during AD.[58-59]Cognition will be measured by a brief battery of reliable and valid tests previously tested for feasibility within the RTOG,[60] including the Hopkins Verbal Learning Test-Revised (HVLT-R)[61-62] for memory, the Controlled Oral Word Association Test (COWAT) for verbal fluency,[63] the Trail Making Test Part A for cognitive processing speed, and the Trail Making Test Part B for executive function.

The incidence of suicide among older men with prostate cancer is higher than previously recognized. Depression, recent diagnosis, pain, and being foreign-born are important clinical correlates.[64] The results of several recent studies suggest that estrogen and testosterone play an important role in the modulation of mood and cognitive function in women and men, and preliminary evidence indicates that these hormones may also modulate the levels of beta-amyloid (Abeta),[65] a 4 Kilo Dalton peptide that is likely to be involved in the pathogenesis of cognitive disorders such as Alzheimer's disease. A recent study assessed the physiological and clinical effects of reversible chemical castration on 40 men with prostate cancer who were treated with androgen blockade therapy (flutamide and leuprolide) for 36 weeks and subsequently followed for another 18 weeks after treatment was discontinued.[66] The results indicated that chemical castration is associated with a significant rise in the plasma levels of Abeta and, clinically, with increased depression and anxiety scores. The discontinuation of treatment is associated with better cognitive performance, most noticeably of verbal memory. The performance of subjects on a word list memory test was negatively correlated with plasma levels of Abeta, but the clinical significance of this finding remains to be determined. Depression and mood will be measured in this study by the Hopkins Symptom Checklist (HSCL-25). Serum levels of beta-amyloid will be assessed at the same time points as the HSCL-25 and the neurocognitive test battery; associations among Abeta levels and cognitive tests will be evaluated.

1.5.1 Urinary symptom and function assessment

Urinary function assessment has become a mainstay of routine clinical practice using the American Urological Association Symptom Index Score (AUA SI) or International Prostate Symptom Score (IPSS) questionnaire.[80] This questionnaire is routinely administered before and after radiotherapy, and treatment decisions, such as the administration of an alpha-blocker, are often based on the results. We propose to collect urinary symptom data on the entire patient cohort (not just those in the HRQOL subset) to explore the relationship between the questionnaire parameters and urinary morbidity using the CTCAE v. 3.0 (see section 7.7) grading system.

1.6 Cost Effectiveness

Almost every incremental improvement in survival or progression-free survival comes at a cost. The cost is both financial and experienced in terms of quality of life. Measurement of primary outcomes such as freedom from progression and the most important aspects of human functioning and quality of life will permit a summary equation allowing for differences in quality of life, clinical outcomes, and cost to be incorporated into one equation. This equation is the Quality Adjusted Life Year (QALY) and a study-specific modification, the Quality Adjusted Freedom From Progression Year (QAFFPY). The QALY has been modified in a similar manner for different treatments where survival is not the primary outcome. Much of the work in modifying the QALY began in ophthalmology, where sight-years, not life-years, are the outcome of interest. Examples of modifications to the QALY have included incremental cost per vision-year gained to assess the cost effectiveness of photodynamic therapy with verteporfin for age-related macular degeneration,[66] costs per sight-year saved with screening for diabetic retinopathy,[67] cost-utility analysis for treatments of retinal detachment associated with severe proliferative vitreoretinopathy,[68] and the cost-utility of cataract surgery.[69] However, the QALY has been used in other studies where survival is not the primary outcome of interest, such as the cost-effectiveness of memantine in the treatment of patients with moderately severe to severe cognitive impairment from Alzheimer's[70] and cochlear implantation for patients unable to gain

effective speech recognition with hearing aids.[71] We will model costs using Medicare reimbursement and measure utilities with the brief five-item EuroQol (EQ-5D).

The EQ-5D is a method for obtaining valuations (utilities) of health-related quality of life (HRQOL) to be used as an adjustment to survival and in the cost-utility analysis. Developed in 1987, the EQ-5D is used by investigators and the pharmaceutical industry throughout the United States, Europe, and Asia. It is one of only several measures recommended for use in cost-effectiveness analyses by the Washington Panel on Cost Effectiveness in Health and Medicine.[72] The EQ-5D instrument is intended to complement other forms of QOL measures, and it has been purposefully developed to generate a generic cardinal index of health, thus giving it considerable potential for use in economic evaluation. The argument by some that a generic measure does not capture some of the disease- or treatment-specific concerns of a given study misses the point. This cost-effectiveness analysis is being done for purposes of exploring the means to inform macro (health policy, payer) decision making, not micro (individual) decision making. The findings from the disease-specific QOL instruments and treatment-related side effect QOL instruments described above will help inform individual decision making. The role of the EQ-5D is to measure HRQOL at a macro level, in the same metric as it has been measured across numerous diseases, including cancer.

This instrument gives us the ability to compare across and within diseases the “big picture” of what the experts who developed the EQ-5D considered the primary health states of interest to humans: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Further, there is no standardized measure to assess and compare disease-specific utilities across or within diseases. Unlike the EQ-5D, the actual content of standard gamble (SG) and time trade-off (TTO) methods vary widely among studies and are subject to wide variations in amount and type of information presented, message framing, and visual aids, making replication of utilities with the SG or TTO extremely difficult. Therefore, using the EQ-5D, an exploratory aim is to evaluate the cost-utility of the treatment arm demonstrating the most significant benefit (in terms of the primary outcome), in comparison to other widely accepted cancer and non-cancer therapies (see Table 2 below). We will also assess cost-utility among the arms to assess which therapy dominates. We will assess the value added of the summary score known as a Quality Adjusted Life Year (QALY), and for this study the Quality Adjusted FFP Year, that combines benefits of duration of freedom from progression (FFP) and decrements of quality of life with financial cost of increasingly aggressive and costly therapy.

Table 2: Common Medical Interventions Ranked by Incremental Cost-Effectiveness $U.S./Life Year Gained[73]

Intervention	Incremental Cost-effectiveness ($U.S.)
Liver transplantation compared with medical management	237,000
Mammography, age < 50 yrs.	232,000
Dialysis compared with medical management	50,000
Drug therapy for moderate hypertension	32,600
Mammography screening for breast cancer in patients aged 50-75 years	20,000-50,000
ABMT compared with salvage CT for Hodgkin’s recurrent after MOPP-ABV	21,100
Induction CT and standard RT on RTOG trials for Non-Small Cell Carcinoma of the Lung	7,500-18,500[73]

The EQ-5D has been used across numerous disease sites, including cancer. For example, the EQ-5D mean score for 95 patients with NSCLC (93% male, mean age 62 years) was 0.58 (SD 0.32) as measured by the questionnaire and 0.58 (SD 0.20) as measured by the visual analogue scale (VAS) version.[75] The EQ-5D has been used to assess QALYs and the economic value of

prostate cancer screening,[76] and treatment of pain related to prostate cancer metastasis.[77] 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 health-related quality of life 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 quality-adjusted life years (QALY) to every man with prostate cancer; the economic value of this welfare loss due to prostate cancer pain was approximately $121,240,000 per year.[78]

1.6.1 Quality-Adjusted Survival and Freedom from Progression

Quality-adjusted survival and freedom from progression can be defined in the same manner, by the weighted sum of different time episodes added up to a total quality-adjusted life-year or freedom from progression–year [**U**= sum of quality ($\mathbf{q_i}$) of health states **K** times the duration ($\mathbf{s_i}$) spent in each health state.[79]

1.6.2 Cost-Effectiveness and Cost-Utility

Cost-utility will be analyzed for planned publication at two time points: 1) at 1 year post-therapy, looking at initial treatment costs and quality of life and 2) at five years post-therapy. The cost-utility analysis will be done after the primary endpoint results are published.

1.6.3 Measurement of Costs

Direct medical costs fall into three categories: 1) initial therapy costs; 2) costs of managing the most common side effects as determined by this study; and 3) costs of managing recurrence. Costs for external beam radiotherapy will be determined using CPT coding and Medicare reimbursement rates. Costs of common management strategies of the most common side effects documented in this study (e.g., Imodium® for diarrhea) will be estimated from regional costs per unit. Costs for managing recurrence will assume the following salvage therapies: hormone therapy and chemotherapy. Costs will include professional fees, cost/inpatient day, drugs, and supplies. Direct non-medical costs such as the cost of work lost or of transportation will not be measured. Incremental differences in costs and outcomes will be compared for the different alternatives and for the dominant alternative to other established therapies documented in the literature.

2.0 OBJECTIVES

2.1 Primary Objectives

2.1.1 To determine whether the addition of NC-STAD to PBRT improves freedom from progression (FFP) [maintenance of a PSA less than the nadir+2 ng/mL, absence of clinical failure and absence of death from any cause] for 5 years, over that of PBRT alone in men treated with salvage RT after radical prostatectomy;

2.1.2 To determine whether NC-STAD+PLNRT+PBRT improves FFP over that of NC-STAD+PBRT and PBRT alone in men treated with salvage RT after radical prostatectomy.

2.2 Secondary Objectives (11/23/11)

2.2.1 To compare the rates of a PSA ≥ 0.4 ng/mL and rising at 5 years after randomization (secondary biochemical failure endpoint), the development of hormone refractory disease (3 rises in PSA during treatment with salvage androgen deprivation therapy), distant metastasis, cause-specific mortality and overall mortality;

2.2.2 To compare acute and late morbidity based on CTCAE, v. 3.0;

2.2.3 To measure the expression of cell kinetic, apoptotic pathway, and angiogenesis-related genes in archival diagnostic tissue to better define the risk of FFP, distant failure, cause-specific mortality, and overall mortality after salvage radiotherapy for prostate cancer, independently of conventional clinical parameters now used;

2.2.4 To quantify blood product–based proteomic and genomic (single nucleotide polymorphisms) patterns, and urine-based genomic patterns before and at different times after treatment to better define the risk of FFP, distant failure, cause-specific mortality, and overall mortality after salvage radiotherapy for prostate cancer, independently of conventional clinical parameters now used;

2.2.5 To assess the degree, duration, and significant differences of disease-specific health related quality of life (HRQOL) decrements among treatment arms; it is hypothesized that QOL as measured by the EPIC will significantly worsen by the increasing aggressiveness of treatment and

that cognition as measured by the neurocognitive test battery (the HVLT-R, Trail Making Test, parts A & B, and the COWAT) will be significantly worse in the arms with NC-STAD.

2.2.6 To assess whether mood is improved and depression is decreased with the more aggressive therapy if it improves FFP; it is hypothesized that QOL as measured by the HSCL-25 will significantly improve with the increasing aggressiveness of treatment due to improved FFP.

2.2.7 An exploratory aim is to assess whether an incremental gain in FFP and survival with more aggressive therapy outweighs decrements in the primary generic domains of health related quality of life (i.e., mobility, self care, usual activities, pain/discomfort, and anxiety/depression). This aim is reported as the Quality Adjusted FFP Year (QAFFPY) and as the Quality Adjusted Life Year (QALY). The QAFFPY and QALY will be compared among treatment arms and to the literature as described in Section 1.6.

2.2.8 An exploratory aim is to evaluate the cost-utility of the treatment arm demonstrating the most significant benefit (in terms of the primary outcome) in comparison with other widely accepted cancer and non-cancer therapies. Cost-utility will be assessed by the EQ-5D among treatment arms to determine which therapy dominates.

2.2.9 An exploratory aim is to assess associations between serum levels of beta-amyloid (Abeta) and measures of cognition (as measured by the HVLT-R, Trail Making Tests, parts A & B, or the COWAT) and mood and depression (as measured by the HSCL-25).

2.2.10 To collect paraffin-embedded tissue blocks, serum, plasma, urine, and whole blood for future translational research analyses

2.2.11 An exploratory aim is to assess the relationship(s) between the American Urological Association Symptom Index (AUA SI) and urinary morbidity using the CTCAE v. 3.0 grading system.

3.0 PATIENT SELECTION

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

3.1 Conditions for Patient Eligibility (12/31/14)

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

3.1.1 Adenocarcinoma of the prostate treated primarily with radical prostatectomy, pathologically proven to be lymph node negative by pelvic lymphadenectomy (N0) or lymph node status pathologically unknown (undissected pelvic lymph nodes [Nx]), i.e. lymph node dissection is not required;

- **Any type of radical prostatectomy will be permitted, including retropubic, perineal, laparoscopic or robotically assisted.** If performed, the number of lymph nodes removed per side of the pelvis and the extent of the pelvic lymph node dissection (obturator vs. extended lymph node dissection) should be noted. There is no time limit for the date of radical prostatectomy.

3.1.2 A post-radical prostatectomy entry PSA of ≥ 0.1 and < 2.0 ng/mL at least 6 weeks (45 days) after prostatectomy and within 30 days of registration;

3.1.3 One of the following pathologic classifications:

- T3N0/Nx disease with or without a positive prostatectomy surgical margin; or
- T2N0/Nx disease with or without a positive prostatectomy surgical margin;

3.1.4 Prostatectomy Gleason score of 9 or less;

3.1.5 Zubrod Performance Status of 0-1;

3.1.6 Age ≥ 18;

3.1.7 No distant metastases, based upon the following minimum diagnostic workup:

- History/physical examination (including digital rectal exam) within 8 weeks (60 days) prior to registration;
- A CT scan of the pelvis (with contrast if renal function is acceptable; a noncontrast CT is permitted if the patient is not a candidate for contrast) or MRI of the pelvis within 120 days prior to registration;
- Bone scan within 120 days prior to registration; if the bone scan is suspicious, a plain x-ray and/or MRI must be obtained to rule out metastasis.

3.1.8 Adequate bone marrow function, within 90 days prior to registration, defined as follows:

- Platelets ≥ 100,000 cells/mm^3 based upon CBC;
- Hemoglobin ≥ 10.0 g/dl based upon CBC (Note: The use of transfusion or other intervention to achieve Hgb ≥ 10.0 g/dl is recommended).

3.1.9 AST or ALT < 2 x the upper limit of normal within 90 days prior to registration;

3.1.10 Serum total testosterone must be ≥ 40% of the lower limit of normal (LLN) of the assay used (testosterone ÷ LLN must be ≥ 0.40) within 90 days prior to registration (Note: Patients who have had a unilateral orchiectomy are eligible as long as this requirement is met);

3.1.11 Patients must sign a study-specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility (11/23/11)

3.2.1 A palpable prostatic fossa abnormality/mass suggestive of recurrence, unless shown by biopsy under ultrasound guidance not to contain cancer;

3.2.2 N1 patients are ineligible, as are those with pelvic lymph node enlargement ≥ 1.5 cm in greatest dimension by CT scan or MRI of the pelvis, unless the enlarged lymph node is sampled and is negative;

3.2.3 Androgen deprivation therapy started prior to prostatectomy for > 6 months (180 days) duration. Note: The use of finasteride or dutasteride (±tamsulosin) for longer periods prior to prostatectomy is acceptable;

3.2.4 Androgen deprivation therapy started after prostatectomy and prior to registration (Note: The use of finasteride or dutasteride (±tamsulosin) after prostatectomy is not acceptable - must be stopped within 3 months after prostatectomy. Androgen deprivation therapy must be stopped within 3 months after prostatectomy);

3.2.5 Neoadjuvant chemotherapy before or after prostatectomy;

3.2.6 Prior chemotherapy for any other disease site if given within 5 years prior to registration;

3.2.7 Prior cryosurgery or brachytherapy of the prostate; prostatectomy should be the primary treatment and not a salvage procedure;

3.2.8 Prior pelvic radiotherapy;

3.2.9 Prior invasive malignancy (except non-melanomatous skin cancer) or superficial bladder cancer unless disease free for a minimum of 5 years [for example, carcinoma *in situ* of the oral cavity is permissible];

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

- History of inflammatory bowel disease;
- History of hepatitis B or C; Blood tests are not required to determine if the patient has had hepatitis B or C, unless the patient reports a history of hepatitis.
- 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 at the time of registration;
- **(01/8/09)**Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; AST or ALT are required (see Section 3.1.9); note, however, that laboratory tests for 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. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may result in increased toxicity and immunosuppression.

3.2.11 Prior allergic reaction to the study drug(s) involved in this protocol.

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 Pretreatment Evaluations/Management (22Jun2017)

4.1.1 A measure of urinary function is the American Urological Association Symptom Index Score (AUA SI) or International Prostate Symptom Score (IPSS),[80] which is now routinely the basis for treatment decisions. This scoring system has been established as a measure of radiation morbidity in patients treated for prostate cancer.[81-84] The American Urological Association Symptom Index (AUA SI) will be administered to all protocol patients. The AUA SI questionnaire should be completed within 30 days prior to the start of treatment.

4.2 Highly Recommended Pretreatment Evaluations/Management (11/23/11)
Within 30 days prior to the start of any protocol treatment:

4.2.1 Baseline alkaline phosphatase;

4.2.2 Some form of apical prostate bed localization, in addition to a non-contrast CT simulation, is recommended, but not required. The methods include CT scan with urethrogram at the time of simulation or MRI (see Section 6.3.1) simulation to localize the inferior aspect of the prostate bed.

5.0 REGISTRATION PROCEDURES (15-Jan-2019)

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.

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

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 be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

NOTE: It is mandatory that the treating physician determine the radiation therapy technique (3D-CRT vs. IMRT) to be used prior to the site registering the patient.

5.1 Pre-Registration Requirements for IMRT (12/31/14)

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 Imaging and Radiation Oncology Core (IROC) Houston web site. Visit http://irochouston.mdanderson.org and select "Credentialing" and "Credentialing Status Inquiry".

An IMRT phantom study with the IROC Houston must be successfully completed (if the institution has not previously met this 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, the IROC Houston will notify both the registering institution and NRG Oncology that the institution has completed this requirement. Subsequently, NRG Oncology will notify the institution that the site can enroll patients on the study.

Institutions that previously have been credentialed for one IMRT delivery technique (e.g., standard gantry mounted linear accelerator using fixed gantry angles) must repeat the credentialing process when they change to a different technology (e.g. tomotherapyor volume delivery methods like RapidArc or VMAT).

The institution or investigator must complete or update an IMRT Facility Questionnaire (one per institution, available on the IROC Houston web site at http://irochouston.mdanderson.org) and send it to IROC Houston for review prior to enrolling any patients. IROC Houston will notify the institution and NRG Oncology when all requirements have been met. NRG Oncology will notify the institution that they are eligible to enter patients onto this study.

5.2 Pre-Registration Requirements for 3D-CRT (12/31/14)

Note: Institutions credentialed for IMRT for this protocol are automatically credentialed for the use of 3D-CRT.

Only institutions that have met the technology requirements and that have provided the baseline physics information may enter patients onto this study.

The new Facility Questionnaire (one per institution, available on the IROC Houston web site at http://irochouston.mdanderson.org) is to be sent to IROC Houston for review prior to enrolling any patients. IROC Houston will notify the institution and NRG Oncology when all requirements have been met. NRG Oncology will notify the institution that they are eligible to enter patients onto this study. Institutions that have previously enrolled patients on 3D-CRT trials of this same disease site may enroll patients on this study without further credentialing with the exception of submitting an updated Facility Questionnaire..

5.3 Digital RT Data Submission to RTOG Using TRIAD

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 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.

5.4 Regulatory Pre-Registration Requirements (19-Feb-2019)

5.4.1 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.

Downloading Site Registration Documents

Site registration forms may be downloaded from the RTOG 0534 protocol page located on the CTSU members' web site. Go to https://www.ctsu.org. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- 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
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand

Click on the Protocols tab in the upper left of your screen

- Click on the link to expand, then select trial protocol, RTOG-0534
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.
- Click on the Site Registration Documents link

Requirements for RTOG 0534 site registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- 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

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.

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

5.4.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

Prior to clinical trial commencement, Canadian institutions must complete and send the following documents to the CTSU Regulatory Office via the Regulatory Submission Portal **(sign in at www.ctsu.org and select the Regulatory Submission sub-tab under the Regulatory tab).**

- Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form,

- Qualified Investigator Undertaking Form, and
- Research Ethics Board Attestation Form.

5.4.3 Pre-Registration Requirements FOR 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.

5.5 REGISTRATION (15-Jan-2019)

5.5.1 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://ctepcore.nci.nih.gov/iam >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type. . 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 (12/10/13)

This trial will not utilize the services of the ITC for dosimetry digital treatment data submission. *PRIOR TO ENROLLING PATIENTS*, please see Section 5.3 for information on installing TRIAD for submission of digital RT data.

Note: Intensity Modulated RT (IMRT) is allowed for this study. See Section 5.0 for pre-registration requirements for IMRT and 3D-CRT treatment techniques.

Radiotherapy will start within 42 days (+/-14 days) after registration in Arm 1 and 60 days (+/-14 days) after starting LHRH agonist treatment in Arms 2 and 3.

Arm 1, PBRT Alone: PBRT 64.8-70.2 Gy (1.8 Gy per fraction)

Arm 2, PBRT + NC-STAD: PBRT 64.8-70.2 Gy (1.8 Gy per fraction) + NC-STAD for 120-180 days, beginning 60 days (+/- 14 days) before RT

Arm 3, PLNRT + PBRT + NC-STAD: PLNRT to 45 Gy (1.8 Gy per fraction) and PBRT to 64.8-70.2 Gy (1.8 Gy per fraction). NC-STAD for 120-180 days, beginning 60 days (+/- 14 days) before RT

6.1 Dose Specifications (11/23/11)

Radiotherapy will start within 42 days (+/-14 days) of registration in Arm 1 and 60 days (+/-14 days) after starting LHRH agonist treatment in Arms 2 and 3. Radiotherapy dose will be specified to the Planning Target Volume (PTV), as described in section 6.4. For the treatment methods outlined for prostate bed RT (3D-CRT, and IMRT), ≥ 95% of the PTV should receive the prescribed dose. The total dose to the prostate bed for all treatment arms is 64.8-70.2 Gy at 1.8 Gy per fraction. IMRT is strongly encouraged over 3D-CRT.

6.2 Technical Factors [Equipment, energies]

Megavoltage equipment is required with effective photon energies ≥ 6 MV.

6.3 Localization, Simulation, and Immobilization (11/23/11)

6.3.1 3D-Conformal Radiotherapy (3D-CRT) or IMRT

A urethrogram or MRI is recommended, but not required, to establish the most inferior portion of the prostate bed. Use of contrast, other than for the urethrogram, is discouraged. The placement of contrast in the rectum may cause the rectum to appear more anterior than it will be during treatment. Simulation should be with the rectum as empty as possible (an enema 1-2 hours prior to simulation) and with a moderately full bladder (the patient should not be uncomfortable at simulation and probably will have more difficulty maintaining a full bladder during treatment). An overly distended rectum can introduce a systematic positioning error that may increase the probability of missing the CTV. This is the reasoning behind an enema before the planning CT scan; although other methods, such as the use of a hollow (robnel) catheter to evacuate flatus to reduce the size of the rectum may accomplish the same result. Immobilization of the hips and feet using a cradle should be considered.

A treatment planning CT scan will be required to define the clinical and planning target volumes, and the critical normal structures. The treatment planning CT will be acquired with the patient set up in the same position as for daily treatments. Each patient will be positioned in the supine position. Prone positioning for treatment is not permitted. Rectal balloons for planning and treatment are not permitted. The CT scan of the pelvis should start at or above the iliac crest down to below the perineum (below the ischial tuberosities). All tissues to be irradiated must be included in the CT scan. CT scan thickness should be ≤ 0.3 cm through the region that contains the target volumes. The regions above and below the target volume region may be scanned with slice thickness ≤ 1.0 cm.

6.4 Treatment Planning/Target Volumes (22Jun2017)

Note: All required structures must be labeled exactly as listed in the table in Section 6.4.3 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.

6.4.1 Prostate Bed Planning for 3D-CRT

The definition of volumes will be in accordance with ICRU Report #50: Prescribing, Recording, and Reporting Photon Beam Therapy. Please see Section 6.8.2 for common contouring mistakes.

CTVp **(1/8/09) (3/24/10)**

Contrast may be used for simulation but can distort the anatomy slightly and so is not recommended. The bladder should be reasonably full for simulation, keeping in mind that patients may not be able to maintain as full a bladder during radiotherapy. Having a somewhat full bladder at simulation ensures that the CTVp will be of maximal dimensions. The seminal vesicles or remnants thereof, if identified on CT or MRI as being present, will receive the full dose. The immediate periprostatic bed surgical clips should receive the full dose. The CTVp will extend from the top of the penile bulb inferiorly, or 1.5 cm below the urethrogram peak if done, to just above the pubic symphysis superiorly (at least for the anterior-most portion of the bladder). Laterally, the

CTVp will extend from the medial edge of one obturator internus muscle to the other. Anteriorly, the CTVp will include the entire bladder neck until above the pubic symphysis, where a gradual reduction off of the anterior bladder is made. Superiorly, above the pubic symphysis, at least the posterior 2 cm of bladder should be included in the CTVp, as well as the area between the bladder and rectum, to the anterior rectal wall. The CTVp should extend superiorly to cover any clips in the seminal vesicle bed and the seminal vesicle remnants if present and should extend at least 2 cm above the pubic symphysis. Posteriorly, the CTVp is defined by the anterior-most aspects of the anus-rectum. The CTVp may be increased (not decreased) beyond these limits based on pre-prostatectomy imaging information.

A consensus definition of the prostate bed[85] and an anatomically-based description[86] should be considered in defining the CTVp. There has been considerable variability in how the prostate bed has been defined in the past. Although consensus definitions are not based on clinical outcome, they are extremely valuable in making the transition from conventional to conformal volumes. The consensus definition is not much different than the CTVp originally described above, but subtle differences are evident and should be considered. Either CTVp definition will be accepted in this clinical trial.

1) Superiorly: The prostatic fossa CTV (CTVp) should extend superiorly from the level of the caudal vas deferens remnant. In some cases, the vas deferens remnant may be difficult to visualize. In the absence of gross disease or seminal vesicle remnants, the superior limit of the CTVp should extend at least 2 cm and need not extend more than 3-4 cm above the level of the pubic symphysis. The consensus definition calls for "inclusion of the seminal vesicle remnants, if present, in the CTVp if there is pathologic evidence of their involvement. However, inclusion of any seminal vesicle remnants seen is recommended.
2) Inferiorly: The CTVp should extend inferiorly to > 8-12 mm inferior to vesicourethral anastomosis (VUA). With axial CT imaging, the VUA can often be seen in the retropubic region as one slice below the most inferior urine-containing image (the bladder must be modestly full). Magnetic resonance (MR) imaging defines this landmark more clearly with the hyperintense urine signal on T2 images. Inferiorly, the border of the CTVp should be at least 8-12 mm below the VUA. A sagittal reconstruction facilitates identification of the position of the VUA and the inferior border of the CTVp below it. If visualization of the VUA is problematic due to image quality or surgical clip artifacts, the inferior limit of the CTVp can extend to a level just above the penile bulb (same border as described above). It should be noted that there was considerable discussion about this definition versus extending the inferior border of the CTVp to just above the penile bulb; both definitions were deemed acceptable.
3) Anteriorly: Below the superior border of the pubic symphysis, the anterior border is at the posterior aspect of the pubis. The CTVp extends posteriorly to the rectum where it may be concave at the level of the VUA. At this level the lateral border extends to the levator ani. Above the pubic symphysis the anterior border should encompass **the posterior 1-2 cm of the bladder wall at the minimum** and posteriorly it is bounded by the mesorectal fascia. At this level the lateral border is the sacrorectogenitopubic fascia. This is not well-defined in textbooks. If in question, the lateral border should extend to the obturator internus muscle.
4) Posteriorly: The CTVp extends posteriorly to the anterior rectal wall, but may be somewhat concave around the anterior-lateral aspect of the rectum to adequately encompass the prostate bed.

PTVp **(11/23/11)**

The PTVp margins should be a minimum of 0.8 cm and a maximum of 1.5 cm in all dimensions. A reduction of the PTVp margin from 0.8 cm to ≥ 0.6 cm to minimize rectal exposure will be considered a variation acceptable. A posterior margin of < 0.6 cm will be considered an unacceptable deviation. A margin for penumbra for 3D-CRT, usually 0.5–0.7 cm beyond the PTVp should be added such that ≥ 95% of the PTVp receives the prescribed dose (64.8-70.2 Gy); an acceptable variation will be noted if < 95% to 90% of the PTVp receives the prescribed dose, and an unacceptable deviation will be noted if < 90% of the PTVp receives the prescribed dose. Care should be taken to conform the prescribed dose as closely to the PTVp as possible, so as to avoid including the entire width of the rectum in the posterior blocked margin at the bladder neck-rectum interface. The maximum dose in the PTVp above the prescribed dose will be 7%; a variation acceptable will be > 7% to ≤ 12% and an unacceptable deviation will be > 12%. The planned

dose between 64.8 to 70.2 will be declared after the patient is planned and all dosimetric parameters finalized.

Normal Tissue Definitions **(11/23/11)**

Normal tissues will be outlined as solid structures, including the rectum, bladder and femoral heads. The penile bulb will be outlined as a reference structure. No constraints will be placed on the penile bulb, but doses will be recorded. The rectum will be outlined from the anterior flexion of the rectosigmoid superiorly to the ischial tuberosities inferiorly. The entire bladder should be outlined down to the anastamosis. The DVH calculations will include doses to the entire bladder and the bladder minus the CTVp (BladdermCTV; Section 6.4.2).The femoral heads should be outlined down to the region between the greater and lesser trochanters. The planning parameters outlined below for IMRT should be used as a guide; formal 3D-CRT normal tissue prostate bed constraints have not been the standard in the past and are not specified here. It should be possible to come close to achieving the constraints outlined for IMRT, at least within the variation range.

6.4.2 Prostate Bed Planning for IMRT

CTVp/PTVp/Normal Tissues

The CTVp and PTVp will be the same as for 3D-CRT. There is no need to add margin for penumbra. A series of dose-volume histograms will be generated and analyzed to determine the adequacy of the plan.

Planning Parameters **(11/23/11)**

The plan will be deemed acceptable under the following conditions.

PTVp: The dose marker levels for bladder and rectum have been modeled after prior studies in men treated definitively with IMRT for prostate cancer.[87-88] At least 95% of the PTVp should receive the prescribed dose (64.8-70.2 Gy); a variation acceptable will be noted if < 95% to 90% of the PTVp receives the prescribed dose, and a deviation unacceptable will be noted if < 90% of the PTVp receives the prescribed dose. The maximum dose within the PTVp, above the prescribed dose, will be 15%; an acceptable variation will be > 15% to ≤ 20% and an unacceptable deviation will be > 20%.

Rectum: Less than or equal to 35% and 55% of the rectum should receive ≥ 65 Gy and ≥ 40 Gy, respectively. An acceptable variation will be noted if up to an additional 10% of the rectal volume at either cutpoint receives above the target doses specified. The inclusion of rectal volumes beyond these constraints will be considered a secondary acceptable variation and the extent of the variation should be recorded. In most patients, these constraints may be easily met and every attempt should be made to achieve the best dose distribution possible. The constraints will be harder to achieve in patients enrolled on Arm 3 (those receiving pelvic irradiation).

Bladder: Less than or equal to 50% and 70% of the **bladder minus CTVp (BladdermCTV)** should receive ≥ 65 Gy and ≥ 40 Gy, respectively. The criteria for the bladder are relaxed because the dosimetric relationship of volume exposed to the specified marker doses is much less clear and the bladder neck is included in the CTVp. Note that the DVH for the entire bladder should be recorded, but the bladder - CTVp is the volume that should be used for the calculations described here. An acceptable primary variation will be noted if up to an additional 7.5% of the bladder volume receives above the target doses specified. The inclusion of bladder volumes beyond these constraints will be considered an acceptable secondary protocol variation; it will not be considered a protocol violation. In some patients, the bladder will be relatively empty and the majority will be in the PTV.

Femoral Heads: Less than or equal to 10% of each femoral head should receive ≥ 50 Gy. A variation will be noted if up to an additional 5.0% of either femoral head receives > 50 Gy.

Penile Bulb: The penile bulb will be outlined as a reference structure. No constraints will be placed on the penile bulb, but doses will be recorded.

Small Bowel: See PLNRT section below.

Use of Cone Beam CT and Plan Adjustment: There may be cases in which the target and surrounding normal tissues are found not to be reproducible relative to the simulation CT and consequent plan. Replanning will invalidate the dosimetry and is considered a deviation. If all attempts to reproduce bladder and rectal filling by coaching the patient do not work and replanning is thought to be necessary, the patient should be replanned in the same supine position with the same target volumes as specified per the randomization. The patient will remain on the trial, despite the deviation.

6.4.3 Pelvic Lymph Node Radiotherapy (PLNRT) **(11/23/11)**

For Arm 3, the prostate bed and pelvic lymph nodes (CTVn/PTVn) will receive 45 Gy at 1.8 Gy per fraction. A total dose of 64.8–70.2 Gy at 1.8 Gy/fraction should be given to the prostate bed (CTVp/PTVp). Planning and treatment of the pelvic lymph nodes must be using the same method (3DCRT or IMRT) as for the prostate bed.

PLNRT Planning for 3D-CRT **(11/23/11))**

The CTVn will include the obturator, external iliac, proximal internal iliac and common iliac nodes, estimated using the vascular structures, up to the level of L5-S1. The recommended volumes are on the NRG Oncology/RTOG website under the "Core Lab/Contouring Atlases" menu (**http://www.rtog.org/CoreLab/ContouringAtlases/ProstatePelvicLymphNodes.aspx**). The CTVn is described as being 7 mm around the iliac vessels, carving out bowel, bladder and bone, which translates into just contouring the iliac/obturator areas with essentially no extra margin because of the proximity to these structures (this is well-illustrated in the contouring Atlas). Thus, the PTVn margins described above are the margins that venture into the potential bowel space, bladder and bone. **The remainder of the CTVn, including the prostate bed and seminal vesicle bed are as described above (Section 6.4.1).** The CTVp will include the prostate bed (64.8 – 70.2 Gy), as described for PBRT above. The PTVn and PTVp margins should be a minimum of 0.8 cm and a maximum of 1.5 cm in all dimensions. A reduction of the PTV margin from 0.8 cm to ≥ 0.6 cm to minimize rectal exposure will be considered an acceptable variation. A posterior margin of < 0.6 cm will be considered an unacceptable deviation. A margin for penumbra (usually 0.5–0.7 cm beyond the PTVs for 3D-CRT) should be added such that ≥ 95% of the PTVs receive the prescribed dose; an acceptable variation will be noted if < 95% to 90% of either PTV receives the prescribed dose, and an unacceptable deviation will be noted if < 90% of the PTV receives the prescribed dose. The maximum dose in the PTVp (the PTVn is expected to have greater heterogeneity and no specific constraints are given) above the prescribed dose will be 7%; an acceptable variation will be > 7% to ≤ 12% and an unacceptable deviation >12%. The planned dose between 64.8 to 70.2 will be declared after the patient is planned and all dosimetric parameters finalized. A minimum of four treatment fields should be used.

The normal tissue outlines will be the same as described in Section 6.4.1, with the added contouring of the potential space for small/large bowel in the pelvis. The potential bowel space will include the space on either side of the bladder to the medial edge of the lymph node outline laterally, beginning approximately at the top of the prostate bed field to one CT axial imaging level above the most superior level displaying a CTVn contour. Care should be taken to avoid the presacral lymph node region in the bowel volume. No constraints will be placed on the bowel for 3D-CRT planning.

PLNRT Planning for IMRT **(11/23/11)**

The volumes, prescriptions and margins for the CTVns and PTVns will be the same as for 3D-CRT and IMRT. The recommended volumes are on the NRG Oncology/RTOG website under the "Core Lab/Contouring Atlases" menu (**http://www.rtog.org/CoreLab/ContouringAtlases/ProstatePelvicLymphNodes.aspx**). No specific field arrangement is required, although typically 5-9 fields are used. Rotational IMRT treatments are permitted, as long as the constraints are met (See Section 5.2). The posterior PTVn margin at the bladder neck-rectum interface should not include the entire width of the rectum. A composite plan should be generated showing that at least 95% of the PTVn and PTVp receive the prescribed dose; a variation acceptable will be noted if < 95% to 90% of the PTV(s) receives the prescribed dose, and a deviation unacceptable will be noted if < 90% of the PTV(s) receives the prescribed dose. The maximum dose within the PTVp (the PTVn is expected to have greater heterogeneity and no specific constraints are given), above the prescribed dose, will be 15%; an acceptable variation will be > 15% to ≤ 20% and an unacceptable deviation > 20%. The other dosimetric parameters for IMRT are the same as for PBRT, except for the addition of a small bowel constraint.

Small/Large Bowel: The volume to be contoured is described in Section 6.4.3. For the patients receiving PLNRT, ≤ 150 cc of potential bowel space should receive ≥ 45 Gy. A variation will be noted if > 150 cc to 200 cc of potential small bowel space receives ≥ 45 Gy. A secondary variation will be noted if >200 cc receives >45 Gy (see Section 6.5.6). Since there are not protocol violations for bowel, treatment volumes should not be dramatically altered to adjust for bowel. In

prior protocols, considerable bowel was in the field and patients tolerated treatment well. Thus, these constraints act as a guide.
Overlap of the Bowel with the Prostate Bed PTV: This situation has been one of concern in cases where the high dose PTVp overlaps with loops of bowel. Since these patients have had prior surgery, bowel is not as mobile as for the patient with an intact prostate. However, it should be kept in mind that such compromises were not done in prior studies and that this should be an infrequent occurrence.
Overlap of the Bowel with the Lymph Node PTV: No adjustments in the PTVn are permitted. Since the potential bowel contour abuts the lymph node CTV, there should be an overlap with the lymph node PTV(PTVn). The overlap is expected.
Use of cone beam CT and plan adjustment: There may be cases in which the target and surrounding normal tissues are found to not be reproducible relative to the simulation CT and consequent plan. It should be emphasized that replanning should be avoided if at all possible because this will be considered a deviation. If the patient must be replanned in the opinion of the treating physician, then a deviation will be recorded, but continue to treat the patient per protocol in terms of dose and CTV/PTV volumes.

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.

RTOG 0534 Structure Names
Arms 1 and 2 Only
CTVp
PTVp
Bladder
BladdermCTV
Rectum
Femur_R
Femur_L
PenileBulb
SeminalVesicle
External
Arm 3 Only
CTVn
CTVp
PTVn
PTVp
Bladder
BladdermCTV
Rectum
Femur_R
Femur_L
PenileBulb
SmallBowel
SeminalVesicle
External

6.5 Critical Structures (12/10/13)

6.5.1 The critical normal structures are the bladder, rectum, small/large bowel above the rectum, and femoral heads. The normal tissues will be contoured and considered as solid organs.

6.5.2 The bladder should be contoured from its base to the dome, excluding the CTVp (the CTVp includes the bladder neck).

6.5.3 The rectum should be contoured from the anus (at the level of the ischial tuberosities) to the rectosigmoid flexure (this is roughly at about 10 cm) or for a maximum length of 15 cm if the sigmoid flexure if felt to be higher.

6.5.4 Each femoral head should be outlined down to the interface between the greater and lesser trochanters. Each femoral head should be considered separately.

6.5.5 For the patients who will undergo PLNRT treatment in Arm 3 using 3D-CRT or IMRT, the external iliac, obturator, internal iliac and common iliac vessels/lymph node regions should be outlined inferiorly from where the external iliacs become the inguinal vessels and superiorly from the level of the common iliacs at L5-S1. The presacral lymph nodes from L5-S1 to S3 should be included.

6.5.6 For the patients who will undergo PLNRT treatment in Arm 3 using 3D-CRT or IMRT, the potential bowel space (not individual loops of bowel) where the small and large bowel may fall should be outlined. The borders are the abdominal wall anteriorly, pelvic sidewalls laterally (excluding the pelvic lymph node regions), superiorly to one cut above the last axial CT image on which the lymph nodes are outlined and inferiorly from the level of the top of CTVp (outlining around the sides of the bladder near the top of the bladder to encompass the bowel that may fall into these regions). Posteriorly, the small bowel potential space should extend to in front of the sacrum, abutting the anterior presacral nodal contours.

6.5.7 The tissue within the skin and outside all other critical normal structures and PTV's is designated as unspecified tissue. See the NRG Oncology/RTOG web site at http://www.rtog,org to view examples of target and normal tissue contours.

6.6 Documentation Requirements (12/31/14)

6.6.1 The institution will archive treatment prescription and verification images for later review by the study chair if requested. For conformal RT, at least one portal image or pretreatment alignment portal image per field along with the digital reconstructed radiographs (DRRs) from the treatment planning software or, alternatively, a simulation verification radiograph shall be acquired and kept for evaluation if requested except where geometrically impractical. For IMRT, at least one portal image from each orthogonal image along with the digital reconstructed radiographs (DRRs) from the treatment planning software shall be acquired and kept for evaluation. **Note**: Images are required to be taken but not submitted.

6.6.2 NRG Oncology will display isodose distributions through the planning target volume to verify correct digital submission and conversion.

6.6.3 NRG Oncology will compare the submitted DVHs for the PTV, designated critical structures, and unspecified tissues with DVHs calculated by NRG Oncology.

6.7 Compliance Criteria (3D-CRT and IMRT) (11/23/11)

6.7.1 Dose Heterogeneity

3D-CRT

The maximum dose in the PTV above the prescribed dose will be 7%; an acceptable variation will be > 7% to ≤ 12% and an unacceptable deviation > 12 (see Section 6.4.1).

IMRT

The dose heterogeneity in IMRT treatment plans is greater than that for 3D-CRT. The maximum dose within the PTV, above the prescribed dose, will be 15%; an acceptable variation will be > 15% to ≤ 20% and an unacceptable deviation > 20%. Although, the maximum dose allowable in the PTV(s) will be 15% above the prescribed dose, it is possible in the vast majority of cases to achieve less than 15%.

6.7.2 Normal Tissue Deviations

3D-CRT

No specific constraints for 3D-CRT are included, but the dose-volume criteria described for IMRT below should be used as a guide. The dose volume histograms for the bladder, rectum, femoral heads, penile bulb, and small/large bowel (for Arm 3–PLNRT plans) should be included and the marker dose volumes when relevant (BladdermCTV, rectum each femoral head and small bowel) for IMRT should be recorded.

IMRT **(11/23/11)**

Less than or equal to 35% and 55% of the rectum should receive ≥ 65 Gy and ≥ 40 Gy, respectively. Less than or equal to 50% and 70% of the **bladder minus CTVp (BladdermCTV)** should receive ≥ 65 Gy and ≥ 40 Gy, respectively. The criteria for the bladder are relaxed because the dosimetric relationship of volume exposed to the specified marker doses is much less clear and the bladder neck is included in the CTVp. Less than or equal to 10% of each femoral head should receive ≥ 50 Gy. A variation acceptable will be noted if up to an additional 5.0% of either the femoral head receives > 50 Gy. For the patients receiving PLNRT, ≤ 150 cc of potential small/large bowel space should receive ≥ 45 Gy. A primary variation will be noted if > 150 cc to 200 cc of potential small/large bowel space receives ≥ 45 Gy. A secondary variation will be noted if > 200 cc of potential small/large bowel space receives ≥ 45 Gy.

6.8 R.T. Quality Assurance Reviews (12/31/14)

6.8.1 The NRG Oncology Radiation Oncologist Study PI and Co-Chair will oversee quality assurance RT reviews as complete RT data is received. These case reviews will be ongoing and facilitated by NRG RTQA. The reviews will be performed remotely.

6.8.2 Common Contouring Mistakes to Avoid

CTVp (prostate bed): Do not follow European or Australian/New Zealand guidelines. The NRG Oncology/RTOG guidelines should be followed very closely. Do not exclude the posterior bladder from the CTVp above the pubic symphysis (this is the Australian/New Zealand consensus, but not ours). The entire bladder neck is in the contour below the pubic symphysis; do not compromise this volume by excluding any bladder. The anterior border is the posterior aspect of the pubic symphysis.

Pelvic Lymph Nodes: Do not leave out the presacral lymph nodes.

Femoral Heads: Do not just contour the heads. The contours should extend down to the interface between the lesser and greater trochanters.

Penile Bulb: Needs to be contoured.

Bowel: Contour the space, not individual loops of bowel.

6.9 Radiation Adverse Events

6.9.1 All patients will be seen weekly by their radiation oncologist during radiation therapy. Any observations regarding radiation reactions will be recorded and should include attention toward the following potential side effects:

- Small bowel or rectal irritation manifesting as abdominal cramping, diarrhea, rectal urgency, proctitis, or hematochezia;
- Bladder complications including urinary frequency/urgency, dysuria, hematuria, urinary tract infection, and incontinence;
- Radiation dermatitis.

6.9.2 Clinical discretion may be exercised to treat side effects from radiation therapy as described in Section 9.1. Examples of typical medications used in the management of rectal side effects, such as diarrhea, include diphenoxylate or loperamide. Bladder or rectal spasms are usually treated with anticholinergic agents or tolterodine. Bladder irritation may be managed with phenazopyridine. Erectile dysfunction is often treated with medical management or mechanical devices.

6.10 Radiation Adverse Event Reporting (22Jun2017)

See Section 7.7 for Adverse Events and 7.8 for Adverse Event Reporting Guidelines.

7.0 DRUG THERAPY

(11/23/11) Short term androgen deprivation (STAD) will be administered to patients randomized to Arms 2 and 3. STAD will begin, from the start of LHRH agonist injection, within 6 weeks (+/- 2 weeks) after registration.

7.1 Treatment (12/31/14)

7.1.1 Dose definition

Short term androgen deprivation (STAD) will be administered to patients randomized to Arms 2 and 3, will begin from the start of LHRH agonist injection within 6 weeks after registration, and will consist of total androgen deprivation, using a combination of antiandrogen and LHRH agonist therapy for a total of 4-6 months. The antiandrogen will be either flutamide at 250 mg p.o. TID or bicalutamide at 50 mg p.o. QD. Antiandrogen therapy should begin at approximately the same time as LHRH agonist injection but may be started up to two weeks earlier (1-14 days prior to

LHRH agonist injection). **The antiandrogen will be stopped on the last day of radiation treatment ± 14 days**, which should be approximately 4 months of antiandrogen therapy. LHRH agonist injection will consist of analogs approved by the FDA (or by Health Canada for Canadian institutions), e.g., leuprolide, goserelin, buserelin, or triptorelin and may be given in any possible combination, such that the total LHRH treatment time is 4-6 months. For example, LHRH agonist injection(s) may be given as a single 4-month injection, a 4-month injection and one to two 1-month injection(s), two 3-month injections, one to three 1-month and a 3-month injection (4-6 months total), four to six 1-month injections, or a 6-month injection.

7.1.2 Duration of treatment

As outlined above, STAD, when administered, will be for a duration of 4-6 months. Antiandrogen therapy will be given for approximately 4 months (started within 1-14 days prior to the LHRH agonist and ending the last day of radiotherapy ± 14 days); LHRH agonists will be given for 4-6 months.

7.1.3 Calcium and Vitamin D supplementation

Patients who are randomized to receive androgen deprivation therapy are encouraged to take calcium at 500-1200 mg/day and vitamin D at 400-800 IU/day during androgen deprivation therapy; however, these supplements are not required.

7.2 Study Agents: LHRH Agonists (11/23/11)

7.2.1 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.

7.2.2 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, Trelstar) or subcutaneous injection (Eligard).The manufacturer's instructions should be followed.

7.2.3 Adverse Events

Consult the package insert for comprehensive adverse event information. Class-related toxicity is generally a manifestation of the mechanism of action and due to low testosterone levels. In the majority of patients testosterone levels increased above baseline during 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, 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.

7.2.4 Storage

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

7.2.5 Supply

Commercially available; Note: Buserelin is not commercially available in the United States. It is commercially available for use in Canada and other countries outside of the United States.

7.3 Eulexin (flutamide)

7.3.1 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.

7.3.2 Administration

The drug 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 between two weeks to one day prior to starting LHRH agonist injection and will continue throughout radiotherapy. Administration will be

suspended only if there is an apparent or suspected reaction to the drug. See Section 7.3.4. **Flutamide will be terminated on the last day of radiotherapy.** During radiotherapy interruptions, flutamide will be continued.

7.3.3 Adverse Events

Consult the package insert for comprehensive adverse event 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.

7.3.4 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 pelvic irradiation, the toxicity will be ascribed to flutamide and the drug will be permanently discontinued. AST or ALT will be measured pretreatment, then about every other month during oral antiandrogen therapy. If AST or ALT increases ≥ 2 x upper institutional limit of normal, flutamide must be discontinued.

7.3.5 Storage

Flutamide should be stored at temperatures ranging from 20-30 °C and protected from excessive moisture.

7.3.6 Supply

Commercially available

7.4 Casodex (bicalutamide)

7.4.1 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.

7.4.2 Administration

Bicalutamide is administered orally at a dose of one 50 mg tablet per day. Bicalutamide will be started from two weeks to one day prior to LHRH administration and continued throughout radiotherapy. Administration will be suspended only if there is an apparent or suspected reaction to the drug. **Bicalutamide will be terminated on the last day of radiotherapy.** During radiotherapy interruptions, bicalutamide will be continued.

7.4.3 Adverse Events

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.

7.4.4 Dose Modifications

Bicalutamide should be discontinued in instances of chemical liver toxicity. AST or ALT will be measured pretreatment and then every other month during antiandrogen therapy. If the AST or ALT rises ≥ 2 x the institutional upper limit of normal, bicalutamide must discontinued.

7.4.5 Storage

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

7.4.6 Supply

Commercially available

7.5 Criteria for Discontinuation of Protocol Treatment (1/8/09)

Protocol treatment may be discontinued for any of the following reasons:

- Progression of disease;
- Unacceptable adverse events at the discretion of the treating physician(s);
- A delay in protocol treatment > 8 weeks.

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

7.6 Modality Review

The Principal Investigator/Radiation Oncologist, Alan Pollack, MD, PhD and the Urology Co-Chair, Leonard G. Gomella, MD will perform a Hormone Delivery Quality Review by sampling of patients who receive or are to receive hormone therapy in this trial. The goal of the review is to evaluate protocol compliance. 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.

7.7 Adverse Events (15-Jan-2019)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 will be utilized until March 31, 2018, for all AE reporting, CTEP-AERS, and case report forms. CTCAE version 5.0 will be utilized for CTEP-AERS reporting beginning April 1, 2018; all study case report forms will continue to use CTCAE version 4.0. All appropriate treatment areas should have access to a copy of CTCAE versions 4.0 and 5.0, which can be downloaded from the CTEP web site (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

All adverse events (AEs) as defined in the table below (7.8) 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 table below (7.8) 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.

7.7.1 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 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report must be entered electronically into CTEP-AERS.

7.7.2 Serious Adverse Events (SAEs) — Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in Section 7.8 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in Section 7.8. **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.

7.7.3 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.

7.8 CTEP-AERS Expedited Reporting Requirements (12/31/14)

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=1398715802346.

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 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report must be entered electronically into CTEP-AERS.

- CTEP-AERS-24 Hour Notification requires that a 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 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 Agents under a non-CTEP IND: CTEP-AERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days[1] of the Last Dose of the Commercially Available Agents in this Study (Arms 2 & 3)

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 an Agent under a non-CTEP-IND:
Not applicable to this study.

8.0 SURGERY

All patients must have undergone radical prostatectomy prior to being considered for enrollment in this study. Any type of radical prostatectomy will be permitted, including retropubic, perineal, laparoscopic or robotically assisted. If performed, the number of lymph nodes removed per side of the pelvis and the extent of the pelvic lymph node dissection (obturator vs. extended lymph node dissection) should be noted.

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 Antidiarrheals

Antidiarrheals, such as loperamide hydrochloride or diphenoxylate-atropine, may be used as needed. The amounts of the drug(s) and dates used should be documented as much as possible.

9.1.2 Antispasmatics

Antispasmatics, such as oxybutynin or tolterodine tartrate, may be used as needed. The amounts of the drug(s) and dates used should be documented as much as possible.

9.1.3 Alpha Blockers

Alpha blockers, such as doxazosin mesylate, terazosin hydrochloride or tamsulosin hydrochloride may be used as needed. The amounts of the drug(s) and dates used should be documented as much as possible.

9.1.4 Analgesics

Analgesics is a broad category, including non-narcotic and narcotic agents. The use of non-narcotic agents, such as acetaminophen, non-steroidal anti-inflammatory agents or

phenazopyridine hydrochloride for radiotherapy treatment-related pain should be documented as much as possible. Narcotic use as a consequence of treatment should also be recorded.

9.1.5 Erectile Dysfunction

Erectile dysfunction may be treated with medical management (e.g., phosphodiesterase inhibitors), vacuum pumps or other devices as appropriate. The amounts of the drug(s) used and the dates that medical management or the use of mechanical devices was started should be documented.

9.2 Treatment of Patients with Subsequent Disease Progression

Treatment of patients who have failed salvage radiotherapy therapy by criteria described in Section 11 may receive additional medical or surgical therapies. The selection of these therapies will be left to the discretion of the treating physician.

10.0 TISSUE/SPECIMEN SUBMISSION (12/31/14)

10.1 General Information (22Jun2017)

The NRG Oncology Biospecimen Bank 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. 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. T

In this study, tissue will be submitted to the NRG Oncology Biospecimen Bank for the purpose of tissue banking for biomarker studies (highly recommended but not required).

(3/31/09) Biomarker studies are being done on all NRG Oncology prostatic cancer protocols using the original diagnostic material. The emphasis has been on proliferation markers (e.g., DNA-ploidy, Ki-67), apoptotic pathway markers (e.g., p53, MDM2, bcl-2, bax, p16), and angiogenesis markers (e.g., COX-2, VEGF) [See Section 1.4]. These markers have shown promise in predicting prostate cancer patient outcome after definitive radiotherapy. A final decision on which markers will be studied awaits the results of completed NRG Oncology prostate cancer trials that have reached maturity (e.g., 86-10, 92-02, 94-13). The trial described here will not be ready for biomarker analysis for several years, with the exception of the Abeta analysis in serum, which will be conducted in conjunction with cognitive outcomes, for those who participate in the neurocognitive battery testing. The goal is to measure approximately 5-10 biomarkers using the archived pathologic material.

10.2 Specimen Collection for Tissue Banking for Biomarker Studies: Strongly recommended (22Jun2017)

For patients who have consented to participate in the tissue/blood/urine component of the study (See sample consent).

10.2.1 Sites may submit the following specimens:

(22Jun2017) An H&E stained slide (can be a duplicate cut slide, does not have to be a diagnostic slide) and corresponding paraffin-embedded tissue block of the tumor (preferred) or at least 10 unstained 5 micron sections on positively charged slides. If tumor heterogeneity is observed, the submission of multiple blocks, including tissue from the area having the highest Gleason score, is desirable. **Note:** Tissue block or slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

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

- A Pathology Report documenting that the submitted block contains 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.
- 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.

Serum, plasma, whole blood, and urine

See Appendix IV for the blood and urine collection kits and instructions. **Note**: Kits include a label for shipping.

The following must be provided in order for the case to be evaluable for the Biospecimen Bank: A Specimen Transmittal Form (STF) documenting the date of collection of the serum, plasma, whole blood, and/or urine; the NRG Oncology protocol number, the patient's case number, and method of storage, for example, stored at -80° C, must be included.

Specimen Collection Summary

Specimen Collection for Tissue Banking			
Specimens taken from patient:	**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 or 3mm punches from block or 10-15 unstained slides on plus slides of the primary tumor taken before initiation of treatment	Pretreatment	Block or unstained slides or one to two 3mm punch biopsies from FFPE block	Block or unstained slides shipped ambient
SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge	Pretreatment Week 6 of RT 3, 6, 12 months (±1 month) after end of RT; then yearly for 6 years (±2 months)	Frozen serum samples containing 0.5 mL per aliquot in 1 mL cryovials (five)	Serum sent frozen on dry ice via overnight carrier
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/ lavender top) and centrifuge	Pretreatment Week 6 of RT 3, 6, 12 months (±1 month) after end of RT; then yearly for 6 years (±2 months)	Frozen plasma samples containing 0.5 mL per aliquot in 1 mL cryovials (five)	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 Week 6 of RT	Frozen whole blood samples containing 1 ml per aliquot in 1ml cryovials (three to five)	Whole blood sent frozen on dry ice via overnight carrier
10-20 mL clean-catch urine	Pretreatment Week 6 of RT and Post-treatment at Year 5 after end of RT (±2 months)*	One-two 5-10 mL urine aliquots in 1-2 sterile 15 ml polypropylene centrifuge tube. Store frozen at -20° or 80° C	Urine sent frozen on dry ice via overnight carrier in batches. Do not ship in Urine Cups.

***** Effective with amendment 6, urine will be collected only at year 5 after completion of RT. If sites collected urine at other timepoints (3, 6, and 12 months after RT, and yearly between 12 months and 5 years) prior to this change they should still submit them to the tis sue bank.

10.2.2 Storage Conditions **(10/22/09)**

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).

OR:

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

OR:

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

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

10.2.3 Submit materials for Tissue Banking as follows:
U.S. Postal Service Mailing Address: For Non-frozen Specimens Only
NRG Oncology Biospecimen Bank- San Francisco
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- San Francisco
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

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

10.3 Confidentiality/Storage (15-Jan-2019)

10.3.1 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.

10.3.2 Specimens for tissue banking will be stored for an indefinite period of time. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix I for a summary of assessments and time frames.

11.2 Evaluation During Treatment (11/23/11)
Radiotherapy for Arm 1 begins within 6 weeks (+/- 2 weeks) after registration. Radiotherapy for Arms 2 and 3 begins 2 months after the start of STAD (+/- 2 weeks).

11.2.1 Prior to radiotherapy

- The AUA SI questionnaire should be administered to all patients prior to protocol treatment. For patients on Arms 2 and 3, the AUA SI questionnaire should be administered within 2 weeks of starting RT.
- For all patients, including those on androgen deprivation (Arms 2 and 3), the following lab evaluations should be done within 30 days prior to starting treatment: CBC, AST or ALT, PSA, and testosterone. For patients on Arms 2 and 3, these same labs should be drawn within 2 weeks of starting RT.
- **(3/31/09)** The QOL measures (EPIC, HSCL-25, EQ-5D, and Utilization of Sexual Medications and/or Devices), the neurocognitive test battery (HVLT-R, Trail Making Test Parts A & B, and COWAT), and serum for biomarkers, including Beta Amyloid, will be obtained at pretreatment (baseline), if the patient has consented to participate in these components of the study. **Note**: Participation in the neurocognitive test battery is optional for the institution as well as the patient. Institutions participating in the neurocognitive test battery must follow the certification process (See Section 11.9.5 and Appendix V).

11.2.2 During radiotherapy

Patients will be seen and evaluated at least weekly during radiation therapy with documentation of performance status and tolerance, including acute reactions.

- During week 6 of RT, a CBC, AST or ALT, and testosterone should be obtained.
- During week 6 of RT, the AUA SI questionnaire should be administered.

- **(3/31/09)** The QOL measures (EPIC, HSCL-25, EQ-5D, and Utilization of Sexual Medications and/or Devices), the neurocognitive test battery (HVLT-R, Trail Making Test Parts A & B, and COWAT), and serum for Beta Amyloid also should be obtained during week 6 of RT, if the patient has consented to participate in these components of the study. **Note**: Participation in the neurocognitive test battery is optional for the institution as well as the patient. Institutions participating in the neurocognitive test battery must follow the certification process (See Section 11.9.5 and Appendix V).
- If the patient has consented to participate in the tissue/blood component of the study, blood (serum, plasma, and whole blood) and urine will be collected during week 6 of RT.

11.3 Evaluation Following Radiotherapy (11/16/15)

11.3.1 At each follow-up visit (3, 6, and 12 months in year 1; q 6 months x 6 years, yearly thereafter unless otherwise indicated; all visits are +/-1month for two years and then +/-2 months thereafter), the patient will have an interval history, physical examination (including digital rectal examination), assessment of specific GU and GI toxicity, and the AUA SI questionnaire will be administered.

11.3.2 The following lab evaluations will be done:

- PSA will be drawn at 1.5 months (+/-2 weeks), 3 months (+/-1 month), 6 months (+/-1 month), 9 months (+/-1 month) and 12 months (+/-1 month) after radiotherapy, at 3 month intervals (+/-1 month) for the next year. The type of PSA assay (e.g., Abbott) should be recorded on the data forms.
- If the PSA is ≤ 0.1 ng/mL, PSA will be drawn as described in Section 11.3.2 and at 6-month intervals thereafter (+/-2 months).
- If the PSA is ≥ 0.2 ng/mL, then PSAs should be obtained at 3-month intervals (+/-1 month) until the PSA is ≤ 0.1 ng/mL or greater than the nadir+2 ng/mL. If the PSA reverts to undetectable, then the frequency of PSAs will revert to that described in Section 11.3.2. **Salvage therapy should not be initiated prior to the time at which the nadir+2 ng/mL endpoint is reached.**
- If the PSA is ≥ 0.2 ng/mL, then follow-up visits should continue at 6-month intervals until the PSA is greater than the nadir+2 ng/mL. Salvage therapy should not be initiated prior to the time at which the nadir+2 ng/mL endpoint is reached.
- Serum testosterone will be obtained with each PSA measurement.
- AST or ALT will be obtained at 1.5 (+/-2 weeks), 3 (+/-1 month), and 6 months (+/-1 month) after radiotherapy.
- A CBC will be performed at 3 and 6 months (+/-1 month) after completion of RT.

11.3.3 The patient should be followed at 3-month intervals (+/-1 month) if ≥ grade 2 GI or GU complications are present, unless these symptoms have been present for more than 6 months and are not changing.

11.3.4 A bone scan and CT scan of the abdomen and pelvis will be performed as clinically indicated, such as if the patient develops a PSA recurrence with a doubling time < 10 months or if the patient develops symptoms suggesting the presence of metastatic disease.

11.3.5 If the patient has consented to participate in the tissue/blood/urine component of the study, specimens are collected after completion of RT per Section 10 and Appendix IV.**11.3.6** **(3/31/09)** If the patient has consented to participate in the QOL and neurocognitive component of the study, the QOL measures (EPIC, HSCL-25, EQ-5D, and Utilization of Sexual Medications and/or Devices) should be obtained at 1 and 5 years post-RT (+/-2 months). The neurocognitive test battery (HVLT-R, Trail Making Test Parts A & B, and the COWAT) should be obtained at 1 and 5 years post-RT (+/-2 months). **Note**: Participation in the neurocognitive test battery is optional for the institution as well as the patient. Institutions participating in the neurocognitive test battery must follow the certification process (See Section 11.9.5 and Appendix V).

11.4 Criteria for Freedom from Progression (FFP)

The primary endpoint is FFP, which includes biochemical (PSA) failure, clinical failure, and death from any cause.

11.4.1 Biochemical (PSA) Failure

The biochemical failure endpoint is defined according to the proposed new Radiation Therapy Oncology Group/American Society for Therapeutic Radiology and Oncology (RTOG-ASTRO) criteria (see Section 1.3), also known as the Phoenix definition. The Phoenix definition is an increase of the PSA level at least 2 ng/mL above the minimum level reached after therapy.[43]

Since the patients in this trial are status-post radical prostatectomy, about 70-80% will achieve an undetectable PSA. In these cases, a PSA of 2 ng/mL is evidence of biochemical failure. All PSA levels done during a follow-up interval will be recorded on the data forms. The initiation of further "salvage" therapy in any form (e.g., androgen deprivation therapy, vaccine therapy, or chemotherapy) after completion of protocol treatment and prior to nadir + 2 ng/mL failure will not be counted as a failure and is strongly discouraged. **The success of the trial depends upon allowing the nadir + 2 ng/mL failure criteria to be met before any other therapeutic intervention.**

11.4.2 Clinical Failure

Clinical failure is defined as any evidence of local, regional or distant failure.

11.4.3 Time to FFP

Time to FFP will be measured from the date of randomization to the date of documented biochemical failure by the Phoenix definition, clinical failure, or death from any cause.

11.5 Criteria for Local Failure

11.5.1 Local Failure

Local failure is defined as the development of a new palpable abnormality in the prostate bed after enrollment in the protocol. The presence of a palpable abnormality in the prostate bed prior to randomization is not permitted unless it is biopsy proven to be negative for cancer. Needle biopsy is recommended for any new palpable abnormality. Patients who have a normal exam and no evidence of biochemical failure by the primary endpoint will be considered controlled locally. Patients with a new prostatic fossa abnormality and biochemical failure will be considered to have local failure. Patients with a new prostatic fossa abnormality and no evidence of biochemical failure should undergo prostatic fossa biopsy. If salvage therapy is instituted prior to biopsy of a new prostatic fossa abnormality, then these patients will be considered to have had local failure. The presence of palpable disease must be recorded on the data collection forms for follow-up evaluations of the patient.

11.5.2 Biopsy of any new palpable abnormality in the prostatic fossa is recommended to document by histologic criteria the presence of prostatic adenocarcinoma.

11.6 Criteria for Nonlocal Failure

11.6.1 Regional Metastasis

Regional metastasis will be documented if there is radiographic evidence (CT or MRI) of lymphadenopathy (lymph node size ≥ 1.5 cm) in a patient without the diagnosis of a hematologic/lymphomatous disorder associated with adenopathy. Histologic confirmation is not required, although it is recommended in the setting of freedom from biochemical failure.

11.6.2 Distant Metastasis

Distant metastasis will be documented if by imaging (e.g., bone scan, CT, MRI) there is evidence of hematogenous spread.

Time to Distant Failure

The time to distant failure will be measured from the date of randomization to the date of documented distant disease.

11.7 Other Response Parameters

11.7.1 Secondary Biochemical Failure Endpoint

A more common biochemical endpoint used in the post-prostatectomy setting is a PSA ≥ 0.4 ng/mL and rising (see Section 1.3). This endpoint requires that the PSA is detectable and rising for at least two values with the second value at 0.4 ng/mL or greater.

Time to Secondary Biochemical Failure

The time to a PSA of 0.4 ng/mL and rising will be calculated from the time of randomization to this event, with a minimum follow-up from randomization of 2 years.

Hormone Refractory Disease

The development of hormone disease will be defined as three rises in PSA after the institution of salvage hormone therapy.

Time to Hormone Refractory Disease

The time to hormone refractory disease will be calculated from the date of randomization to the date of the third rise in PSA.

11.7.3 Cause-Specific Mortality

Time to cause-specific mortality will be measured from the date of randomization to the date of death due to prostate cancer. Causes of death may require review by the study chair or their designee. Death due to prostate cancer will be defined as:

- Primary cause of death certified as due to prostate cancer or
- Death in association with any of the following conditions:
  - Further clinical or biochemical tumor progression occurring after initiation of "salvage" anti-tumor (e.g., androgen deprivation) therapy;
  - Three consecutive rises in the serum PSA level at > 3-month intervals that occur during or after "salvage" androgen suppression therapy;
  - Disease progression in the absence of any anti-tumor therapy;
  - Death from a complication of therapy.

11.7.4 Overall Mortality

Time to overall mortality will be measured from the date of randomization to the date of death from any cause. A post-mortem examination will be performed whenever possible and a copy of the final post-mortem report will be sent to NRG Oncology.

11.8 Health-Related Quality of Life (HRQOL) (12/10/13)

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 in follow up as specified in Appendix I of the protocol.

11.8.1 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 radiotherapy and hormonal therapy.[57] 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.[89] Utilization of Sexual Medications/Devices will be collected to provide a context for interpreting the sexual domain score of the EPIC questionnaire.

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. Sites can contact the Quality of Life/Outcomes Co-Chair, Dr. Bruner, deborah.w.bruner@emory.edu, to obtain translations.

11.8.2 Mood and Depression: HSCL-25

The 25-item version of the Hopkins Symptom Checklist (HSCL-25)[90] will be used as a baseline and follow-up measure of depressive symptoms.[90-92] The patient self-administered measure is closely related to the Brief Symptom Inventory[93] and is widely used as a screening instrument in the cancer patient population. Using a cutoff of 44 and above for caseness, Hough and colleagues[90] found that the HSCL-25 was comparable or superior to the Center for Epidemiological Studies–Depression Scale in detecting psychiatric disorder. **Note**: If the research nurse (or other person administering the QOL assessments) determines that a patient scores 44 or greater on the HSCL-25, they should bring to the attention of the treating radiation oncologist that the patient is possibly depressed. The treating physicians should evaluate the patient and consider treatment or a referral to a psychiatrist.

The HSCL-25 has demonstrated reliability (Cronbach's alpha >.90) and validity across a variety of general and medical populations.[94] Patients can complete the HSCL-25 in approximately 3-5

minutes. The HSCL-25 has been translated into Bosnian, Cambodian, Japanese, Laotian, and Vietnamese. These translations can be ordered for a cost at http://www.hprt-cambridge.org/Layer3.asp?page_id=10.

11.9 Neurocognitive Test Battery (12/10/13)

Note: The neurocognitive test battery component of this study closed to patient accrual on March 22, 2012. If the patient provided consent to participate in the neurocognitive test battery component (a part of Quality of Life component) of this study prior to closure to new patient accrual, the site is required to administer the neurocognitive assessments in follow up as specified in Appendix I of the protocol.

The tests in the neurocognitive test cognitive battery were selected because they are widely-used standardized psychometric instruments that have been shown to be sensitive to the neurotoxic effects of cancer treatment in other clinical trials.[95] The tests have published normative data that takes into account age, and where appropriate, education and gender. All of the tests have been translated into multiple languages. Sites can contact the Neuropsychology Co-Chair, Dr. Wefel, jwefel@mdanderson.org, to obtain translations.

The tests are given by trained site administrators (see Section 11.9.5), and the total time for the cognitive assessment is approximately 20 minutes, as follows:

Cognitive Domain	**Test**	**Administration Time** (minutes)
Memory	Hopkins Verbal Learning Test-Revised (HVLT-R)	5
Verbal fluency	Controlled Oral Word Association Test (COWAT)	5
Cognitive Processing Speed	Trail Making Test, Part A	2
Executive Function	Trail Making Test, Part B	5

11.9.1 *Hopkins Verbal Learning Test-Revised (HVLT-R)*[96]

The patient is asked to recall a list of 12 words in three semantic categories over three trials. After a delay of at least 15 minutes, the patient is asked to recall the words. The patient is then asked to identify the list words from distractors (both semantically related and unrelated). There are six alternate forms of this test to minimize practice effects. The test measures learning efficiency (total words recalled, Trials 1–3), delayed memory retrieval (delayed recall), and consolidation (storage) of the information (delayed recognition). This measure has been widely used in clinical trials.

11.9.2 *Controlled Oral Word Association Test (COWAT)*[97]

This is a test of phonemic verbal fluency. The patient is asked to produce as many words as possible in 60 seconds beginning with a specified letter. There are two alternate forms of this test.

11.9.3 *Trail Making Test, Part A*[98]

This is a measure of visual-motor cognitive processing speed, requiring the patient to connect dots in numerical order from 1 to 25 as fast as possible.

11.9.4 *Trail Making Test, Part B*[98]

This is similar to Trail Making Test Part A, with the additional requirement of shifting mental set (an executive function). The patient connects dots alternating numbers and letters as fast as possible.

11.9.5 Quality Assurance for Neurocognitive Test Administration **(1/17/12)**

All persons administering the cognitive test battery must be certified. Previous certification for RTOG 0212, RTOG 0214, RTOG 0424, or PCYC-0211A is not sufficient as the administration of the HVLT-R has been changed. However, previous certification for RTOG 0525, 0614, or 0825 within the past 6 months will be accepted. Instructions for accessing the training video and post-test are available from NRG Oncology (see "Neurocognitive Training Procedure Letter" on the NRG Oncology/RTOG website, www.rtog.org). Dr. Wefel, Neuropsychology Co-Chair and Chief *ad interim* of Neuropsychology at M.D. Anderson Cancer Center, will oversee the training and will be available to answer questions. Certification procedures and test instructions are provided in

Appendix V. The instructions must be reviewed and retained for reference. Data forms are available from NRG Oncology. With training, administrators of the neurocognitive test battery should be able to complete testing in approximately 20 minutes. **Note**: Participation in the neurocognitive test battery is optional for the institution as well as the patient. Institutions participating in the neurocognitive test battery must follow the certification process (See Appendix V).

11.10 Beta-amyloid (Abeta) and Measures of Cognition and Mood and Depression (3/31/09)

As a correlative study, serum levels of beta-amyloid (Abeta) will be assessed at the same time points as the HSCL-25, the HVLT-R, the COWAT, and the cognitive test battery; associations among Abeta levels and cognitive tests will be evaluated. Beta-amyloid levels will be correlated with testosterone levels to further elucidate the mechanism of any cognitive decline.

Note: Participation in the neurocognitive test battery is optional for the institution as well as the patient. However, even if participation in the neurocognitive test battery is declined, blood drawing for biosample collection and banking will continue as specified in Section 10.0 of the protocol for patients that agree to participate in banking.

11.11 Cost Utility Analysis: EuroQol (EQ-5D)

The EQ-5D is a two-part patient self-administrated questionnaire that takes approximately 5 minutes to complete.[99] 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 including: 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 (35) health states to which unconsciousness and death are added.[100] The second part is a visual analogue scale (VAS) valuing current health state, measured on a 20-cm 10-point interval scale. Worst imaginable health state is scored as 0 at the bottom of the scale, and best imaginable health state is scored as 100 at the top. The Quality of Life/Outcomes Co-Chair, Dr. Bruner, will review and specify the VAS score for each case.

Both the 5-item index score and the VAS score are transformed into a utility score between 0 “Worst health state” and 1 “Best health state.” The index score or the VAS score or the cost-utility equation, can be used in the quality adjusted survival analysis depending on the health state(s) of interest.[101] For this study we will plan to report both the multidimensional and the VAS utilities for comparative purposes between standardized HRQOL and current health state but will only use the multidimensional utilities for the cost-utility analysis. 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 http://www.euroquol.com.

12.0 DATA COLLECTION (15-Jan-2019)

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation

Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.**Data is to be entered into the legacy RTOG Data Center Logon.**
***If a data form is not available for web entry, it must be submitted to**

NRG Oncology*
Attention-Data Management
1818 Market Street, Suite 1720
Philadelphia, PA 19103

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 (12/10/13)

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Pathology Report **(P1)** Slides/Blocks **(P2)**	Within 2 weeks of study entry
American Urological Association Symptom Index (AUA SI) **(PQ)**	
HRQOL: EPIC **(FA)**; HSCL-25 **(HP)**; EQ-5D **(QF)** Utilization of Sexual Meds/Devices **(SA)**	
Neurocognitive Evaluation Summary Form **(CS)**: HVLT-R; Trail Making Test, Parts A & B; COWAT	
Interim Follow-up Form **(F0)**	Arms 2 and 3 only: Prior to RT start, 3 months after RT (includes report of androgen suppression treatment)
Follow-up Form **(F1)**	Arm 1: 3, 6, and 12 months after RT; then every 6 months x 6 years; then annually Arms 2 and 3: 6 and 12 months after RT, then every 6 months x 6 years; then annually
Radiotherapy Form **(T1)**	Within 1 week from end of RT
(AUA SI) **(PQ)**	Arm 1: During week 6 of RT; 3, 6, and 12 months after RT; then every 6 months x 6 years; then annually Arms 2 and 3: 2 weeks prior to RT start; during week 6 of RT; 3, 6, and 12 months

	after RT; then every 6 months x 6 years; then annually
Neurocognitive Evaluation Summary Form **(CS)**: HVLT-R; Trail Making Test, Parts A & B; COWAT	During week 6 of RT, 1 year and 5 years post-RT
HRQOL: EPIC **(FA);** HSCL-25 **(HP)**; EQ-5D **(QF)** Utilization of Sexual Meds/Devices **(SA)**	During week 6 of RT, 1 year and 5 years post-RT
Autopsy Report **(D3)**	As applicable

12.2 Summary of Dosimetry Digital Data Submission for 3D-CRT or IMRT (Submit to TRIAD; see Section 5 for account access and installation instructions) [12/31/14]

Item	**Due**
Preliminary Dosimetry Information (DD) Digital Data Submission – Treatment **Digital data submission includes the following, all in DICOM format:** • CT data, all critical normal structures, CTV and PTV contours • Digital beam geometry for initial and boost beam sets • Doses for initial, boost and composite concurrently treated beams • Digital DVH data for all required critical normal structures, CTV, and PTVs for total dose plan • All required structures **MUST** be labeled per the table in Section 6.4 **Upon submission of the digital data via TRIAD, complete an online Digital Data Submission Information Form (DDSI) (Form located on RTOG/NRG Oncology web site at** http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study= 0534**)**	**Within 1 week of start of RT**
Final Dosimetry Information Radiotherapy Form **(T1)** Daily Treatment Chart **(T5) [copy of RT treatment chart to HQ]** Note**:** All simulation and portal images will be kept by the institution and submitted to NRG Oncology ONLY if specifically requested.	**Within 1 week of RT end**

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints (11/23/11)

13.1.1 Primary Endpoint

Freedom from progression (FFP): FFP (Section 11.4), will be the first occurrence of biochemical failure by the Phoenix definition (PSA ≥ 2 ng/ml over the nadir PSA),[43] clinical failure (local, regional or distant), or death from any cause.

13.1.2 Secondary Endpoints

- Secondary biochemical failure: See Section 11.7.1;
- Hormone-refractory disease: See Section 11.7.2;
- Local Failure: See Section 11.5.1;
- Distant metastasis: See Section 11.6.2;
- Cause-specific mortality: See Section 11.7.3;
- Overall mortality: See Section 11.7.4;
- 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 ≤ 90 days of the completion of RT.
- Time to "late" grade 2+ and 3+ adverse events (based on CTCAE, v. 3.0.): The time of a first late grade 2+ or 3+ adverse event, defined as > 90 days from the completion of RT.
- Comparison of disease-specific health related quality of life (HRQOL) change by EPIC, HVLT-R, Trail Making Test, parts A & B, and COWAT;
- Assessment of mood and depression change using QOL measured by the HSCL-25;
- Assessment and comparison of Quality Adjusted Life Year (QALY) and Quality Adjusted FFP Year (QAFFPY);
- Evaluation and comparison of the cost-utility using EQ-5D;
- Association between serum levels of beta-amyloid (Abeta) and measures of HSCL-25, the HVLT-R, Trail Making Test, parts A & B, or the COWAT.
- Prognostic value of genomic and proteomic markers for the primary and secondary clinical endpoints.
- To collect paraffin-embedded tissue blocks, serum, plasma, urine, and whole blood for future translational research analyses.
- To assess the relationship(s) between the American Urological Association Symptom Index (AUA SI) and urinary morbidity (Adverse Event terms: Urinary frequency/urgency) using the CTCAE v. 3.0 grading system.

13.2 Sample Size

13.2.1 Stratification and Randomization **(1/8/09) (3/24/10)**

Patients will be stratified before randomization according to seminal vesicle involvement (No vs. Yes); prostatectomy Gleason score (≤ 7 vs. 8-9); pre-radiotherapy PSA (≥ 0.1 and ≤ 1.0 ng/ml vs. >1.0 and <2.0 ng/ml), and pathology stage (pT2 and margin negative vs. all others). The treatment allocation scheme described by Zelen[102] will be used because it balances patient factors other than institution. Patients will be randomized to PBRT alone (Arm 1), PBRT+NC-STAD (Arm 2), or PLNRT+PBRT+NC-STAD (Arm 3). The patients are randomized to one of three arms until a treatment effect is detected or the total information time is reached. If a decision is made regarding treatment effect during the accrual, patients will be randomized as specified in Section 13.5.7.

13.2.2 Sample Size Derivation

The sample size calculation is based on the primary endpoint FFP rate by 5 years and the assumption that patients are randomized to all three arms until the end of accrual. Based on the prior results from a multi-institutional pooled analysis[35-36] we project that the rate of 5-year FFP of Arm 1, p_1 is 70% and hypothesize a 10% improvement in patients treated in Arm 2, i.e., p_2=80%, and a 20% improvement in patients treated in Arm 3, i.e., p_3=90%. The sample size calculation is based on the backward elimination decision rule in Chen and Simon[103] because this approach has the least favorable configuration property. We assume that the three treatment arms are ranked with Arm 1 as the least favorable arm, Arm 2 as the second one, and Arm 3 as the most favorable arm ($p_1 > p_2 > p_3$). We define the probability of selecting Arm i under hypothesis i (i=1, 2, 3) as $P(D=i \mid H_i) = 1-\alpha_i$. The three hypotheses are as follows:

H_1: $p_1 = p_2 = p_3$ where, $P(D=1 \mid H_1) = 1-\alpha_1$
H_2: $p_1 + \delta\sigma = p_2 = p_3$ where, $P(D=2 \mid H_2) = 1-\alpha_2$
H_3: $p_1 + \delta\sigma = p_2 + \delta\sigma = p_3$ where, $P(D=3 \mid H_3) = 1-\alpha_3$

Assume that the rates for all three arms are independently approximately normally distributed and have the same variance $\sigma^2/n = 0.25/n$. We wish to detect a difference of 10% ($\delta*\sigma = \delta*0.5 = 0.1$). Assume that $\alpha_1 = 0.025$, $\alpha_2 = \alpha_3 = 0.15$, and $\zeta = 3.25$ (from Table 4 in Chen and Simon[103]), the sample size for each treatment arm, $n = 2*\zeta^2/\delta^2 = 2*3.25^2/0.2^2 = 529$ patients are needed to have a statistical power of 90.1%.

Three interim analyses and a final analysis are planned for early stopping for efficacy and futility. For efficacy, testing will be done at the significance level of 0.001, which is similar to the Haybittle-Peto test[104,105] and the futility testing is based on the Freidlin and Korn[106] method. Guarding against an ineligibility or lack-of-data rate of up to 10%, the final targeted accrual for this study will be 1764 (588 per arm) patients.

13.3 Patient Accrual (11/23/11)

The proposed trial, RTOG 0534, builds on the experience obtained in RTOG 96-01. RTOG 96-01 involved a similar group of patients treated postoperatively with salvage radiotherapy and accrued 840 patients over 5 years at an average rate of 14 cases per month. As described above, we anticipate at the minimum a similar accrual rate; however, what is notable about the accrual in RTOG 96-01 is that at the end of the trial over 30 patients were being entered per month. There was an extended ramp-up period in RTOG 96-01; it took 2.5 years for accrual in RTOG 96-01 to reach 20 patients per month, and the trial reached targeted accrual and closed in less than five years. We anticipate that accrual to RTOG 0534 will be faster during the ramp-up period because the group has experience in accruing postoperative patients to randomized trials. Moreover, in RTOG 0534, androgen deprivation therapy is only used for 4 months, whereas in RTOG 96-01, it was used for 2 years. Many men are reluctant to take prolonged androgen deprivation, and for this reason accrual to the new study might be more robust. We are conservatively estimating an average of 16 cases per month in the new trial. We expect to complete accrual in 9.2 years. Based on patient accrual in previous 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 15 (14.7) years from the time the first patient is entered to the final analysis with 5 years of follow-up for each patient, and a uniform accrual rate of 16 patients per month.

The NRG Oncology Data Monitoring Committee (DMC) will begin evaluating patient accrual semi-annually 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., less than 8 patients per month), the trial will be placed on probation for six 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 institutions through CTSU is expected to follow a similar pattern as seen in NRG Oncology.

13.4 Power Calculations for Selected Secondary Endpoints

13.4.1 Secondary Biochemical Failure

The prior results from a multi-institutional pooled analysis[35-36] show that Arm 1 has a 59% rate of 5-year freedom from biochemical failure, and we project Arm 2 will have a 5-year freedom from biochemical failure rate of 69%, and Arm 3 will have a 7-year freedom from biochemical failure rate of 79%. With 529 analyzable patients per arm, we would have at least 87% statistical power of detecting at least a 10% absolute improvement in the biochemical failure rate in Arm 2 by 5 years compared to Arm 1 using a Z-test for the difference between the two rates with the standard errors estimated by Greenwood's method at the 0.0125 significance level. Also, with 529 analyzable patients per arm, we would have at least 93% statistical power of detecting at least a 10% absolute reduction in the biochemical failure rate in Arm 3 at 5 years compared to Arm 2 using a Z-test for the difference between the two rates with the standard errors estimated by Greenwood's method at the 0.0125 significance level.

13.4.2 Overall Mortality **(1/8/09)**

The prior results from a multi-institutional pooled analysis[36] show that Arm 1 has an 85% rate of 10 year overall survival, which translates to a yearly hazard rate of 0.0163. Based on this result,

we project Arm 2 will have a 10-year overall survival rate of 90%, which translates to a yearly hazard rate of 0.0105, and Arm 3 will have a 10-year overall survival rate of 95%, which translates to a yearly hazard rate of 0.0051. With 529 analyzable patients per arm, we would have at least 47% statistical power of detecting at least a 6% (or a hazard rate of 0.648) relative reduction in the yearly overall survival rate using a one-sided log-rank test at the 0.0125 significance level for patients in Arm 2. Also, with 496 analyzable patients per arm, we would have at least 46% statistical power of detecting at least a 6% (or a hazard rate of 0.487) relative reduction in the yearly overall survival rate using a one-sided log-rank test at the 0.0125 significance level for patients in Arm 3 compared to Arm 2.

13.4.3 Genomic and Proteomic Biomarkers **(1/8/09)**

Genomic or proteomic biomarkers will be categorized into either overexpressed or underexpressed. At a minimum, the analyses will include DNA-ploidy, Ki-67, p53, MDM2, bcl-2, bax, p16 and Cox-2. These biomarkers have shown promise in complementing the standard clinical parameters of PSA, Gleason score, and stage in prior analyses of men treated primarily for prostate cancer with RT. While these markers have been selected based on prior analyses, it is likely that some other markers and/or methods will be investigated when the proposed trial matures. Group 1 denotes a group with a better survival rate and Group 0 denotes the adverse group with the overexpressed or underexpressed marker. Tests will be performed to determine whether there is a difference in the survival functions for the primary endpoint, secondary biochemical failure, hormone refractory disease, distant metastasis, cause-specific survival, and overall survival. The number of events needed to obtain 1-β statistical power under these assumptions is calculated based on Schoenfeld.[107] In treatment efficacy trials, the targeted hazard ratios are usually not that large and the Schoenfeld formula works well.

$N_d = (z_\alpha + z_\beta)^2/[(\log(\Lambda))^2 P_0 P_1]$
Where P_i = the proportion of patients allocated to group I. i=0,1
$\Lambda = \lambda_0/\lambda_1$ (>1)
n_d = The number of events (failure)
Z_u=the uth percentile of the standard normal distribution

Tables 2 through 9 show the number of events for each biomarker required to demonstrate the hazard ratio Λ at a significance level α = 0.025 with statistical power of 80% and 90%. P_0 or P_1 values for each biomarker are based on the previous studies.

Table 2: Number of events for Ki-67: P_0 or P_1=46%

	HAZARD RATIO (Λ)		
STATISTICAL POWER	1.5	1.75	2
90%	258	136	89
80%	193	101	66

Table 3: Number of events for p53: P_0 or P_1=22%

	HAZARD RATIO (Λ)		
STATISTICAL POWER	1.5	1.75	2
90%	373	196	128
80%	279	147	96

Table 4: Number of events for MDM2: P_0 or P_1=50%

	HAZARD RATIO (Λ)		
STATISTICAL POWER (Z_B)	1.5	1.75	2
90%	256	135	88
80%	191	101	66

Table 5: Number of events for Bcl-2: P_0 or P_1=20%

	HAZARD RATIO (Λ)		
STATISTICAL POWER (Z_B)	1.5	1.75	2
90%	400	210	137
80%	299	157	103

Table 6: Number of events for Bax: P_0 or P_1=47%

	HAZARD RATIO (Λ)		
STATISTICAL POWER (Z_B)	1.5	1.75	2
90%	257	135	88
80%	192	101	66

Table 7: Number of events for Cox-2: P_0 or P_1=50%

	HAZARD RATIO (Λ)		
STATISTICAL POWER (Z_B)	1.5	1.75	2
90%	256	135	88
80%	191	101	66

Table 8: Number of events for DNA-ploidy: P_0 or P_1=40%

	HAZARD RATIO (Λ)		
STATISTICAL POWER (Z_B)	1.5	1.75	2
90%	267	140	92
80%	199	105	69

Table 9: Number of events for p16: P_0 or P_1= 27%

	HAZARD RATIO (Λ)		
STATISTICAL POWER (Z_B)	1.5	1.75	2
90%	325	171	111
80%	243	128	83

13.5 Analysis Plan (22Jun2017)

All eligible patients who are randomized to the study will be included in the comparison of treatment arms (intent-to-treat analysis).

13.5.1 Analysis of the Primary Endpoint **(1/8/09)**

FFP failure will be the first occurrence of local failure, regional failure, distant metastasis, biochemical failure defined by the Phoenix definition (PSA ≥ 2 ng/ml + nadir PSA), or death from any cause. Patients who are event free with less than 5 years of follow-up or who receive any secondary salvage therapy (e.g., salvage androgen deprivation, vaccine therapy, biologic/small molecule therapy, or chemotherapy) will be censored. The primary endpoint FFP rate by 5 years is defined as the proportion of patients with a FFP failure by 5 years from the randomization among all eligible patients at baseline and will be estimated by the Kaplan-Meier method. The Z-test statistic for the difference between the two rates with the standard errors estimated by

Greenwood's method will be used with an overall significance level of 0.025. The following test statistics will be used for testing between Arm i and Arm j.

$$T_{ij} = \frac{\hat{p}_i - \hat{p}_j}{\sqrt{\hat{p}_i^2 \sum_{i=1}^{n_i} \frac{f_i}{r_i(r_i - f_i)} + \hat{p}_j^2 \sum_{i=1}^{n_j} \frac{f_j}{r_j(r_j - f_j)}}} \quad \text{where, i,j =1,2,3}$$

eq (1)

where, $\hat{p}_i$ is FFP rate of Arm i estimated by Kaplan-Meier method, r_i is the number of patients who are at risk and f_i is the number of patients who have FFP events. Using the backward elimination decision procedure, we will first compare Arm 3 with Arm 2 at a critical value (Z-score) of 1.6249. The following hypotheses are of interest to be tested, where, p_1, p_2, and p_3 are the rate of 5-year FFP of Arm 1, Arm 2 and Arm 3, respectively.

$H_{01}: p_3 \leq p_2$ vs. $H_{A1}: p_3 > p_2$

If Arm 3 is not better than Arm 2 ($p_3 \leq p_2$), then we compare Arm 2 with Arm 1. If Arm 3 is better than Arm 2 ($p_3 > p_2$), then we compare Arm 3 with Arm 1.

If H_{01} is rejected ($T_{23} > 1.6249$), then we conclude that Arm 3 is better than Arm 2 and the following hypotheses are tested.

$H_{02}: p_3 \leq p_1$ vs. $H_{A2}: p_3 > p_1$

If the H_{02} is rejected ($T_{13} > 2.0768$), then we conclude that the 5-year FFP of Arm 3 will be better than Arm 1. If the H_{02} is not rejected ($T_{13} \leq 2.0768$), then we conclude that the 5-year FFP of Arm 3 will not be better than Arm 1.

If H_{01} is not rejected ($T_{23} \leq 1.6249$), then we conclude that Arm 3 is not better than Arm 2 and the following hypotheses are tested.

$H_{02}: p_2 \leq p_1$ vs. $H_{A2}: p_2 > p_1$

If the H_{02} is rejected ($T_{12} > 2.0768$), then we conclude that the 5-year FFP of Arm 2 will be better than Arm 1. If the H_{02} is not rejected ($T_{12} \leq 2.0768$), then we conclude that the 5-year FFP of Arm 2 will not be better than Arm 2.

In addition, univariate and multivariate logistic regression[108] will be used to compare the treatment differences in each hypothesis. Odds ratios from univariate and multivariate logistic regression and the respective 97.5% confidence intervals will be computed. Treatment arm, SV involvement, prostatectomy Gleason score, pre-radiotherapy PSA, pathology stage, age, and race (as appropriate) will be adjusted for in the Multivariate analysis.

13.5.2 Biochemical Failure-Related Endpoints **(1/8/09)**

The secondary biochemical failure (BF) endpoint is defined as having a detectable PSA (PSA ≥ 0.1 ng/ml) and rising for at least two values with the second value at 0.4 ng/ml or greater, or the initiation of salvage therapy. Hormone refractory disease is defined as three rises in PSA after the institution of second salvage hormone therapy. The rate pi (i=1, 2, 3) is defined as the proportion of patients with an event among all eligible patients at baseline in Arm i. The Z-test statistics for the difference between the two rates with the standard errors estimated by Greenwood's method, eq. (1), will be used with an overall significance level of 0.025. In the test statistics, $\hat{p}_i$ is the rate of Arm i estimated by Kaplan-Meier method, r_i is the number of patients who are at risk and f_i is the number of patients who have events by 5 years. Using the backward elimination decision procedure, we first compare Arm 3 with Arm 2. The following hypotheses are of interest to be tested, where, p_1, p_2, and p_3 are the rate of 5-year of Arm 1, Arm 2 and Arm 3, respectively.

$H_{01}: p_3 \leq p_2$ vs. $H_{A1}: p_3 > p_2$

If Arm 3 is not better than Arm 2 ($p_3 \leq p_2$), then we compare Arm 2 with Arm 1. If Arm 3 is better than Arm 2 ($p_3 > p_2$), then compare Arm 3 with Arm 1.

If H_{01} is rejected ($T_{23} > 1.6249$), then we conclude that Arm 3 is better than Arm 2 and the following hypotheses are tested.

H_{02}: $p_3 \leq p_1$ vs. H_{A2}: $p_3 > p_1$
If the H_{02} is rejected ($T_{13} > 2.0768$), then we conclude that the 5-year rate of Arm 3 will be better than Arm 1. If the H_{02} is not rejected ($T_{13} \leq 2.0768$), then we conclude that the 5-year rate of Arm 3 will not be better than Arm 1.
If H_{01} is not rejected ($T_{23} \leq 1.6249$), then we conclude that Arm 3 is not better than Arm 2 and the following hypotheses are tested.
H_{02}: $p_2 \leq p_1$ vs. H_{A2}: $p_2 > p_1$
If the H02 is rejected (T12 > 2.0768), then we conclude that the 5-year rate of Arm 2 will be better than Arm 1. If the H02 is not rejected (T12 ≤ 2.0768), then we conclude that the 5-year rate of Arm 2 will not be better than Arm 2.

In addition, the univariate and multivariate logistic regression will be used to compare the treatment differences in each hypothesis. Odds ratios from the univariate and multivariate logistic regression and the respective 97.5% confidence interval will be computed. The treatment arm, SV involvement, prostatectomy Gleason score, pre-radiotherapy PSA, pathology staging, age, and race (as appropriate) will be adjusted for in the multivariate analysis.

13.5.3 Time to Failure of Secondary Survival Endpoints **(1/8/09)**

The time to failure for secondary endpoints (second biochemical failure, hormone refractory disease, distant metastasis, cause-specific mortality, and overall mortality) will be measured from the date of randomization to the date of the event of interest. The events for secondary endpoints and time-to-events are defined in Sections 11.4-11.7. Using the backward elimination decision procedure, we will first compare Arm 3 with Arm 2 at the significance level of 0.0125. If Arm 3 is not better than Arm 2, then Arm 2 will be compared with Arm 1 at the significance level of 0.0125. If we conclude that Arm 2 will be better than Arm 1, then we can conclude that the 5-year FFP of Arm 2 will be the best. If Arm 3 is better than Arm 2, then Arm 3 will be compared with Arm 1 at the significance level of 0.0125. If we conclude that Arm 3 will be better than Arm 1, then we can conclude that Arm 3 will be the best. The time-to-event distribution of overall mortality will be estimated using the Kaplan-Meier method[109] and the log-rank test[110-111] will be used to test whether the overall mortality rate in one arm is higher than the other arm for each hypothesis at the significance level of 0.0125. However, the treatment effect on other types of failure may impact the observable measures of distant metastasis and cause-specific mortality and other competing risks may dilute the sensitivity of hormone refractory disease, distant metastasis and cause-specific mortality.[106] We will use the cause-specific hazard rate[112-113] (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[106] showed that the cause-specific hazard rate approach is better than other approaches, for example, the cumulative incidence method,[114]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 0.0125. In this approach, patients who experience other failure first are censored.[112]

In addition, the Cox regression model[115] will be used to compare the treatment differences. Both unadjusted and adjusted hazard ratios and the respective 97.5% confidence interval will be computed. At least the treatment arm, the stratification variables (SV involvement, prostatectomy Gleason score, pre-radiotherapy PSA, pathology stage), age, and race (as appropriate) will be adjusted for in this analysis.

13.5.4 Comparison of the Incidence of Acute Toxicity and Time to Late Grade 3+ Toxicity **(1/8/09)**

Adverse events are scored according to CTCAE, v. 3.0. An acute adverse event will be defined as the worst severity of the adverse event occurring less than or equal to 90 days of treatment. Both acute grade 2+ and 3+ toxicity will be examined separately. Univariate logistic regression[107] will be used to model the distribution of acute adverse events. Multivariate logistic regression[107] will be used to model the distribution of acute adverse events, adjusting for covariates. Treatment arm, SV involvement, prostatectomy Gleason score, pre-radiotherapy PSA, pathology stage, and age (as appropriate) will be adjusted for in the multivariate analysis. Both unadjusted and adjusted odds ratios (H_1: Arm 1 vs. Arm 2 and H_2: Arm 2 vs. Arm 3, respectively) and the respective 97.5% confidence interval will be computed and tested using a one-sided chi-square test with the significance level of 0.025 for each hypothesis.

Late grade 2+ or 3+ adverse events will be defined as an a grade 2+ or 3+ adverse events occurring more than 90 days of the completion of treatment. The time to late grade 2+ or 3+ adverse events will be measured from the time protocol treatment started to the time of the worst late grade 2+ or 3+ adverse event, respectively. 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. The distribution of time to late grade 2+ or 3+ adverse events will be estimated using the Kaplan-Meier method[109] and tested using a one-sided log-rank test[110-111] with the significance level of 0.025 for each hypothesis. A multivariate Cox regression model[115] will be used to compare the treatment differences of time to late adverse event. Both unadjusted and adjusted hazard ratios (H_1: Arm 1 vs. Arm 2 and H_2: Arm 2 vs. Arm 3, respectively) and the respective 97.5% confidence interval will be computed. Treatment arm, SV involvement, prostatectomy Gleason score, pre-radiotherapy PSA, pathology stage, age, and race (as appropriate) will be adjusted for in this analysis.

A Chi-square test will be used at a significance level of 0.05 to test the correlation between the common toxicity categories in the American Urological Association Symptom Index (AUA SI) and urinary morbidity (Adverse Event terms: Urinary frequency/urgency) using the CTCAE v. 3.0.

13.5.5 Modeling the Relationship of Genomic and Proteomic Biomarkers to the Study Endpoints **(1/8/09)**

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. The following is a general guideline for the statistical consideration for this analysis. This analysis will be done in each arm separately to test the prognostic vales of biomarkers.

A genomic or proteomic biomarker will be categorized into two subgroups based upon previously defined (or hypothesized) cut-off points and these two groups will be referred to as favorable and unfavorable risk groups. The patients with genomic and proteomic biomarkers will be compared with the patients without a value for that biomarker to determine if there are any differences with respect to distribution of baseline variables (SV involvement, prostatectomy Gleason score, pre-radiotherapy PSA, and pathology stage). We want to know if there is a difference in survival rate between these two groups. The null (H_0) and alternative (H_A) hypotheses for survival distribution (S) are

$$H_0: S_0(t) \geq S_1(t) \text{ vs. } H_A: S_0(t) < S_1(t), \text{ where t is time}$$

Tests will be performed to see if one group is statistically significantly better than the other in the primary endpoint and secondary endpoints that are related to time to failure (hormone refractory disease, distant metastasis, cause-specific survival, and overall survival). However, the selection of the cut-off point for each biomarker is not established. If the hypothesized cut-off points do not yield statistical significance, other cut-off points may be evaluated. Therefore, various cut-off points are evaluated for their statistical significance. To correct the problem from the multiple testing, the Bonferroni correction will be used. The overall survival functions will be estimated by the Kaplan-Meier method and will be tested for the overall survival difference between the favorable and unfavorable groups using the log-rank test. We will use the cause-specific hazard rate approach[106] to estimate other survival/failure distributions and test the survival/failure difference between the two groups using the cause-specific log-rank test. The multivariate analysis will be performed using the Cox proportional hazards model[115] for both groups. Potential covariates evaluated for the multivariate models are SV involvement, prostatectomy Gleason score, pre-radiotherapy PSA, pathology stage, and assigned treatment. A stepwise procedure will be used to develop the base model for each outcome endpoint prior to evaluating the prognostic impact of the biomarkers. This approach will be employed to account for as much variation as possible for each outcome before it is tested. It is entirely possible that factors shown to be prognostic in other published series may not be found prognostic here.

If high-dimensional data, such as two-color Microarray data, are generated from blood/urine-based proteomic and genomic data, the following guideline could be applied for the data pre-processing. A careful examination of array images of each gene's spots on the array images will

be carried out to find the spots affected by experiment artifacts. This is a general guideline for the statistical consideration for the two-color Microarray data analysis.

We will not include genes whose intensity is less than 100[116-117] n both green and red intensities. Local background hybridization signals will be subtracted from the intensities. Let R_j be the background-adjusted fluorescence intensity for the cancer or benign sample and G_j be the background-adjusted fluorescence intensity for the reference sample for gene j on a particular array. The gene expression ratio is computed as R_j / G_j and undergoes normalization and transformation to the log-2 scale. Normalization will be applied to remove systematic differences due to extraneous factors such as array effects, global dye effects, print tip effects, etc. Simple normalization methods such as global median centering[116] will be considered as well as more complex methods such as print tip-specific corrections and intensity-based normalization methods such as lowess smoothing[118] if diagnostic plots (e.g., M vs A plots[119]) suggest they are needed. These log-transformed, normalized gene expression ratios are used as the basic data in subsequent analyses. If one of the two intensities in a spot is less than 100, that intensity will be set to 100. Genes with greater than 20% of spots missing intensities will be removed from the analysis. For remaining genes, individual missing log ratio values will be imputed using the k-nearest neighbors approach, with k = 10.[120]

The high-dimensional data from patients who yield both pre- and post-treatment tissue specimens will be used to see the gene expression difference. Let m be the number of genes that will be tested. Let d_{iij} be the gene expression difference between pre- and post- treatment for patient i and gene j on a treatment arm. Denote the mean difference between pre- and post- treatment gene expression for gene j as D_j. A test will be conducted to test the following null (H_0) and alternative (H_A) hypotheses for each gene:

$H_0: D_j = 0$ vs. $H_A: D_j \neq 0$

We will control the false discovery proportion when a test for a gene is called significant. A paired t-test will be used to calculate the unadjusted univariate p-value for each gene. We will identify all genes with adjusted p-values[121] ≤ 0.05 as being differentially expressed between pre- and post-treatment to be 95% confident that the false discovery proportion is no more than 10%.

13.5.6 Analysis for Endpoints Related to Quality of Life (QOL) **[2/13/08] [1/8/09]**

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

We will use seven instruments to assess quality of life (QOL): the Expanded Prostate Cancer Index (EPIC), EPIC Sexual Medications/Devices Supplement (Utilization of Sexual Meds/Devices), the 25-item version of the Hopkins Symptom Checklist (HSCL-25), the EuroQol (EQ-5D), Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test, parts A & B, and the Controlled Oral Word Association Test (COWAT). 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, Utilization of Sexual Meds/Devices, HSCL-25, EQ-5D, HVLT-R, Trail Making Test, parts A & B, and COWAT) will be collected on all cases participating in the trial. 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[122] will be performed to describe the change trend of the EPIC, Utilization of Sexual Meds/Devices, HVLT-R, Trail Making Test parts A & B, COWAT, HSCL-25, and EQ-5D scores over time across the three 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 (SV involvement, prostatectomy Gleason score, pre-radiotherapy PSA, pathology stage).

The EPIC and HSCL-25 will be collected at pretreatment (baseline), the end of RT, and at 1 year and 5 years after therapy starts. Patient self-assessment of symptoms will be performed using

four primary EPIC domains: urinary, bowel, sexual, and hormonal symptoms. The data about the use of erectile aids from Utilization of Sexual Meds/Devices will be reported along with question 17-b in the EPIC. The HSCL-25 has 25 items and is scored by a four point Likert scale (1-not at all, 2-a little, 3-quite a bit, and 4-extremely). A higher score means a worse mood or depression. The HVLT-R, Trail Making Test, parts A & B, and COWAT will be collected at pretreatment (baseline), the end of RT, and at 1 year after the therapy starts. There are three immediate recall responses, one delayed recall response, and one delayed recognition response in the HVLT-R. The response is the number of words the patient can recall out of 12 words for recall responses and the difference of the listed words correctly and incorrectly recalled for recognition response. The response from Trail Making Test, parts A & B is the time takes to finish each test less than 3 and 5 minutes, respectively. There are three responses for the COWAT, and each response is the number of words starting with a provided letter of the alphabet that the patient can produce in one minute. The EQ-5D will be collected at pretreatment (baseline), at 1 year and 5 years after therapy starts. The EQ-5D is a two-part self-assessment questionnaire. The first part consists of 5 items covering 5 dimensions (mobility, self care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a three point Likert scale (1-no problems, 2-moderate problems, and 3-extreme problems). There are 243 ($=3^5$) health states. The second part is a visual analog scale (VAS) valuing the current health state measured by 100 point scale with 10 point interval (0-worst imaginable health state, 100-best imaginable health state). The QOL Co-Chair, Dr. Bruner, will review and specify the VAS score for each case. We will transform the 5-item index score and VAS score into a utility score between 0 (Worst health state) and 1 (Best health state) for comparative purposes.

We hypothesize that the measurements from EPIC, HVLT-R, Trail Making Test, parts A & B, and COWAT will be worse in the arms with NC-STAD than in the PBRT arm. We also hypothesize that measurements from HSCL-25 will be lower in the arms with NC-STAD than in the PBRT arm. For all QOL analyses, we will conduct two comparisons between the two treatment arms (Arm 1 vs. Arm 2 and Arm 1 vs. Arm 3) with a two-sided test. The significance level α for the pair-wise comparison will be adjusted by the Bonferroni method[123] to α =0.05/2 to maintain the overall significance level of α =0.05. To address the non-ignorable missing data caused by censoring survival time, the data analysis also will include patients who have not died.

The required sample size per treatment arm when we use 1 domain is 64 with 80% statistical power and 86 with 90% statistical power, respectively, based on an effect size of 0.5 according to the EPIC web site.[124] The required sample size per treatment arm when we use 4 domains is 91 with 80% statistical power and 116 with 90% statistical power, respectively, based on an effect size of 0.5. Therefore, there will be sufficient statistical power to detect a difference of 0.5 in four domain scores of HRQOL measurements in the EPIC instrument among the treatment arms. Because the participation rate in QOL assessments will be less than 100%, the expected sample size for the QOL analysis must be adjusted according to the participation rate. Table 11 shows adjusted sample sizes for a range of participation rates. Considering the possible low response rate, 200 cases per arm are required. Accrual for the QOL studies will be limited to 200 cases per randomization arm.

Table 11: Adjusted sample size* per treatment with four domains in EPIC

RESPONSE RATE	80% POWER	90% POWER
100%	91	116
90%	102	129
80%	114	145
70%	130	166
60%	152	194

*The sample size is calculated by dividing the sample size at 100% by participation rate

To examine trade-offs between the survival time and QOL, we will combine them for each patient into two single measurements: Quality Adjusted Life Year (QALY) and Quality Adjusted FFP Year (QAFFPY). 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 and QAFFPY are defined by the weighted sum of different time episodes added up to a total quality-adjusted survival time and a total quality-adjusted FFP time, respectively. These health state-based methods of quality-adjusted survival analysis are known as Q-TwiST,[79] the quality-adjusted time without symptoms and toxicity method.

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

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[125] 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 a health state.

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.

The Medicare reimbursement in dollars/QALY and the Medicare reimbursement in dollars/QAFFPY will be calculated as a function of the monetary cost per relative value of each health state and its duration. Cost-utility will be analyzed at two time points: at 1 year and 5 years post-therapy. We will use the five-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 two treatment arms (Arm 1 vs. Arm 2 and Arm 1 vs. Arm 3) is the same with significance level of 0.05/2=0.025 and a two-sided test. We will compare the cost-utility using the Medicare reimbursement in dollars/QALY and the Medicare reimbursement in dollars/QAFFPY between the two treatment arms after adjusting for the baseline and stratification variables.

We will evaluate the cost-utility of the treatment arm in terms of the primary outcome and will also compare the cost-utility among the three treatment arms. The cost-utility analysis will only include patients whose care are reimbursed under the federal Medicare payment system but will exclude those in Medicare HMOs as well as those under alternative federal coverage (including Medicaid, DOD, and the VA) as well as those covered by private payers or other payment systems. Cost-utility will be analyzed for planned publication at two time-points: looking at initial treatment costs and quality of life at 1 year post-therapy and at 5 years post-therapy. The cost-utility analysis will not be done until after the primary endpoint results are published. We will use the 5-item utility score in EQ-5D for the cost-utility analysis and the Medicare costs defined as in Section 1.6.3. The Medicare cost in dollars/QALY will be calculated as a function of the monetary cost per relative value of each health state and its duration. We will use Analysis of Variance (ANOVA) to compare the cost-utility among the three treatment arms at a significance level of 0.05. If there is a statistically significant difference, a Z-test will be used to compare it between each combination of two treatment arms (Arm 1 vs. Arm 2 and Arm 1 vs. Arm 3, and Arm 2 and Arm 3) after adjusting for the baseline and stratification factors with a significance level of 0.05/3=0.017 and a two-sided test.

A multivariate regression model will be used to model the association between serum levels of beta-amyloid (Abeta) and measures of the HVLT-R, Trail Making Test, parts A & B, COWAT, and HSCL-25, respectively. The model will include at least the baseline and stratification factors (SV involvement, prostatectomy Gleason score, pre-radiotherapy PSA, pathology stage) as covariates.

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[126] 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: worst-case scenario (in which missing data are assumed to be unfavorable for those on the experimental treatment and favorable of those in the control group); use of the mean response for individual patients who withdrew from the trial from either all or similar (matched) patients remaining in the trial; last observation carried forward (LOCF) [using the last observation as the final observation]; or linear mixed-effects models, to obtain separate estimates for the QOL outcome within strata based on missing data patterns.[126-127] RTOG recognizes that all options are subject to bias and analysis of more than one method for consistency across methods is prudent.

13.5.7 Group Sequential Testing for Early Termination and Reporting of Efficacy and Futility **(1/8/09)**

A group sequential test with three planned interim analyses and a final analysis will be performed. The interim analysis will be carried out when the cumulative accrual (patients whose follow-up is at least 5 years from the randomization date) are met. For each interim analysis, one efficacy and two futility tests will be carried out. At each planned interim analysis, the p-value from the Z-test statistics, eq.1, for the difference between the two FFP rates assessing treatment efficacy or futility with respect to the primary endpoint will be compared to the nominal significance level. The significance level of 0.001, which is similar to the Haybittle-Peto test[104-105], was chosen for efficacy testing. For the futility testing boundary, we will use a less aggressive boundary, Rule C in Freidlin and Korn.[106]

We will first compare Arm 3 with Arm 2 and choose the arm that has the higher FFP rate (if they are the same, Arm 2 will be chosen). Let p1, p2, and p3 equal the rate of 5-year FFP of Arm 1, Arm 2 and Arm 3, respectively. If Arm 2 is better than Arm 3 ($p2 \geq p3$), then we compare Arm 2 with Arm 1. The following hypothesis is tested.

H02: $p2 \leq p1$ vs. HA2: $p2 > p1$

If H02 is rejected (p-value ≤ 0.001), then we conclude that the 5-year FFP of Arm 2 is better than Arm 1. We report that Arm 2 is better than arm 1 and stop accrual to arm 1 if applicable. If H02 is not rejected (p-value > 0.001), then we continue following the trial and proceed to the next interim analysis without any results reporting.

With respect to interim evaluation of Arm 2 vs. Arm 3, if H02 is rejected, then the following hypothesis is tested.

H03: $p2 \leq p3$ vs. HA3: $p2 > p3$

If H03 is rejected (p-value ≤ 0.001), then Arm 2 is declared best and the complete trial results

(superior arm identified) are reported. If H03 is not rejected (p-value > 0.001), then we continue following the trial to the next interim analysis to evaluate Arm 2 vs. Arm 3.

If Arm 3 is better than Arm 2 (p2 < p3), then we compare Arm 3 with Arm 1. The following hypothesis is tested.

H04: p3 ≤ p1 vs. HA4: p3 > p1

If H04 is rejected (p-value ≤ 0.001), then we conclude that the 5-year FFP of Arm 3 is better than Arm 1. We report that Arm 3 is better than arm 1 and stop accrual to arm 1 if applicable. If H04 is not rejected (p-value > 0.001), then we continue following the trial and proceed to the next interim analysis without any results reporting.

With respect to interim evaluation of Arm 2 vs. Arm 3, if H04 is rejected, then the following hypothesis is tested.

H05: p3≤ p2 vs. HA5: p3 > p2

If H05 is rejected (p-value ≤ 0.001), then Arm 3 is declared best and the complete trial results (superior arm identified) are reported. If H05 is not rejected (p-value > 0.001), then we continue following the trial to the next interim analysis to evaluate Arm 2 vs. Arm 3.

Note that if H02 [H04] is rejected but H03 [H05] is not rejected, the trial will continue in order to further evaluate the relative efficacy of arms 2 and 3. A recommendation from the DMC will be sought regarding whether to continue follow-up in Arm 1 and the process for informing arm 1 patients of the findings.

For futility testing, we compare Arm 3 vs. Arm 1 and Arm 2 vs. Arm 1 if applicable. The following hypotheses are tested.

H_{01}: $p_1 \geq p_2$ vs. H_{A1}: $p_1 < p_2$ and H_{03}: $p_1 \geq p_3$ vs. H_{A3}: $p_1 < p_3$

The alternative hypotheses, HA1 (p1 = p2 + 0.1) and HA3 (p1 = p3 + 0.1) will be tested at 0.001 level (the futility nominal significance level). If the computed p-value is less than 0.001 then we will consider stopping the trial in favor of H_{01} or H_{03} and report the results. If we stop the trial for futility, then we will conclude that the 5-year FFP of Arm 1 will be better than Arm 2 or Arm 3 and continue the trial for the other two remaining arms. Otherwise, we will continue the trial.

Table 12: The Schedule for the Planned Interim Analysis

Information Time	Estimated Analysis Time*	Cumulative Accrual in the Three Arms**
0.25	7 years	397
0.50	9 years	794
0.75	11 years	1191
1.0	13 years	1587

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

**The number of eligible patients whose follow-up is at least 5 years from the randomization date

Based on the results of each interim analysis, the following action will be taken and the responsible statistician will recommend to the 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.

13.6 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.

13.7 Reporting the Initial Treatment Analysis (1/8/09)

The analysis reporting the treatment results will be carried out after the criteria for early stopping/reporting are met. Three interim comparisons and one final analysis will be performed for efficacy and futility of the experimental treatment will be carried out as described in Section 13.5.7. The Z-test statistics for the difference between the two rates with the standard errors estimated by Greenwood's method, eq. (1), will be used with an overall significance level of 0.025. 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 proportional hazard model[114] that includes treatment arms, the stratification factors (SV involvement, prostatectomy Gleason score, pre-radiation PSA level, and pathology stage), age, and race (as appropriate).

13.8 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 are White, 15% are Black or African American, 3% are Hispanic, 0.5% are Asian, 0.3% are Pacific Islander and 0.2% are 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**
Hispanic or Latino	N/A	53	53
Not Hispanic or Latino	N/A	1711	1711
Ethnic Category: Total of all subjects	N/A	1764	**1764**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	N/A	6	6
Asian	N/A	9	9
Black or African American	N/A	251	251
Native Hawaiian or other Pacific Islander	N/A	4	4
White	N/A	1494	1494
Racial Category: Total of all subjects	N/A	1764	**1764**

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APPENDIX I (19-Feb-2019)

STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENTS

Assessments ***(May be required for eligibility)***	120 days prior to registration	90 days prior to registration	60 days prior to registration	45 days prior to registration	30 days prior to registration
Prostate biopsy with Gleason score	Prostatectomy Gleason				
History/physical			X		
Digital rectal exam			X		
Performance status	X				
CT or MRI of pelvis*	X				
Bone Scan*	X				
CBC w/ diff		X			
AST or ALT		X			
PSA *					X
Testosterone		X			
Alk phos					Recommended
CT-sim					X
Urethrogram or MRI-sim					Recommended
Tissue for banking	If patient consents				
Blood Plasma Serum†, urine for banking	If patient consents				
AUA SI					X

*And as needed based on reporting requirements.
† Includes serum for beta-amyloid testing.
-Continued on next page-

APPENDIX I
STUDY PARAMETER TABLE: ASSESSMENTS DURING TREATMENT

Assessments	During Treatment		
	Arms 2 & 3: Within 2 wks prior to start of RT	Weekly during RT	During 6th week of RT
History/physical		X	
Performance status		X	
CBC w/ diff	X		X
AST or ALT	X		X
PSA *	X		
Testosterone	X		X
Blood, Plasma, serum†, urine for banking			X
AUA SI	X		X
Adverse event evaluation*		X	
*And as needed based on reporting requirements. † Includes serum for beta-amyloid testing. **-Continued on next page-**			

APPENDIX I
STUDY PARAMETER TABLE: ASSESSMENTS IN FOLLOW-UP

Assessments	**Follow up After RT**									**Long-term Follow up**
	1.5 mo	3 mo	6 mo	9 mo	12 mo (yr1)	q 3 mos. for 1 yr.	q 6 mos. for 6 yrs.	q 6 mo there-after	Annually thereafter	As indicated in Sections 11.2 and 11.3
History/physical		X	X		X		X		X	X
Performance status		X	X		X		X			X
CT or MRI of pelvis*										X
Bone Scan*										X
Digital rectal exam		X	X		X		X		X	X
CBC w/ diff		X	X							
AST or ALT	X*	X*	X							
PSA *	X	X**	X**	X**	X**	X**		X**		X
Testosterone	X	X	X	X	X	X		X		
Urine for banking									Year 5	
Serum†, plasma, for banking		X	X		X				Years 2-6 yrs	
AUA SI		X	X		X		X		X	
EPIC, HSCL-25, EQ-5D, Document use of sexual meds/devices^					X					Year 5
HVLT-R, Trail making A & B, COWAT^					x					Year 5
Adverse event eval*		X	X		X		X		X	X

*And as needed based on reporting requirements.
** If the PSA is ≤ 0.1 ng/mL, PSA will be drawn every 3 months from the completion of radiotherapy for two years, and at 6-month intervals thereafter.
If PSA post-radiotherapy is ≥ 0.2 ng/mL, then continue at 3-month intervals (See Section 11.3.2).
† Includes serum for beta-amyloid testing.
^ Completion of QOL assessments in follow up are for patients who provided consent for the QOL portion of the study prior to QOL closure.

APPENDIX II (10/22/09)

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 nor 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 not classified as T3, but as T2.

Regional Lymph Nodes (N) (1/8/09)

Clinical

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

Pathologic

pNX Regional nodes not sampled
pN0 No positive regional nodes
pN1 Metastases in regional node(s)

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).
***Note: The type of prostatectomy (radical retropubic, perineal, robotic) should be recorded.

AJCC STAGING SYSTEM
PROSTATE, 6th Edition

Distant Metastasis (M)*

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

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

Histopathologic Grade (G)

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

Stage Grouping

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

APPENDIX IV (22JUN2017)

APPENDICES FOR NRG ONCOLOGY BIOSPECIMEN COLLECTION
Blood Collection Kit Instructions
Urine Collection Kit Instructions

Shipping Instructions:

U.S. Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
NRG Oncology Biospecimen Bank- San Francisco 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- San Francisco
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 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.**

APPENDIX IV

BLOOD COLLECTION KIT AND INSTRUCTIONS

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

Kit contents: Sites will have to provide their own blood draw tubes

- Fifteen (15) 1 ml cryovials for first time point, Ten (10) 1 ml cryovials for subsequent timepoints
- Biohazard bags (3) and Absorbent shipping material (3)
- 1 Styrofoam container (inner) and Cardboard shipping (outer) box
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form and Kit Instructions

PREPARATION AND PROCESSING OF SERUM, PLASMA AND WHOLE BLOOD:

(A) Serum (if requested): Red Top Tube

- ❑ Label Five (5) 1ml cryovials for the serum collected. Label them with the NRG Oncology study and case number, collection date, time, and time point, and clearly mark cryovials "serum".

Process:

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

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the Specimen Transmittal Form.

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

- ❑ Label Five (5) 1ml cryovials 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:

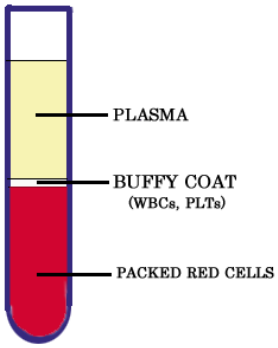
1. After collection of blood into a purple top tube,, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C 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 for the plasma collected into five cryovials 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 Specimen Transmittal Form.

(continued on next page)

APPENDIX IV

BLOOD COLLECTION KIT INSTRUCTIONS (continued)



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

- ❑ Label as many 1ml cryovials (3 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".

Process:

1. After collection of blood into a purple top tube, 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 (3-5) as are necessary for the blood collected 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 Specimen Transmittal Form.

Freezing and Storage:

- ☐ 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).

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

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

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all 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.

(continued on next page)

APPENDIX IV

BLOOD COLLECTION KIT INSTRUCTIONS (continued)

- *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- San Francisco
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

APPENDIX IV (continued)
URINE COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of urine specimens.

Kit Contents:

- One (1) Sterile Urine collection cup
- Two 7 ml disposable pipettes
- Absorbent paper towel
- one-two 15 ml polypropylene centrifuge tubes
- Biohazard bags
- Parafilm for sealing outside of tubes

Preparation and Processing of Urine Specimens:

Process:

- A clean catch urine specimen will be collected. To collect the specimen, use the following instructions:
  - Males should wipe clean the head of the penis and females need to wipe between the labia with soapy water/cleansing wipes to remove any contaminants.
  - After urinating a small amount into the toilet bowl to clear the urethra of contaminants, collect a sample of urine in the collection cup.
  - After 10-25 mL urine has been collected, remove the container from the urine stream without stopping the flow of urine.
  - Finish voiding the bladder into the toilet bowl.
- Aliquot 5-10 mls of Urine one-two 15 ml polypropylene centrifuge tubes (disposable pipets are provided in the kit). Do not fill with more than 10 mls to avoid cracking of tubes due to expansion during freezing. Replace the cap and tighten on the tubes. Make sure the cap is not cross-threaded or placed on incorrectly or leaking will occur.
- Use parafilm to seal the cap around the outside rim of the urine tube to prevent leakage.
- Discard remaining Urine and collection cup.
- Clearly label the specimen with the NRG Oncology study and case number, collection date and time, time point of collection, and clearly mark specimens as “urine”. Labels can fall off at cold temperatures so label the tube with a sharpie first before using a label, or don’t use a sticky label.
- Wrap Urine Tubes with absorbent material (paper towels) and place into biohazard bag and seal the bag. Freeze and store Urine samples in a -20°C or -80°C freezer until ready to ship.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED with NRG Oncology study and case numbers, collection date/time, and time point collected (e.g. pretreatment, post-treatment).

Storage and Shipping:

Freezing and Storage:

- ❑ Urine specimens may be sent in batches or with other frozen biospecimens, if within 30-60 days of collection. Store at -20°C or -80°C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:
  - Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
  - Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all NRG Oncology paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- ❑ Place sealed 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.***
- ❑ Samples received thawed will be discarded, and a notification will be sent immediately to the Principal Investigator and Clinical Research Assistant of the submitting institution. The institution should send a subsequent sample, collected as close as possible to the original planned collection date.
- ❑ **For questions regarding ordering, collection, or shipping of a Urine Collection Kit, please e-mail NRGBB@ucsf.edu or call (415)476-7864 or fax (415) 476-5271.**

Shipping Address: FedEx/UPS/Courier address (For all frozen samples)
NRG Oncology Biospecimen Bank - San Francisco
2340 Sutter Street, Room S341, San Francisco, CA 94115
Contact Phone: (415) 476-7864

APPENDIX V (12/10/13)
RTOG 0534 Neurocognitive Battery: Certification Process and Test Instructions

Examiner Certification
Prior to testing a patient, potential examiners must view the training video and take the post-test. Administrators that have previously been certified for RTOG 0525, 0614, or 0825 do not need to go through the training procedure again, but must fax the certification worksheet to Dr. Wefel, and indicate that they have previously been certified. Please note previous certification for RTOG 0212, 0214 and 0424 is not sufficient. Training, which takes 15-30 minutes, will involve review of the forms and instructions for the administration and scoring of the neurocognitive test battery (Hopkins Verbal Learning Test - Revised, Trail Making Test Parts A and B, and Controlled Oral Word Association Test) and discussion of study-specific logistics.

The trainee will then complete a practice assessment for review. This assessment must be faxed to Dr. Wefel (see certification worksheet below), and he will review the results with the trainee. If the trainee demonstrates competency, he/she will be approved to administer the tests to study subjects as part of RTOG 0534. Dr. Wefel will fax his approval to the CTSU for documentation and to ensure that only certified examiners are testing subjects on RTOG 0534.

Examiner Certification Worksheet
This worksheet must be completed and signed by the person requesting certification and submitted to Dr. Wefel prior to the registration of patients to RTOG 0534.

_____(Y) 1. Have you reviewed the Neuropsychological Test Instructions in Appendix VI of the 0534 protocol?

_____(Y) 2. Have you been trained by Dr. Wefel at an RTOG meeting or by teleconference, watched the 0534 Neuropsychological Test Administration video, or previously been certified for RTOG 0525, 0614, or 0825 within the past 6 months?

_____(Y) 3. Have you completed and submitted the post-test associated with the training video and a "practice" neuropsychological assessment?

_____(Y) 4. Have you contacted Dr. Wefel (See Section 11.9) for test translations and found that no translations are available for your institution?

_____ _____
Signature of test administrator Date
(Person who read Appendix VI, completed a RTOG meeting training or teleconference or watched video and completed the "practice" Neuropsychological Assessment)

_____ _____
Printed name of test administrator Institution number/Name-NCI Code

_____ _____
Telephone number of test administrator Fax number of test administrator

If you have any questions regarding the certification, please contact Dr. Wefel. Once you have completed this form, please attach the Neuropsychological Assessment forms from the "practice" individual and the training video post test and and fax to:

Dr. Jeffrey S. Wefel; phone: 713.563.0514; **FAX: 713.794.4999**; e-mail: jwefel@mdanderson.org

For Dr. Wefel's Use Only (*To fax to 215-569-0206, CTSU)*

_____(Y/N) The above individual has been certified for administering the neurocognitive assessments for this study.

Signature_____ Date_____

Testing: General Information

1. As noted above, copies of the test forms and summary sheets for the first case from each site must be faxed to Dr. Wefel for review.
2. Testing should be completed in one session. Test instructions must be followed verbatim with every patient at every assessment visit.
3. Tests should be administered in the following order to every patient and at each assessment visit: HVLT-R Part A (Learning Trials); Trail Making Test Part A; Trail Making Test Part B; COWAT; HVLT-R Part B (Delayed Recall); and the HVLT-R Part C (Delayed Recognition).
4. Follow the instructions on the Forms Packet Index before submitting forms to RTOG.
5. All test results are recorded on the Neurocognitive Evaluation Summary Form (CS), which is found in the Forms Packet. Study/case-specific labels must be applied to all forms.
6. **Note**: Test results are not submitted to Dr. Wefel, nor to RTOG Headquarters (test results are recorded on forms and submitted). Sites should keep all original test records, and test results must remain on file at the institution as source documentation pending request for submission by RTOG or a Study Chair. In the event of questions, contact Dr. Wefel.
7. Patients should not be given copies of their tests to avoid learning the material between test administrations.
8. The HVLT-R and the COWAT have alternate forms or versions in order to reduce the effects of practice. See the test instructions below for the versions to be administered at pre-treatment and subsequent sessions. The forms should continue to be alternated in this order for the duration of the study. The forms packet will contain alternate versions of these neuropsychological tests.

Before dismissing the patient, thank him/her for their cooperation. Remind the patient of their next appointment and that these tests will be repeated.

In the event that a patient cannot complete a given test, please write the reason(s) on the test form AND the data summary form.

Testing: Specific Instructions

Note: Administer the tests in the following order to every patient at each assessment visit.

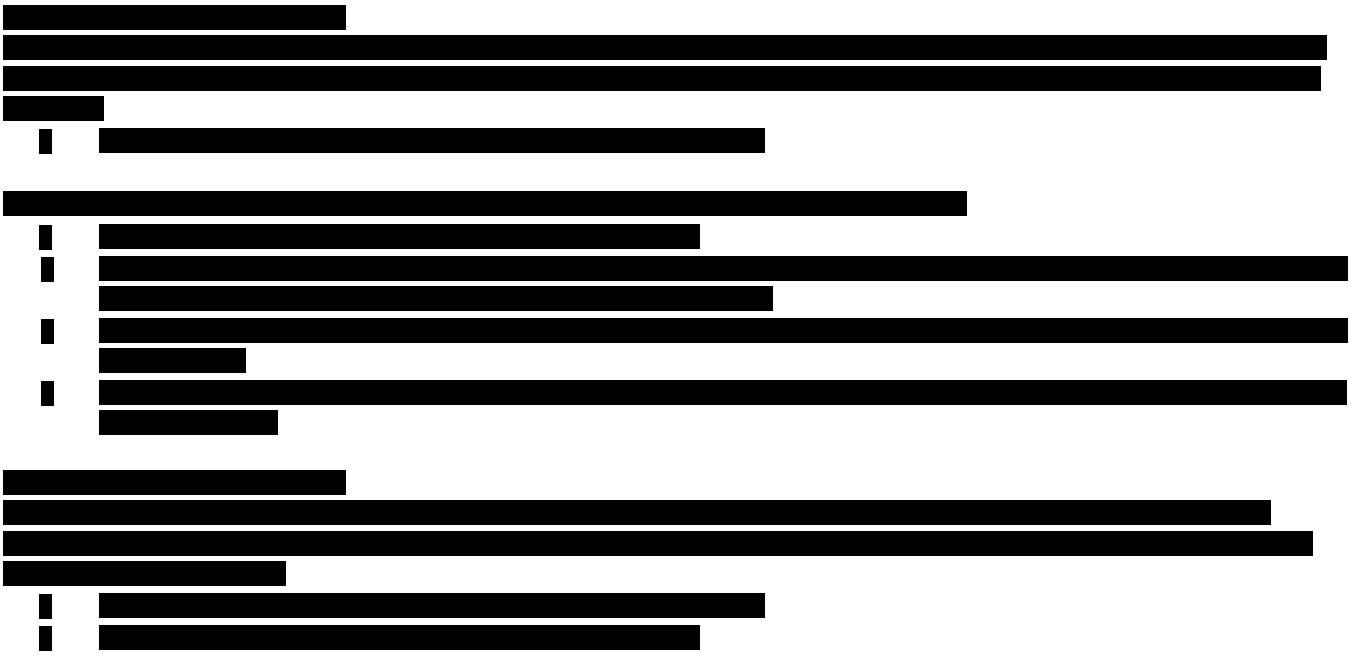
1. HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)

This test has three parts and six alternate forms (only the first 4 forms will be used in this study):

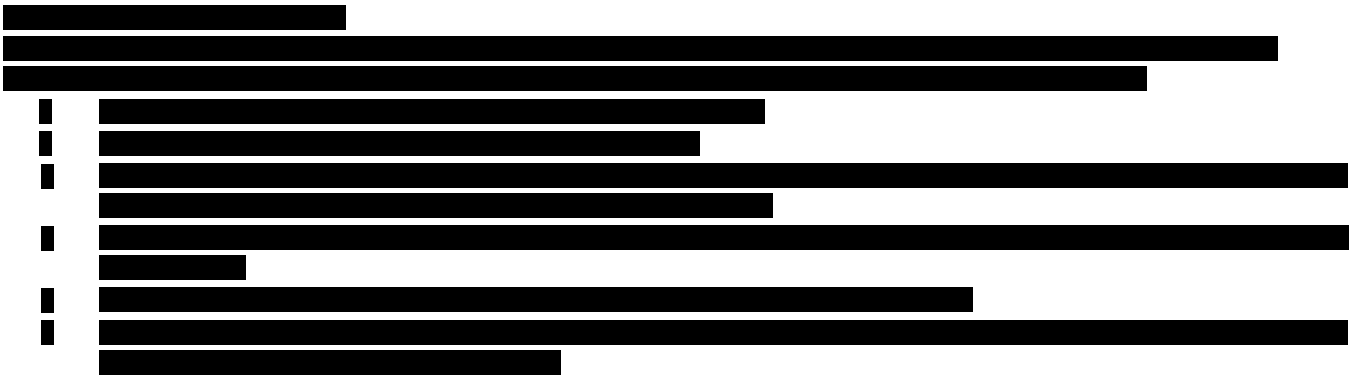
Part A - Free Recall: Complete the three learning trials first

Part B - Delayed Recall: Complete after Trail Making Tests and COWAT

Part C - Delayed Recognition: Complete after Delayed Recall



[redacted]



2. TRAIL MAKING TEST [Timed Test]

Part A – Sample*:* Place the Sample A worksheet flat on the table, directly in front of the patient *(the bottom of the worksheet should be approximately six inches from the edge of the table)*. Give the patient a black pen and say:
Examiner*: "On this page* **(point)** *are some numbers. Begin at number 1* **(point to 1)** *and draw a line from 1 to 2* **(point to 2),** *2 to 3* **(point to 3),** *3 to 4* **(point to 4),** *and so on, in order, until you reach the end* **(point to the circle marked END).** *Draw the lines as fast as you can. Ready, begin."*

If the patient completes Sample A correctly, and in a manner demonstrating that s/he understands what to do, proceed immediately to Test A. If the patient makes a mistake on Sample A, point out the error and explain it. The following explanations of mistakes serve as illustrations:

- ***This is where you start (point to number 1).***
- ***You skipped this circle (point to the circle omitted).***
- ***You should go from number 1 to 2, 2 to 3, and so on, until you reach the circle marked END.***

If it is clear that the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample A, take his/her hand and guide him/her through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on he copy. Then say:
Examiner*: "Remember, begin at number 1 (***point to 1***) and draw a line from 1 to 2 (***point to 2***), 2 to 3 (***point to 3***), 3 to 4 (***point to 4***) and so on, in order, until you reach the circle marked END (***point***). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."*

If the patient does not succeed, or it becomes evident that s/he cannot do the task, DISCONTINUE testing **and** indicate the corresponding reason on the Trail Making Data Sheet. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

Part A – Test: After the patient has completed Sample A, place the Part A test worksheet directly in front of the patient and say:
Examiner*: "Good! Let's try the next one. On this page are numbers from 1 to 25. Do this the same way. Begin at number 1 (***point***) and draw a line from 1 to 2 (***point to 2***), 2 to 3 (***point to 3***), 3 to 4 (***point to 4***) and so on, in order, until you reach the circle marked END (***point***). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."*

- Start timing as soon as the instruction is given to "begin"

- Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred
- The patient must complete the test in **3 minutes** or less.
- **DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED "END".**
- Collect the worksheet and record the time to completion on the Trail Making Data Sheet in minutes and seconds
- If the patient does not complete the test within **3 minutes** terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Collect the worksheet and complete the Trail Making Data Sheet indicating the reason the test was terminated and the last correct number reached on the test.

Part B – Sample: Place the Sample B worksheet flat on the table, directly in front of the patient (the bottom of the worksheet should be approximately six inches from the edge of the table) and say:
Examiner*: "On this page (***point***) are some numbers and letters. Begin at number 1 (***point to 1***) and draw a line from 1 to A (***point***), A to 2 (***point to 2***), 2 to B (***point to B***), B to 3 (***point to 3***), 3 to C (***point to C***) and so on, in order, until you reach the end (***point to the circle marked END***). Remember, first you have a number (***point to 1***), then a letter (***point to A***), then a number (***point to 2***), then a letter (point to B), and so on. Draw the lines as fast as you can. Ready, begin."*

If the patient completes Sample B correctly, and in a manner demonstrating that s/he understands what to do, proceed immediately to Part B. If the patient makes a mistake on Sample B, point out the error and explain it. The following explanations of mistakes serve as illustrations:

- ***You started with the wrong circle. This is where you start (point to number 1)***
- ***You skipped this circle (point to the circle omitted)***
- ***You should go from number 1 (***point***) to A (***point***), A to 2 (***point to 2***), 2 to B (***point to B***), B to 3 (***point to 3***) and so on, until you reach the circle marked END (***point***).***

If it is clear the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample B, take their hand and guide them through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. Then say:
Examiner*: "Now you try it. Remember, begin at number 1 (***point to 1***) and draw a line from 1 to A (***point to A***), A to 2 (***point to 2***), 2 to B (***point to B***), B to 3 (***point to 3***) and so on, in order, until you reach the circle marked END (***point***). Ready, begin."*

If the patient does not succeed or it becomes evident that s/he cannot do the task, DISCONTINUE testing **and** indicate the corresponding reason on the Trail Making Data Sheet. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

Part B – Test:
After the patient has completed Sample B, place the Part B Worksheet directly in front of the patient and say:
Examiner*: "Good! Let's try the next one. On this page are both numbers and letters. Do this the same way. Begin at number 1 (***point***) and draw a line from 1 to A (***point to A***), A to 2 (***point to 2***), 2 to B (***point to B***), B to 3 (***point to 3***), 3 to C (***point to C***) and so on, in order, until you reach the circle marked END (***point***). Remember, first you have a number (***point to 1***), then a letter (***point to A***), then a number (***point to 2***), then a letter (***point to B***), and so on. Do not skip around, but go from one circle to the next in the proper order. Draw the lines as fast as you can. Ready, begin."*

- Start timing as soon as the instruction is given to "begin".
- Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred
- The patient must complete the test in **5 minutes** or less.
- **DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED "END".**
- Collect the worksheet and record the time to completion on the Trail Making Data Sheet in minutes and seconds.

- If the patient does not complete the test within **5 minutes** terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Collect the worksheet and complete the Trail Making Data Sheet indicating the reason the test was terminated and the last correct number or letter reached on the test.

3. CONTROLLED ORAL WORD ASSOCIATION TEST (COWAT) [Timed Test]

[redacted]

[redacted]

4. HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)

[redacted]