NRG ONCOLOGY

NRG-GU003

(ClinicalTrials.gov NCT #: **03274687***)*

A RANDOMIZED PHASE III TRIAL OF HYPOFRACTIONATED POST-PROSTATECTOMY RADIATION THERAPY (HYPORT) VERSUS CONVENTIONAL POST-PROSTATECTOMY RADIATION THERAPY (COPORT)

Amendment 1: April 26, 2019

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(ClinicalTrials.gov NCT # 03274687)(26-APR-2019)

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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 Group; and SWOG.

Coordinating Center:
NRG Oncology
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Study Team *(26-APR-2019)*

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

Document History

	VersionDate	Broadcast Date
Amendment 1	**April 26, 2019**	**N/A**
Activation	June 26, 2017	July 28, 2017

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CONTACT INFORMATION(26-APR-2019)		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the 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.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
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 Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For clinical questions, contact the Study PI of the Lead Protocol Organization. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (via the contact list on the protocol cover page). For radiation therapy-related eligibility questions, please contact RTQA (via the contact list on the protocol cover page).		
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.		
The CTSU Website is located at https://www.ctsu.org.		

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SCHEMA

STEP 1 REGISTRATION
Completion of the Step 1 eligibility checklist then completion of the Step 1 registration process

↓

STEP 2 RANDOMIZATION
Completion and submission of the Expanded Prostate Composite Index (EPIC)

Completion and submission of the step 2 eligibility checklist

STRATIFY

1. Baseline EPIC score group (A vs. B vs. C vs. D)
   A = high bowel and urinary scores
   B = high bowel and low urinary scores
   C = low bowel and high urinary scores
   D = low bowel and urinary scores†

2. Androgen Deprivation Therapy (Yes vs. No)

↓ ↓

ARM I (COPORT)

Radiation Therapy:*
66.6 Gy in 37 fractions of 1.8 Gy to the prostate bed;
EQD_2 (1.5 Gy) = 63 Gy

ARM II (HYPORT)

Radiation Therapy:*
62.5 Gy in 25 fractions of 2.5 Gy to the prostate bed;
EQD_2 (1.5 Gy) = 71 Gy

*ADT is allowed and if given, no more than 6 months will be administered
**Lymph node RT is not permitted.
†High bowel score > 96, low bowel score ≤ 96, high urinary score > 84, low urinary score ≤84
Accrual goal = 282

1. OBJECTIVES

1.1 Primary Objective

The primary objective is to demonstrate that hypofractionated post-prostatectomy radiotherapy (HYPORT) does not increase patient-reported GI and GU symptoms over conventionally fractionated post-prostatectomy (COPORT) at the 2-year time point.

1.2 Secondary Objectives

- To compare patient-reported GI symptoms using the EPIC at end of RT and 6, 12, 24, and 60 months from end of treatment;
- To compare patient-reported GU symptoms using the EPIC at end of RT and 6, 12, 24, and 60 months from end of treatment;
- To compare time to progression (TTP) where progression is defined as the first occurrence of biochemical failure (BF), local failure, regional failure, distant metastasis (DM), institution of new unplanned anticancer treatment, or death from prostate cancer (PCSM);
- To compare freedom from biochemical failure (FFBF) and TTP rates with an alternate PSA ≥ PSA nadir + 2 ng/mL definition of BF;
- To compare local failure, regional failure, salvage therapy (i.e. institution of new unplanned anticancer treatment), DM, PCSM, and overall survival (OS) rates;
- Assessment of adverse events;

1.3 Exploratory Objectives

- To compare utilities for health outcomes using the EQ-5D;
- Paraffin-embedded tissue block, serum, plasma, whole blood, and urine for future translational research analyses for predictors of toxicity following hypofractionated or conventionally fractionated post-prostatectomy radiotherapy. Note: Testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

2. BACKGROUND

STUDY DISEASE

2.1 Prostate Cancer is the Second Most Common Cancer in Men

Worldwide, prostate cancer is the second most frequently diagnosed cancer of men (1,111,689 new cases, representing 15% of the total in 2012) and the fifth most common cancer overall. Prostate cancer is the sixth leading cause of death from cancer in men (6.6% of the total). It is predicted that the number of cases will almost double by 2030. (GLOBOCAN 2012)

Radical Prostatectomy is the Most Common Treatment for Prostate Cancer

Radical prostatectomy is the most common treatment for prostate cancer according to the National Cancer Institute's Patterns of Care study from 14 regional cancer registries.[4] The proportion of men undergoing prostatectomy was 70% for age <60 years, 51% for 60-64 years, and 39% for 65-75 years. (Hamilton 2011)

Adjuvant and Salvage Therapy

An estimated 15-25% of prostatectomy patients will develop a prostate specific antigen (PSA) recurrence. (Stephenson 2012) High-risk features for recurrence include extra-capsular extension and/or seminal vesicle invasion (pT3 disease) and positive surgical margins, which occur in an estimated 20% and 16% of patients, respectively. (Tewari 2012) Post-prostatectomy radiotherapy (RT) to the prostate bed for pT3 disease or positive surgical margins has been shown to reduce the risk of recurrence in three randomized trials: Southwest Oncology Group (SWOG) (Thompson 2006); European Organization for Research and Treatment of Cancer (EORTC) (Bolla 2012); and Auckland Radiation Oncology (ARO). (Wiegel 2009) As a result, post-prostatectomy RT is a well-accepted practice standard for adverse pathologic features following surgery or at the first sign of PSA recurrence. (Prostate Cancer 2016, Thompson 2013)

Rationale for Dose Escalation

2.1.1 Lessons From Intact Prostate RT

Central to the success of RT for intact prostate cancer has been dose escalation where an additional 8 - 10 Gy in 2 Gy fractions has been shown to effectively reduce the risk of biochemical failure (BF) [Dearnaley 2007, Fuks 1991, Kuban 1987, 1989, 2008, 2011, Zietman 2010], as well as prevent distant metastasis and death (Kuban 2011). The eradication of local disease for intact prostate cancer has also been shown to reduce the risk of distant metastasis and death from prostate cancer (Coen 2002, Zelefsky 2008, Kuban 1987, Fuks 1991). Rectal complications have been the primary dose limiting toxicity with dose escalation.

2.1.2 Post-prostatectomy Dose Escalation

Radiotherapy dose escalation is rooted in the fundamental radiobiological principle that higher doses are needed to eradicate an increasing burden of disease (Hall 2012). A biochemical tumor control probability (TCP) analysis of dose–response curves for adjuvant and salvage post-prostatectomy RT has estimated a 3%/Gy improvement in FFBF with dose escalation (2.6%/Gy, 95% CI, 2.3–3.0 for adjuvant; 3.8%/Gy, 95% CI, 2.5–7.6 for salvage) [King 2008]. Various treatment planning studies have shown that adequate rectal sparing for dose escalation in the > 70 Gy in 2 Gy fraction range is achievable with modern RT techniques employing image guidance [Bernard 2010, De Meerleer 2008, King 2008, Harrison 2011]. Several studies have indicated a benefit to dose escalation post-prostatectomy (King 2008b, King 2008a, Cozzarini 2009, Valicenti 1998, Anscher 2000). And clinical studies have indicated the risk of toxicity with RT dose ≥ 70 Gy in 2 Gy fractions is low with less than 3% of late grade 3 proctitis or genitourinary side effects, respectively (De Meerleer 2008, Wiegel 2009, Van Der Poel 2008, Feng 2007, Hunter 2012).

2.2 Rationale for Hypofractionation

2.2.1 Hypofractionation Definition

Post-prostatectomy RT has traditionally been delivered in conventional fractionation (i.e. 1.8 or 2.0 Gy per fraction) that can take as long as 6 to 8 weeks to deliver (Thompson 2009, Bolla 2005, Wiegel 2009). The proposed study explores an alternative RT dose-fractionation schedule that exploits the radiobiological properties of prostate cancer to shorten overall treatment time called hypofractionation. Hypofractionation uses larger

daily fraction sizes (i.e. 2 to 5 Gy) to deliver a RT over a shorter duration.

2.2.2 Hypofractionation Advantages

The potential advantages of hypofractionation are: 1) increased convenience to patients because of fewer treatment days, 2) reduced cost to patients because of reduced travel expenses and copays, 3) improved resource utilization for physicians because of the fewer number of treatments per patient and overall, 4) and consequently reduced cost to society. All of these factors may increase the utilization of post-prostatectomy RT, which is estimated to be < 20% for patients with pT3 disease and positive margins who are most likely to benefit, and unaltered by the results of the randomized trials (Ghia 2010, Hoffman 2011). In prostate cancer specifically, hypofractionation has the added potential advantage of not increasing toxicity (primary endpoint of Phase II) compared to standard fractionation, while delivering a higher biological dose and therefore increase efficacy (primary endpoint for Phase III).

2.2.3 Similarities to Breast Hypofractionation

This proposed trial mirrors the practice changing Ontario Clinical Oncology Group (OCOG) [Whelan 2010], UK Standardization of Breast Radiotherapy (START) Trial A (Bentzen 2008a), and START Trial B (Bentzen 2008b) breast cancer trials that sought the advantages of hypofractionation following lumpectomy for early-stage breast cancer and redefined the standard of care (Smith 2011). There are three important comparisons between the current trial and the breast trials: 1) the rationale for hypofractionation, 2) the reduction in overall treatment time, and 3) the primary endpoint. Regarding the rationale, hypofractionation for breast cancer has evolved on an empirical basis, while prostate hypofractionation has evolved more closely rooted to radiobiologic modeling. Furthermore, the magnitude of the radiobiologic advantage for hypofractionation for breast cancer is three times less than that of prostate cancer. Second, the reduction in overall treatment duration with breast hypofractionation is less compared to prostate cancer: 13-14 total treatment days for breast, and 18 days for prostate.

Last, the primary endpoint for the breast trials employed a local control primary endpoint, opposed to a survival based end-point, which is similar to a BF endpoint in prostate cancer because both local and distant recurrences are counted. The publication of the breast cancer hypofractionation trials has led to practice changes in the US and internationally. Therefore, similar if not more enthusiasm is expected for HYPORT that could also change the international standard of care.

2.2.4 Intact Prostate Hypofractionation

Results from definitive in-tact prostate hypofractionation from the Cleveland Clinic Phase II trial (Kupelian 2007, Kupelian 2005), the Fox Chase Phase III trial (Pollack 2011, Pollack 2006), and the Italian Phase III trial (Arcangeli 2012, Arcangeli 2011, Lee 2016) indicate that hypofractionation over 5 weeks is at least as effective and not more toxic than conventional fractionation with fraction sizes of 2.5 Gy, 2.7 Gy or 3.1 Gy, respectively. Therefore, at least similar effectiveness with hypofractionation in the proposed trial is hypothesized.

2.2.5 Preliminary HYPORT Data

The preliminary post-prostatectomy dose-escalated hypofractionation experience from the University of Wisconsin has demonstrated promising efficacy and acceptable toxicity delivering 65 Gy in 26 fractions of 2.5 Gy to the prostate bed. The 4-year actuarial PFS rate was 67.0% with a median overall follow-up of 32.4 months (range, 5.8-70.5) [Kruser

2011]. And, in a subset analysis of the first 50 patients, with a longer median follow-up of 43 months, actuarial 5-year PFS was also 67.0%. Acute grade 2 or greater GU toxicities were noted in 8 (7%) patients. And at last follow-up, only 3 (3%) patients had grade 2 late GU toxicity. Acute grade 3 GU toxicity (obstruction) was noted in only one patient with previous bladder neck contracture. No acute grade 4 or late grade ≥ 3 urinary toxicities were documented. Acute grade 2 gastrointestinal (GI) toxicities occurred in 15 (14%) patients, consisting of rectal pain requiring medication (n = 4), diarrhea requiring medication (n = 6), and/or bleeding or hemorrhoid exacerbation (n = 6). No acute grade ≥ 3 GI toxicities were noted. Late grade 2 GI toxicities were noted in 4 (4%) patients, all consisting of radiation proctitis. Two of these patients had endoscopic cautery to treat rectal bleeding. At the time of last follow-up, one patient had grade 2 late GI toxicity. No late grade ≥ 3 GI toxicities were documented.

2.2.6 Dose-escalated Hypofractionation

The traditional method for equating doses delivered in varying fractionation employs the linear-quadratic equation that can calculate a biologic equivalent dose (BED) and derive an iso-effective dose in 2 Gy fractions (EQD2) assuming an α/β for the tissue of interest. The α/β is a measure of the sensitivity to fraction size and lower values are less sensitive. Tissues with a small α/β ratio (i.e., 2 – 4 Gy) are more sensitive to changes in fractionation than tissue with a large α/β ratio (i.e., >8 Gy).

Table 1 shows the EQD2 values for the University of Wisconsin experience assuming an α/β of 1.5 Gy for prostate (Leborgne 2012, Vogelius 2013, Proust-Lima 2011, Dasu 2007, Dasu 2012) and 5 Gy for rectum (Brenner 2004). The α/β for bladder is not as well defined and may range from 3 to 10 Gy (Hall 2012, van der Kogel 2009). An α/β for bladder for the purpose of this trial is conservatively assumed to be 3 Gy. The low toxicity observed with this fractionation schedule (see Section 2.2.5) is in agreement with the reports of acceptable toxicity with EQD2 escalation ≥ 70 Gy in conventional fractionation (De Meerleer 2008, Wiegel 2009, Van Der Poel 2008, Feng 2007, Hunter 2012, Goenka 2012).

Table 1: EQD_2 values for COPORT and *α/β* values for prostate, bladder, and rectum

D (Gy)	*d* (Gy)	*α/β* (Gy)	EQD_2 (Gy)
75	2.5	1.5 (prostate cancer)	74
75	2.5	3 (bladder)	72
75	2.5	5 (rectum)	70

Abbreviations: COPORT = conventionally fractionated post-prostatectomy radiotherapy; *D* = total dose; *d* = fraction size; EQD_2 = equivalent dose in 2 Gy fractions

2.2.7 Selection of RT Doses for COPORT and HYPORT

COPORT, ARM I, 66.6 Gy in 37 fractions of 1.8 Gy over approximately 7.4 weeks

Adjuvant RT Dose: The three randomized trials supporting adjuvant post-prostatectomy

RT used a range of doses from 60 - 64 Gy in 2 Gy fractions (Thompson 2006, Bolla 2005, Wiegel 2009).

Standard Fraction Size: A fraction size of 1.8 Gy is preferred for ARM I because the NRG Oncology standard for conventional fractionation is 1.8 Gy with which the RTOG/NRG Oncology has enjoyed great success in trial completion. The reported post-prostatectomy trial RTOG 9601 (Shipley 2010) and not yet reported RTOG 0534 (NCT00567580) have used 1.8 Gy per fraction. It is unknown if there will be similar success with a fractions size of 2 Gy. Therefore, the conventional arm of the proposed trial will be consistent with other NRG Oncology/RTOG legacy trials, which is based on 1.8 Gy fractions.

Equivalent Dose Calculation For COPORT: Table 2 shows the EQD2 values for COPORT. The 66.6 Gy dose is preferred for COPORT because: 1) the EQD2 for prostate cancer falls within the ranges of doses used the randomized trials of adjuvant RT (Thompson 2006, Bolla 2005, Wiegel 2009), 2) it is in agreement with patterns of salvage RT that will also be used in the trial (Stephenson 2007), and 3) it was preferred by the NRG Oncology GU steering committee.

Table 2: EQD_2 values for COPORT and α/β values for prostate, bladder, and rectum

D (Gy)	*d* (Gy)	α/β (Gy)	EQD_2 (Gy)
66.6	1.8	1.5 (prostate cancer)	63
66.6	1.8	3 (bladder)	64
66.6	1.8	5 (rectum)	65

Abbreviations: COPORT = conventionally fractionated post-prostatectomy radiotherapy; *D* = total dose; *d* = fraction size; EQD_2 = equivalent dose in 2 Gy fractions

HYPORT, ARM II, 62.5 Gy in 25 fractions of 2.5 Gy over 5 weeks

A 2.5 Gy fraction size is preferred for HYPORT because: 1) it is identical to the fraction size used in the University of Wisconsin prostate bed hypofractionation Phase II trial that provides preliminary toxicity and efficacy data (Kruser 2011), 2) it is identical to the fraction size used in the hypofractionated arm of the randomized trial RTOG 0415 (NCT00331773) that provides EPIC results for the Phase II sample size calculation, and 3) it is in line with the fraction sizes used by the Cleveland Clinic (Kupelian 2007, Kupelian 2005) and Fox Chase (Pollack 2011, Pollack 2006).

Equivalent Dose Calculation For HYPORT: The trial is designed such that the HYPORT dose represents an 8 Gy dose escalation compared to COPORT. HYPORT is designed to deliver an EQD2 for prostate cancer of 71 Gy (i.e. 63 Gy + 8 Gy), which is equivalent to 62.5 Gy in 2.5 Gy fractions. Table 3 shows EQD2 values for the prostate, rectum, and bladder with HYPORT.

Table 3: EQD_2values for HYPORT and α/β values for prostate, bladder, and rectum

D (Gy)	*d* (Gy)	α/β (Gy)	EQD_2 (Gy)
62.5	2.5	1.5 (prostate cancer)	71
62.5	2.5	3 (bladder)	69
62.5	2.5	5 (rectum)	67

Abbreviations: HYPORT = hypofractionated post-prostatectomy radiotherapy; *D* = total dose; *d* = fraction size; EQD_2= equivalent dose in 2 Gy fractions

While there is dose escalation hypothesized for the rectum and bladder with HYPORT compared to COPORT, radiobiologically equivalent rectal and bladder treatment planning dose constraints will be used to safeguard against the risk of greater rectal and/or bladder toxicity with HYPORT related to dose escalation.

2.3 This trial is important because:

- It is the only Phase III trial in the world exploring hypofractionation in the postoperative arena.
- It may redefine the standard of care to include HYPORT. The potential advantages of HYPORT are:
    - Increase access for patients to postprostatectomy radiotherapy because of fewer treatment days,
    - Increase convenience to patients because of fewer treatment days,
    - Reduced cost to patients because of fewer travel expenses and copays,
    - Improved resource utilization for physicians because fewer number of treatments per patient and overall,
    - Reduced cost to society,
    - Increased RT utilization,
    - Improved efficacy of radiation treatment due to biological dose escalation.

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILTY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (via the contact list on the NRG web site). For radiation therapy-related eligibility questions, please contact RTQA (via the contact list on the NRG web site).

3.1 Patient Selection Guidelines

Although the guidelines provided below are not inclusion/exclusion criteria, investigators

should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up, including all quality of life surveys through 5 years of follow-up.

3.2 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

Prior to Step 1 Registration

3.2.1 Adenocarcinoma of the prostate treated primarily with radical prostatectomy.

- Any type of radical prostatectomy will be permitted, including retropubic, perineal, laparoscopic or robotically assisted. There is no time limit for the date of radical prostatectomy.

3.2.2 One of the following pathologic T-classifications: pT2 or pT3.

- Patients with positive surgical margins are eligible.

3.2.3 One of the following pathologic N-classifications: pN0, pNX.

- If a lymph node dissection is 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 whenever possible.

3.2.4 No clinical evidence of regional lymph node metastasis.

- CT (with contrast if renal function is acceptable; a noncontrast CT is permitted if the patient is not a candidate for contrast), MRI, nodal sampling, or dissection of the pelvis within 120 days prior to Step 1 registration.
- Patients with pelvic lymph nodes equivocal or questionable by imaging are eligible if the nodes are ≤ 1 cm in the short axis.

3.2.5 A post-radical prostatectomy study entry PSA ≥45 days after prostatectomy and within 30 days prior to Step 1, < 2.0 ng/mL.

3.2.6 No evidence of a local recurrence in the prostate fossa based on a digital rectal examination (DRE) within 60 days prior to Step 1 registration.

- Patients with equivocal or questionable DRE findings should have an MRI of the pelvis to exclude the presence of a prostate fossa mass.
- Patients with equivocal or questionable exam findings by DRE or MRI are eligible if a biopsy of the lesion is negative for tumor.

3.2.7 No evidence of bone metastases (M0) on bone scan (Na F PET/CT is an acceptable substitute) within 120 days prior to Step 1 registration.

- Equivocal bone scan findings are allowed if plain films and/or MRI are negative for metastasis.

3.2.8 Zubrod Performance Status 0-1 within 60 days prior to Step 1 registration.
3.2.9 Age ≥ 18
3.2.10 The patient or a legally authorized representative must provide study-specific informed consent prior to Step 1 registration.
3.2.11 Willingness and ability to complete the Expanded Prostate Cancer Index Composite (EPIC) questionnaire (**see Section 11.2.1**).
3.2.12 Only English and French-speaking patients are eligible to participate as these are the only language the EPIC has been validated in.

Prior to Step 2 Registration
3.2.13 The EPIC must be completed in full and entered within 10 business days after Step 1 registration. NRG Oncology Statistical and Data Management Center has 3 business days to score the results and send a notification to the site to proceed to Step 2 Randomization.

3.3 Ineligibility Criteria

Patients with any of the following conditions are NOT eligible for this study.

3.3.1 A post-prostatectomy PSA nadir ≥ 0.2 ng/mL AND Gleason ≥ 7 (Considered for NRG-GU002, PI: Hurwitz).
3.3.2 pT2 with a negative surgical margin and PSA < 0.1 ng/mL
3.3.3 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.
3.3.4 Androgen deprivation therapy started after prostatectomy and prior to Step 1 registration for > 6 weeks (42 days).
3.3.5 Neoadjuvant chemotherapy before or after prostatectomy.
3.3.6 Prior invasive (except non-melanoma skin cancer) malignancy unless disease-free for a minimum of 3 years and not in the pelvis. (For example, carcinoma in situ of the oral cavity is permissible if disease free for a minimum of 3 years; however, patients with prior history of bladder cancer are not allowed no matter the disease free duration). Prior hematological (e.g., leukemia, lymphoma, myeloma) malignancy is not allowed.
3.3.7 Previous chemotherapy for any other disease site if given within 3 years prior to Step 1 (see Section 3.3.6).
3.3.8 Prior radiotherapy, including brachytherapy, to the region of the study cancer that would result in overlap of radiation therapy treatment volumes.
3.3.9 Severe, active co-morbidity, defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
- Transmural myocardial infarction within the last 6 months
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of Step 1 registration

- Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of Step 1 registration
- Severe hepatic disease, defined as a diagnosis of Child-Pugh Class B or C hepatic disease
- HIV positive with CD4 count < 200 cells/microliter. Note that patients who are HIV positive are eligible, provided they are under treatment with highly active antiretroviral therapy (HAART) and have a CD4 count ≥ 200 cells/microliter within 30 days prior to registration. Note also that HIV testing is not required for eligibility for this protocol.
- End-stage renal disease (ie, on dialysis or dialysis has been recommended)

3.3.10 Prior allergic reaction to the study drugs involved in this protocol

3.3.11 History of inflammatory bowel disease, prior bowel surgeries (or colostomy) for any reason, or prior partial/radical cystectomy for any reason

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP (26-APR-2019)

PRE-TREATMENT ASSESSMENTS

Assessments	**Time Point *(may be required for eligibility)***			
	No more than 120 days prior to Step 1 registration	No more than 90 days prior to Step 1 registration	No more than 60 days prior to Step 1 registration	No more than 30 days prior to Step 1 registration
History & Physical with DRE and Zubrod Performance Status (required)			X	
Serum PSA (required)				X
CT/MRI (Pelvic +/- Abdominal)	X			
Bone scan (required) *(see Section 3.2.7)*	X			
EPIC (required)	Completed and submitted prior to Step 2 registration			
EQ-5D	Completed and submitted prior to Step 2 registration			
Whole blood, serum, plasma, & urine *(if patient consents, see section 10)*	Pre-radiation therapy			

ASSESSMENTS DURING TREATMENT (radiotherapy)

Assessment	Time Point	
Assessment	Weekly	Last Week
History & Physical and AE evaluation	**X**	
Serum, plasma, and urine *(if patient consents)* See Section 10		**X**

ASSESSMENTS IN FOLLOW UP ARE TO BE SCHEDULED FROM THE START OF RADIATION STARTING FROM 6 MONTHS

Assessment	End of RT	q 6 months during yrs 1-2	1 year	2 year	q 12 months during yrs 3-5	5 years	Yearly after 5 yrs
Physical exam with DRE		**X**			**X**		**X**
Serum PSA	**X**	**X**			**X**		**X**
AE evaluation	**X**	**X**			**X**		**X**
EPIC *(required)*	**X**	**X (only at 6 months)**	**X**	**X**		**X**	
EQ-5D	**X**	**X (only at 6 months)**	**X**	**X**		**X**	
Serum & plasma *(if patient consents)*			**X**				

Definition of Disease Assessments

- Biochemical failure: Two definitions of biochemical failure will be assessed:
  - Primary: PSA ≥ 0.4 ng/mL and rising (i.e. PSA ≥ 0.4 ng/mL followed by a value higher than the first by any amount) or initiation of salvage hormones.
  - Alternate: PSA ≥ PSA nadir + 2 ng/mL where nadir is the lowest post-RT PSA level.
- Local failure: development of a new biopsy-proven mass in the prostate bed, after enrollment in the protocol.

- Regional failure: radiographic evidence (CT or MRI) of lymphadenopathy (lymph node size ≥ 1.0 cm in the short axis) in a patient without the diagnosis of a hematologic/lymphomatous disorder associated with adenopathy.
- Distant metastases: radiographic evidence of hematogenous spread (e.g., bone scan, CT, MRI)
- Progression: first occurrence of biochemical failure, local failure, regional failure, distant metastasis, initiation of new unplanned anticancer treatment, or death from prostate cancer.

5. TREATMENT PLAN/REGIMEN DESCRIPTION

5.1 Chemotherapy/Hormonal Therapy/Other Agent-Based Therapy

For patients receiving RT + androgen deprivation therapy (ADT), ADT may begin at any time following Step I registration but prior to the start of RT. ADT prior to Step I registration is allowed but, patient may have received prior ADT for up to 6 weeks (42 days) prior to Step 1 registration.

5.1.1 Androgen Deprivation Therapy (ADT)

Any LHRH agonist/antagomist with or without an oral antiandrogen can be used; however, ADT cannot be administered for more than a 6 month administration dose (i.e. for Lupron this would be 45 mg, etc.). **An oral antiandrogen alone cannot be used.** The total administered duration as well as the specific agent (s) used will be submitted on the appropriate case report form.

5.2 Radiation Therapy (26-APR-2019)

Start of Radiotherapy (RT)

For patients receiving RT alone (no androgen deprivation therapy [ADT]), RT must begin within 4 weeks after Step 1 registration. For patients receiving RT+ADT, RT must begin 8 weeks (plus or minus 1 week) after the first LHRH analog injection. Patient may have received prior ADT up to 6 weeks (42 days) prior to Step 1 registration.

Radiation Therapy Schema

Schema at the beginning of the protocol should be followed.

5.2.1 Treatment Technology

Photon energies ranging from ^{60}Co to <18 MV are recommended. The following techniques such as 3D CRT, IMRT, VMAT, Viewray, Cyberknife or Tomotherapy are allowed.

5.2.2 Immobilization and Simulation

Immobilization

Proper immobilization is critical for this protocol. Patient setup reproducibility must be achieved

using appropriate clinical devices.

Immobilization of the hips and feet using a cradle should be considered. Each patient will be positioned in the supine position. Prone positioning for treatment is not permitted.

Simulation

Rectal Filling - An overly distended rectum can introduce a systematic positioning error that may increase the probability of missing the clinical target volume (CTV). Patients should be simulated with the rectum as empty as possible and <3 cm in the anterior-posterior dimension is ideal. This can be achieved with an enema 1-2 hours prior to simulation. If the size of the rectum is large due to flatus, a hollow (robnel) catheter introduceted into the rectum may be helpful. Rectal balloons for planning and treatment are not permitted.

Bladder Filling - Patients should also have a comfortably full bladder (the patient should not be uncomfortable at simulation because it is likely that he will have more difficulty maintaining a full bladder during treatment).

Identification of the most inferior portion Prostate Fossa - A retrograde urethrogram or MRI is recommended, but not required, to establish the most inferior portion of the prostate fossa. Note: Use of contrast, other than for the urethrogram, is discouraged.

Image Scanning Parameters - 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. 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.

5.2.3 Imaging for Structure Definition, Image Registration/Fusion and Follow-up

MRI may be used to assist in volume delineation and precision in all eligible patients. However, care should be taken to ensure that the geometric and special orientation of the structure set are accurate on the treatment planning CT because CT is used for the dose calculation and basis for image guidance.

5.2.4 Definition of Target Volumes and Margins

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable.

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Arm 1 (COPORT)		
Standard DICOM Name	**Description**	**Validation**
CTV_6660	Clinical Target Volume receiving 66.6 Gy	Required
PTV_6660	Planning Target Volume receiving 66.6 Gy	Required
Arm 2 (HYPORT)		
Standard DICOM Name	**Description**	**Validation**
CTV_6250	Clinical Target Volume receiving 62.5 Gy	Required
PTV_6250	Planning Target Volume receiving 62.5 Gy	Required

Detailed Specifications

CTV and Critical Structure Volumes
All contouring should be done in accordance with the RTOG consensus recommendations for the prostate bed (Michalski 2010) and normal pelvic structures (Gay 2012). The RTOG contouring atlas for the prostate bed CTV can be accessed at http://www.rtog.org/CoreLab/ContouringAtlases/ProstatePostOp.aspx and for the normal pelvic structures at http://www.rtog.org/CoreLab/ContouringAtlases/MaleRTOGNormalPelvisAtlas.aspx.

CTV
The contouring of the prostate bed should be in accordance with the RTOG consensus guidelines (Michalski 2010). Briefly, the CTV should extend superiorly from the level of the caudal vas deferens remnant to >8-12 mm inferior to vesicourethral anastomosis (VUA). Below the superior

border of the pubic symphysis, the anterior border extends to the posterior aspect of the pubis and 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; posteriorly, it is bounded by the mesorectal fascia. At this level, the lateral border is the sacrorectogenitopubic fascia. Seminal vesicle remnants, if present, should be included in the CTV if there is pathologic evidence of their involvement.

PTV
The PTV margins should be a minimum of 0.7 cm and a maximum of 1.0 cm in all dimensions. Plans must be normalized to cover 95% of the PTV with the prescribed dose. Care should be taken to conform the prescribed dose as closely to the PTV as possible, so as to avoid including the entire width of the rectum in the posterior blocked margin at the bladder neck-rectum interface.

5.2.5 Definition of Critical Structures and Margins

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable.
Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

The normal critical structures are the bladder, rectum, and femoral heads. The normal tissues will be contoured and considered as solid organs.

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

Rectum
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. Care should be taken to avoid bowel as needed.

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

External
The tissue within the skin and outside all other critical normal structures and PTV's is designated as unspecified tissue.

The following table outlines the naming of the various normal and critical structures for submission to RTOG via TRIAD.

Standard DICOM Name	**Description**	**Validation**
Bladder	Bladder	Required
Rectum	Rectum	Required
External	Skin	Required
Femur_L	Left Femur	Required
Femur_R	Right Femur	Required
Femurs	Right Femur + Left Femur	Required

Detailed Specifications

5.2.6 Dose Prescription

Note: The information provided in this section can be used for adjusting the dose constraints for treatment planning purposes. This table together with the planning priority table should be used during dose optimization. It is important to remember that ideal plans might not be achievable in all cases. Thus, the Compliance Criteria table could be different than the information given here. Cases will be scored using the Compliance Criteria table.

Target Standard Name	**Dose (Gy)**	**Fraction Size** (Gy)	**# of fractions**	**Dose specification technique**
PTV_6660	66.60	1.8	37	Covering 95% of PTV
PTV_6250	62.5	2.5	25	Covering 95% of PTV

5.2.7 Compliance criteria

The compliance criteria listed here will be used to score each case. Given the limitations inherent in the treatment planning process, the numbers given in this section can be different than the prescription table. The Per Protocol and Variation Acceptable categories are both considered to be acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is recommended.

Normalization of Dose: The plan is normalized such that at least 95% of the PTV_6660 volume receives prescription dose of 66.6 Gy for ARM I (COPORT) or at least 95% of the PTV_6250 volume receives prescription dose of 62.5 Gy for ARM II (HYPORT).

Note: Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met

Target Volume Constraints and Compliance Criteria

Structure	Dosimetric Parameter	Per Protocol	Variation Acceptable	Deviation Unacceptable
PTV	V100%[%]	>=95	>=94	<94
PTV maximum dose	D0.03cc[%]	<= 115	>115 - <=120	>120
PTV minimum dose	D99%[%]	>= 95	>= 93 – < 95	< 93

Per Protocol range is excluded from Variation Acceptable range.

Normal Structure Constraints and Compliance Criteria

The following normal tissue dose constraints represent the minimum level of acceptablibility for protocol therapy. Whever possible, maximal sparing of normal tissues should be achieved to minimize the risk of toxicity.

Normal Tissue Dose Constraints (ARM I, COPORT)

Structure	Dosimetric Parameter	Per Protocol	Variation Acceptable
Rectum	V40 Gy[%] V65 Gy[%]	< 55 < 35	< 60 < 39
Bladder	V40 Gy[%] V65 Gy[%]	< 70 < 50	< 77 < 55
Femoral Heads	V50 Gy[%]	< 10	< 11

Normal Tissue Dose Constraints (ARM II, HYPORT)

Structure	Dosimetric Parameter	Per Protocol	Variation Acceptable
Rectum	V36 Gy[%] V59 Gy[%]	< 55 < 35	< 60 < 39
Bladder	V35 Gy[%] V57 Gy[%]	< 70 < 50	< 77 < 55
Femoral Heads	V44 Gy[%]	< 10	< 11

Per Protocol range is excluded from Variation Acceptable range.

5.2.8 Treatment Planning Priorities and Instructions

In order of priority, the following critical structure are listed in order of decreasing importance. The following list is given as an example

1. Rectum
2. Bladder
3. Femoral Heads

Dose matrix resolution
Dose grid size should be ≤ 3 mm in all directions.

5.2.9 Patient specific QA

Any patient-specific QA that needs to be acquired should follow institutional guidelines. For IMRT/VMAT plans, patient specific QA is highly recommended. QA is performed by delivering the plan onto a phantom and measuring the dose using an ion chamber array or other 2D/3D device. Measured dose distribution will be compared to planned dose distribution using a Gamma criterion of 3% dose difference and 3 mm distance to agreement. The pass rate should be at least 90% measured for the entire plan.

5.2.10 Daily Treatment Localization/IGRT

Image-guided radiation therapy (IGRT) is radiation therapy using imaging to facilitate accuracy and precision throughout its entire process from target and normal tissue delineation, to radiation delivery, to adaptation of therapy to anatomic and biological changes over time in individual patients. In this section we use the terminology IGRT tofocus on image-guidance at the time of radiation delivery to ensure its adherence to the planned treatment.

At the start of each fraction, patients should be initially positioned by laser alignment of skin surface tattoos.

Daily IGRT is required. Fiducial marker placement is preferred but not required. Daily fiducial based volumetric IGRT is ideal because fiducials aid in the interpretation by radiation therapists. If fiducial markers are not present, volumetric IGRT based on soft-tissue alignment needs to be performed. Finally, volumetric 3D IGRT is preferred because bladder and rectal filling can be assessed for patient coaching purposes. Orthogonal 2D kV imaging requires fiducials. Electromagnetic transponders or transabdominal ultrasound to identify the VUA may also be used for daily IGRT.

Fiducial markers or electromagnetic transponders may be placed at the bilateral vesicourethral anatamosis (VUA) and one in the retrovesicle (RV) space under sterile conditions with antibiotic prophylaxis consistent with local practice standards. The three markers or electromagnetic transponders should be identified and contoured on the simulation CT and designated right VUA, left VUA, and RV according to their relative positions. The appropriate shifts should be made to ensure daily registration of the markers or transponders with the position defined by the treatment plan.

All image/signal-guidance data should be recorded and archived at the site and available for review, if requested.

5.2.11 Case Review

The Principal Investigator, Mark Buyyounouski, MD and his designee(s) will perform ongoing remote RT Quality Assurance Review after complete data in TRIAD for cases enrolled has been received at IROC Philadelphia-RT.

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 Permitted Supportive/Ancillary Care and Concomitant Medications

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.

- Anticonvulsants
- Antiemetics
- Anticoagulants
- Antidiarrheals
- Analgesics
- Hematopoietic Growth Factors
- Herbal products
- Nutritional supplementation
- Highly active antiretroviral therapy (HAART)

5.3.2 Prohibited Therapies

- Care should be taken to avoid therapies that may contribute or exacerbate GI or GU toxicity from radiotherapy.

5.3.3 Participation in Other Trials *[if applicable]*

Patients are prohibited from participating in any therapeutic intervention trial.

5.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as described in Section 7
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6. TREATMENT MODIFICATIONS/MANAGEMENT

Not applicable

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Not applicable

7.2 Adverse Events and Serious Adverse Events (26-APR-2019)

7.2.1 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)

7.2.2 Definition of an Adverse Event (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).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.3 Expedited Reporting of Adverse Events

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

Submitting a report via CTEP-AERS serves as notification to the NRG Biostatistical/Data Management Center and satisfies NRG 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 the NRG Operations Center by phone, 215-574-3191. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.3.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting Requirements, a CTEP-AERS 24-hour notification must be submitted with 24 hours of learning of the adverse event.
- Supporting source documentation is requested by NRG as needed to complete adverse event review. When submitting supporting source documentation, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and contact the NRG Operations Center (215-574-3191) for source document submission information.

A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action *not* recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.3.2 Expedited Reporting Requirements for Adverse Events

For Arm 1: Any Phase Study Utilizing Standard of Care Radiation Therapy[1]

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

NOTE: Investigators **MUST** immediately report to the sponsor **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.

Attribution	Grade 4		Grade 5	
	Unexpected	Expected	Unexpected	Expected

Unrelated Unlikely			10 day	10 day
Possible Probable Definite	24-h/5 day	10 day	24-h/5 day	24-h/5 day

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:

- Unexpected Grade 4 and all Grade 5 AEs

For Arm 2: Phase III Study Utilizing Radiation Therapy (including chemoRT studies)[1]

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

NOTE: Investigators **MUST** immediately report to the sponsor **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.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

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 3 adverse events

Additional Protocol-Specific Instructions or Exceptions to Expedited Reporting Requirements: None

7.3.3 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.3.4 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 during or subsequent to treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS . In addition, secondary malignancies following radiation therapy must 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.

8. REGISTRATION AND STUDY ENTRY PROCEDURES (26-APR-2019)

CTEP Registration Procedures and Access requirements for OPEN, Medidata Rave, and TRIAD

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 at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

8.1 Site Registration Requirements (26-APR-2019)

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.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the NRG-GU003 protocol page located on the CTSU members' website.

- 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 NRG Oncology link to expand, then select trial protocol NRG-GU003
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements For NRG-GU003 Site Registration:

- IRB approval letter (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 Informed Consent (English and native language versions*****)
  ***Note**: Institutions must provide certification/verification of IRB/REB consent translation to NRG Headquarters (described below).
- IRB/REB registration number renewal information as appropriate.
- CTSU RT Facilities Inventory Form
  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. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility
- Credentialing documentation received from IROC Houston for this trial- See Section 8.2 Table for details.

Non-English Speaking Canadian and International 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 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.

8.2 RT-Specific Pre-Registration Requirements (26-APR-2019)

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions.

The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. Specific credentialing components may require you to work with various QA centers; however, the IROC Houston QA Center will notify your institution when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study. The credentialing notification document (email) must be uploaded by the site to the CTSU Regulatory Submission Portal for RSS to be updated.

RT Credentialing Requirements	Web Link for Credentialing Procedures and Instructions **http://irochouston.mdanderson.org**	
	Treatment Modality Photons	**Key Information**
Facility Questionnaire	✓	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email **irochouston@mdanderson.org** to receive your FQ link.
Credentialing Status Inquiry Form	✓	To determine if your institution has completed the requirements above, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (**http://irochouston.mdanderson.org**).
Phantom Irradiation	✓	An IMRT phantom study provided by the IROC Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (**http://irochouston.mdanderson.org**). Note that only the most sophisticated treatment modality needs to be credentialed, e.g., if credentialed for IMRT, 3DCRT may be used. Tomotherapy, Cyberknife and Viewray treatment delivery modalities must be credentialed individually.
Credentialing Issued to:		
Institution		IROC Houston QA Center will notify the site that all desired credentialing requirements have been met. The site will need to upload a PDF of approval email from IROC Houston to the CTSU Regulatory Portal for RSS to be updated.

8.2.1 Digital RT Data Submission to NRG Using TRIAD

TRIAD is the image exchange application used by the NRG. 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 the beginning of Section 8 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 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 IROC website https://www.irocqa.org/Resources/TRIAD**.**

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.

8.3 Patient Enrollment (26-APR-2019)

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.

8.3.1 Oncology Patient Enrollment Network (OPEN)

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster. All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the 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.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: 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 OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. 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 NRG web support for assistance with web registration: websupport@acr.org or call the NRG 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.

9.0 DRUG INFORMATION

9.1 Commercial Agents

ADT can be prescribed at the discretion of the treating physician.

10. PATHOLOGY/BIOSPECIMEN

10.1 Biospecimen Submission Tables (26-APR-2019)

10.1.1 Optional Specimen Submissions

(Patients must be offered the opportunity to consent to optional specimen collection. If the patient consents to participate, the site is required to submit the patient's specimens as specified per protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent.)

See detailed specimen collection/processing/shipping instructions on the protocol-specific page of the CTSU website.

Optional Study Description #1

1. Tissue, urine, and blood (including serum and plasma) samples will be collected and banked for future research studies. These exploratory studies will include identifying genes or proteins, expressed in the tissue, urine, or blood, that may be associated with toxicity following hypofractionated or conventionally fractionated post-prostatectomy radiation. These studies will include assessment of both baseline and follow-up samples, to determine if early post-treatment changes in genes or proteins can predict subsequent toxicity or response.
2. Specimen collection kits and instructions are available for frozen specimens from NRGBB@ucsf.edu. 5 mm punch kits for FFPE specimens are also available upon request.
3. Forms- Submit with NRG label on them with Study#, Case#, patient initials, submitting site name and NCI number.
   -ST forms are to be included with all submissions.
   -FFPE submissions must also include pathology reports with all PHI redacted except the pathology accession number and date of procedure.
4. Shipping days for Frozen biospecimens: Monday-Wednesday (US Sites). Monday-Tuesday (Canada and overseas). Check NRG Oncology broadcasts for holiday shipping information.
5. Shipping costs- One prepaid label for each case in provided with kits to be used for batch

shipment of frozen specimen shipments.

For kit requests and questions, contact:
NRG-GU003
NRG Oncology Biospecimen Bank—San Francisco
2340 Sutter Street, Room S341
University of California San Francisco – Box 1800
San Francisco, CA 94115
415-476-7864; NRGBB@ucsf.edu

Specimen Type	**Collection Time Points**	**Collection Information and Requirements/Instructions for Site**	**Shipping**
Representative H&E stained slides of the primary tumor from prostatectomy	Pre-radiation treatment	H&E stained slides Slides can be duplicate cut H&Es, they do not have to be the diagnostic slides. H&E slides cannot be returned to sites.	Slide shipped ambient to NRGBB-SF
A paraffin-embedded tissue block of the primary tumor from prostatectomy or a 5 mm diameter core of tissue, punched from the tissue block with a punch tool	Pre-radiation treatment	Paraffin-embedded tissue block or 5mm punch biopsy. Must be same block as H&E being submitted. Sites with resources to embed the punch should do so and submit a matching H&E in addition to the H&E from the original block	Block or punch shipped ambient or with a cold pack in warmer weather to NRGBB-SF
Plasma- EDTA tube 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/ lavender top) and centrifuge	Pre-radiation treatment Last week of RT At 12 months from the start of RT	Frozen plasma samples containing minimum **0.5 mL per aliquot** in 1 mL cryovials (five)	Plasma sent frozen in batch shipments on dry ice via overnight carrier to NRGBB-SF
Serum- Red top tube 5-10 mL of whole blood in 1 red-top tube and centrifuge	Pre-radiation treatment Last week of RT At 12 months from the start of RT	Frozen serum samples containing minimum of **0.5 mL per aliquot** in 1 mL cryovials (five)	Serum sent frozen in batch shipments on dry ice via overnight carrier to NRG BB-SF
Whole Blood- EDTA tube Whole blood for DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix	Pre-radiation treatment Note: if site misses this collection they may collect it at any of the other noted timepoints instead.	Frozen whole blood samples containing **1-1.5 ml per aliquot** in 1ml cryovials (three to five)	Whole blood sent frozen in batch shipments on dry ice via overnight carrier to NRG BB-SF
10-20 mL clean-catch urine	Pre-radiation treatment Last week of RT	5-10 mL urine aliquots in 1 or 2 sterile 15 ml polypropylene centrifuge tubes. Store frozen at -20° or -80° C. (-20°C storage is only advisable for short term storage)	Urine sent frozen in batch shipments on dry ice via overnight carrier to NRG BB-SF

11. SPECIAL STUDIES (NON-TISSUE)

11.1 The Expanded Prostate Cancer Index Composite (EPIC; required assessment)

Health Related Quality of Life as measured by the EPIC questionnaire is the primary endpoint in this study. Therefore, every randomized, eligible, analyzable patient on the study will complete the EPIC. Patients will complete the EPIC per the schedule in Section 4.

11.1.1 The 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 prostate cancer treatments, including prostatectomy, radiotherapy, and hormonal therapy (van Andel 2003). 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 $r \geq 0.80$ 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. The domains were validated separately, and because each domain will be used intact, there is no threat to validity.

Response options for each item form a Likert scale with scores transformed linearly to a 0-100 scale. Domain scores are also on a 0-100 scale with higher scores representing better HRQOL. Some items have 5 response options while others have 4. The bowel domain contains 14 questions, the urinary domain contains 12 items, the sexual domain contains 13 questions, and the hormonal domain contains 11 questions.

11.1.2 EuroQol (EQ-5D)

The EQ-5D is a 6-item validated utility assessment instrument that takes less than 5 minutes to complete (van Agt 1994, Conner-Spady 2001, Brooks 1991, Nord 1991). The first part consists of 5 items covering 5 dimensions including: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is graded on 5 levels: 1-no problems, 2-slight problems, 3-moderate problems, 4-severe problems, and 5-unable to perform/extreme problems. Health states are defined by the combination of the leveled responses to the 5 dimensions, generating 3, 125 health states. The sixth item is a visual analogue scale for overall health. The 5-item index score is transformed into a utility score between 0, "Worst health state," and 1, "Best health state." The index score can be used in a quality adjusted survival analysis depending on the health state(s) of interest (Wu 2002). For this study we plan to report the multidimensional utilities for comparative purposes. The measured utility values for each patient on this study will be combined with overall survival to calculate the "QALY" quality-adjusted life years. This will then be used for cost-effectiveness analysis comparing the two arms in this trial. Patients will complete the EQ-5D as specified in the Study Parameter Table in Section 4.

12. MODALITY REVIEWS

12.1 Radiation Therapy Quality Assurance Reviews(26-APR-2019)

The Principal Investigator, Mark Buyyounouski, M.D. and his designee(s), will perform a RT Quality Assurance Review after IROC Philadelphia-RT has received complete data in TRIAD for the cases enrolled. The reviews will be completed remotely and will be ongoing. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as IROC Philadelphia-RT has received complete data in TRIAD for all cases enrolled, whichever occurs first. The scoring mechanism is: **Per Protocol, Acceptable Variation, and Unacceptable Deviation**.

13. DATA AND RECORDS

13.1 Data Management/Collection (26-APR-2019)

Data collection for this study will be done exclusively through Medidata Rave®. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS (Regulatory Support System). To access iMedidata/Rave, the site user must have an active CTEP-IAM account and the appropriate Rave role (Rave CRA, Rave Read-Only, Rave CRA (Lab Admin), Rave SLA or Rave Investigator) on either the LPO or participating organization rosters at the enrolling site. To the hold Rave CRA role or Rave CRA (Lab Admin) role, the user must hold a minimum of an AP registration type. To hold the Rave Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

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 (iMedidata-Notification@mdsol.com) to activate their account. 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 will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts also will 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 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.

13.2 Summary of Data Submission

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Section 7.3 for information about expedited and routine reporting.

Summary of Data Submission: Refer to the CTSU website.

See Section 8 for TRIAD account access and installation instructions.

13.3 Global Reporting/Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

Note: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS, but expedited adverse events are still required to be submitted via CTEP-AERS.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design

This is a randomized phase III non-inferiority trial comparing hypofractionated post-prostatectomy radiation therapy (HYPORT) and conventional post-prostatectomy radiation therapy (COPORT). Patients will be stratified according to baseline EPIC bowel and urinary domain scores (high bowel score and high urinary score vs. high bowel score and low urinary score vs. low bowel score and high urinary score vs. low bowel score and low urinary score) and androgen deprivation therapy (ADT; yes vs. no) then randomized 1:1 to receive HYPORT or COPORT according to the permuted block design by Zelen (1974). Combination RT and ADT has been associated with increased risks of GI toxicity (Feigenberg 2005, Roach 2003) and GU toxicity (Lawton 2008) that may confound the primary endpoint. A high bowel score > 96, low bowel score ≤ 96, high urinary score > 84, and low urinary score ≤84. Determination of high vs. low bowel and urinary scores was from baseline scores on RTOG 0534. This is an intent-to-treat analysis and all randomized patients will be included in the primary analysis.

14.2 Study Endpoints (26-APR-2019)

14.2.1 Co-primary endpoints:

1. Two-year change score from baseline for the GI domain of the Expanded Prostate Cancer Index (EPIC).
2. Two-year change score from baseline for the GU domain of the EPIC.

14.2.2 Secondary endpoints

1. Patient-reported gastrointestinal (GI) symptoms using the EPIC at the end of RT, 6 months, 1 and 5 years.

2. Patient-reported genitourinary (GU) symptoms using the EPIC at the end of RT, 6 months, 1 and 5 years.
3. Freedom from biochemical failure (FBF)
4. Time to progression (TTP) where progression is defined as the first occurrence of, BF, local failure, regional failure, distant metastasis (DM), institution of new unplanned anticancer treatment, or death from prostate cancer (PCSM)
5. Local failure, regional failure, salvage therapy (i.e. institution of new unplanned anticancer treatment), DM, PCSM, and OS rates.
6. Adverse events using the Common Terminology Criteria for Adverse Events (CTCAE v. 4.0).

14.2.3 Exploratory endpoints

1. Measured utilities for health outcomes using the EQ5D.
2. Paraffin-embedded tissue block, serum, plasma, whole blood, and urine for future translational research analyses for predictors of toxicity following hypofractionated or conventionally fractionated post-prostatectomy radiotherapy.

14.3 Primary Objectives Study Design

14.3.1 Primary Hypothesis and Endpoints

1. Hypofractionated postprostatectomy radiotherapy (HYPORT) delivering 62.5 Gy in 25 fractions of 2.5 Gy to the prostate bed is not associated with excess patient-reported GI symptoms, as measured by the EPIC bowel domain, compared to conventionally fractionated postprostatectomy radiotherapy (COPORT) delivering 66.6 Gy in 37 fractions of 1.8 Gy to the prostate bed.
2. HYPORT delivering 62.5 Gy in 25 fractions of 2.5 Gy to the prostate bed is not associated with excess patient-reported GU symptoms, as measured by the EPIC urinary domain, compared to COPORT delivering 66.6 Gy in 37 fractions of 1.8 Gy to the prostate bed.

14.3.2 How Primary Endpoints Will Be Analyzed

Analysis of the Primary Endpoints

The co-primary endpoints are GI and GU toxicity as measured by the bowel and urinary EPIC domains, respectively. The change scores, calculated as baseline score subtracted from 2-year score, will be analyzed using a t-test with a significance level of 0.025. If the data are determined to be non-normal, a Wilcoxon test may be used instead. Missing data will be assessed and is described in more detail in Section 14.6.2. All patients will EPIC bowel and urinary domain scores will be included in the primary endpoint analysis. The EPIC scoring manual will be followed which requires ≥ 80% of items in a domain to be completed in order to obtain a score for that domain.

14.3.3 Sample Size and Power Calculations:

The primary goal of this phase III study is to determine if HYPORT does not increase GI and GU toxicity over COPORT. The primary endpoint is based on change scores from the bowel (GI) and urinary (GU) domains of the EPIC. The change scores will be based on the 2-year score minus the pretreatment (baseline) score. The hypothesis for this endpoint is that the EPIC mean change score is no worse in the HYPORT than it is in the

COPORT arm for either type of toxicity. Section 11.1.2 contains more information about the EPIC, such as validation information, number of questions, possible responses, and ranges of the scores.

RTOG 0534 has a similar population to this study, however it did not collect EPIC scores at 2 years. Therefore, data from the conventionally-fractionated arm of RTOG 0415 was used to aid in calculation the sample size for this study. To verify that RTOG 0415 data is similar to the patient population in this study, EPIC data from the conventionally-fractionated arm of RTOG 0415 was compared to the results of a recent paper where conventionally-fractionated post-prostatectomy patients were surveyed with the EPIC questionnaire as to their quality of life (Pinkawa 2008). Pretreatment and 1-year results were compared. For the post-prostatectomy paper, the reported pretreatment and 1-year, respectively, mean bowel function scores are 92 and 91, respectively, while for the RTOG 0415 control arm, the mean bowel function scores at the corresponding time points are 93.0 and 90.2, respectively. For post-prostatectomy, the pretreatment and 1-year mean bowel bother scores are 94 and 90, respectively, while for RTOG 0415 control, the corresponding time point scores are 94.1 and 89.5, respectively.

From the conventional arm of RTOG 0415, in an analysis of 170 eligible patients with the bowel domain completed at both baseline and 2 years from the start of RT, the mean change (2-years minus baseline) in EPIC bowel domain score was -4.3 points (SE=13.2). In a similar analysis of 173 eligible patients with the urinary domain completed at both baseline and 2 years, the mean EPIC urinary domain change score was 0.42 (SE=10.5).

Based on these results an EPIC bowel domain mean change-score of -4 will be hypothesized for the COPORT arm, with a non-inferiority margin of 6 for the HYPORT arm corresponding to a bowel domain change score at 2 years of -10 in the HYPORT arm. An EPIC urinary domain score of 0.4 is hypothesized for the COPORT arm, with a non-inferiority margin of 5 for the HYPORT arm corresponding to a urinary domain change score at 2 years of -4.6 in the HYPORT arm. So, if the mean bowel or urinary domain change score for the HYPORT arm is no more than 6 points worse for bowel or 5 points worse for urinary than the mean change score for the COPORT arm, then the HYPORT arm will be considered non-inferior. For the primary endpoint, the null hypothesis (H_0) of this test is that the mean change score of HYPORT (Δ_2) is worse than the mean change score of COPORT (Δ_1). The alternative hypothesis (H_A) is that the mean change score of HYPORT is not worse than the mean change score of COPORT.

The non-inferiority margin is based on 0.5*SE from the RTOG 0415 analysis due to 0.5*SD being the cutoff for clinical difference (Barry 1999). To put the non-inferiority margins in context, a change score of 6 points corresponds to two symptoms worsening by 1 level (i.e. loose stools and frequency of bowel movements change from “no problem” to “very small problem”) or one of the symptoms worsening by 2 levels (i.e. loose stool change from “no problem” to “small problem”).

The study sample size is based on 90% power for GI endpoint and 91% power for the GU endpoint (resulting in 81.9% statistical power to reject the null hypothesis for both

endpoints) and a one-sided alpha=0.025 with an overall type I error of 0.05 with a Bonferroni adjustment. With these design parameters, the sample size is 198 patients. Adjusting for a projected 30% EPIC/non-compliance rate, **the required sample size is 282 patients (141 per arm)**.

14.4 Study Monitoring of Primary Objectives

Interim Analysis for the DMC

The NRG Oncology Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. The DMC also will review the study on an "as needed" basis.

Interim Futility Analysis

There will be a single futility analysis once 50% of patients have 2 years of follow-up. If the upper 95% confidence limit of the mean difference in 2 year change scores between the treatment arms is less than the pre-specified non-inferiority margin, then the HYPORT arm will be deemed inferior to the COPORT arm. Specifically, if the upper 95% confidence limit of the mean difference between arms in 2 year change scores is < -6 for the bowel domain and/or < -5 for the urinary domain, then the HYPORT arm will be deemed inferior to the COPORT arm. Early reporting of the treatment results will be recommended to the DMC, who will review these results. This approach has a minimal effect on statistical power.

Monitoring of EPIC Compliance

Completion rates of the bowel and urinary domains of EPIC will be monitored monthly. Since the study is projected to close within 26 months, 2 year data may not be monitored while the study is open to accrual. Therefore, the rates at 6 months and 1 year will be used to assess feasibility of the primary endpoint analysis. If the EPIC non-compliance rate is $\geq 20\%$ at either of these time points, the study PI and QOL co-chair will work in collaboration with the NRG Oncology Statistics and Data Management Center to contact sites and RAs with delinquent data, assessments completed too early or too late, and assessments not completed due to institution errors. If the EPIC non-compliance rate is $> 40\%$ at either time point, the study will be presented to the DMC for reassessment of feasibility or change in study design.

Interim Analysis to Monitor the Study Progress

Interim reports with statistical analyses will be prepared twice per year until the initial treatment results have been presented/published. In general, the interim reports will contain the following information:

- patient accrual rate with a projected completion date (while the study is still accruing)
- total patients accrued
- distributions of important pre-treatment and prognostic baseline variables
- the frequencies and severity of adverse events by treatment arm

The interim reports will not contain the results from the treatment comparisons with respect to the primary and secondary endpoints, with the exception of reporting of

adverse events.

14.5 Accrual/Study Duration Considerations

Based on patient accrual in previous RTOG legacy/NRG Oncology studies, the initial 6 months accrual is projected to be negligible while institutions are obtaining IRB approval. This protocol has a similar patient population (post-prostatectomy) to RTOG 0534. The accrual rate for the QOL component on that study was 11.3 patients per month. Therefore, the projected accrual rate is 11 patients per month. Based on this information, it is projected that the study will complete accrual in about 26 months from the end of the 6-month period of negligibility (32 months from activation). The primary endpoint analysis will occur approximately 5 years from study activation. Accrual will be monitored in accordance to CTEP accrual guidelines.

14.6 Secondary Endpoints

14.6.1 Secondary Hypotheses and Endpoints:

1. Hypofractionated postprostatectomy radiotherapy (HYPORT) delivering 62.5 Gy in 25 fractions of 2.5 Gy to the prostate bed is not associated with excess patient-reported GI symptoms compared to conventionally fractionated postprostatectomy radiotherapy (COPORT) delivering 66.6 Gy in 37 fractions of 1.8 Gy to the prostate bed at the end of RT, and 6 months, 1 and 5 years from the start of RT.
2. HYPORT delivering 62.5 Gy in 25 fractions of 2.5 Gy to the prostate bed is not associated with excess patient-reported GU symptoms compared to COPORT delivering 66.6 Gy in 37 fractions of 1.8 Gy to the prostate bed at the end of RT, and 6 months, 1 and 5 years from the start of RT.
3. Comparison of freedom from biochemical failure (FBF) between the HYPORT arm and COPORT arm.
4. Comparison of time to progression (TTP) where progression is defined as the first occurrence of, BF, local failure, regional failure, distant metastasis (DM), initiation of new unplanned anticancer treatment, or death from prostate cancer (PCSM) between the HYPORT arm and COPORT arm.
5. Comparison of local failure, regional failure, salvage therapy (i.e. initiation of new unplanned anticancer treatment), DM, PCSM, and OS rates between the HYPORT arm and COPORT arm.
6. HYPORT is not associated with excess adverse events (AEs) compared to COPORT

14.6.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

Additional EPIC Endpoints

All four domains of the EPIC will be analyzed, bowel, urinary, sexual, and hormonal. The change scores, calculated as baseline score subtracted from follow-up score, will be analyzed using a t-test. If the data are determined to be non-normal, a Wilcoxon test may be used instead. The follow-up timepoints of interest are end of RT, 6 months, 1, 2 (for sexual and hormonal domains) and 5 years from the start of treatment. A longitudinal analysis incorporating all follow-up time points, will be conducted separately for each domain score using a general linear model with maximum likelihood estimation, adjusting for baseline domain score, treatment arm, Gleason score, baseline PSA, T-stage, age, and

race. These analyses will be conducted regardless the outcomes of the primary t-test. For the comparison of primary endpoints at 2 years adjusting for other variables using the longitudinal model, especially stratification variables, the results will be similar to those of the primary analysis in general. In the rare case when it is different, we will examine very carefully the impact of missing data and the adjusted variables and make a meaningful conclusion regarding the outcome.

If any of the domains are found to significantly differ between arms, then analysis of that domain's subscales will be undertaken to assess which particular subscale is driving the significant difference. The subscales are function both incontinency and irritative/obstructive for the urinary domain, and function and bother for the bowel, sexual, and hormonal domains.

Prior to performing analyses, an evaluation of the amount, reasons and patterns of missing data will be performed, using the well-known categories of missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR) (Fairclough 2010, Verbeke 2000). If ≥15% of the data is missing at any time point for the EPIC bowel and urinary domain scores, patient characteristics will be compared between patients with completed assessments and those with missing assessments. If any are found to differ significantly, they will be included in the mixed effects model which assumes that the data is MAR. If the missingness is determined to be non-ignorable, other methods may be performed. Specifically, a joint model that allows a shared parameter between the repeated measurements and time to death or drop out can be used if considered MNAR due to the high number of patient deaths or dropouts (Rizopoulos 2012). Other options for MNAR data are pattern mixture and selection models (Fairclough 2010, Little 1995). Sensitivity analyses will be performed to compare the results of different analytic strategies (Fairclough 1998).

Secondary Efficacy Endpoints

OS is defined as a death from any cause and will be measured from the date of randomization to the date of death. BF is defined as a PSA ≥ 0.4 ng/mL and rising (i.e. PSA ≥ 0.4 ng/mL followed by a value higher than the first by any amount) or followed by inititation of salvage hormones. The time of the first occurrence of PSA ≥ 0.4 ng/mL will be considered the event time. An alternative definition of BF will also be assessed: PSA ≥ PSA nadir + 2 ng/mL where nadir is the lowest post-RT PSA value. PCSM will be measured from the date of randomization to the date of death due to prostate cancer. LF is defined as the development of a new biopsy-proven mass in the prostate bed after enrollment in the protocol and will be measured from the date of randomization to the date of documented local failure. RF will be defined as radiographic evidence (CT or MRI) of lymphadenopathy (lymph node size ≥ 1.0 cm in the short axis) in a patient without the diagnosis of a hematologic/lymphomatous disorder associated with adenopathy and will be measured from the date of randomization to the date of documented regional metastasis. DM is defined as radiographic evidence of hematogenous spread (e.g., bone scan, CT, MRI) and will be measured from the date of randomization to the date of documented DM. For LF, RF, and DM, a BF is required prior to the LF, RF, and DM but will not be

considered as an event. TTP will be measured from the date of randomization to the date of the first occurrence of BF, LF, RF, DM, of PCSM. Since TTP includes BF as a failure, both definitions of BF will be used resulting in two TTP estimates.

Since baseline PSA level is not a stratification factor, hazard ratios and p-values for all efficacy endpoints will be analyzed and reported after adjustment for baseline PSA. Patients not experiencing an event will be censored at the last known follow-up time. Competing-risk endpoints PCSM, LF, RF, TTP, and DM will treat death as a competing risk (for PCSM and TTP, any death not due to prostate cancer) and be estimated by the cumulative incidence method (Gray 1988). OS and FFBF will be estimated by the Kaplan-Meier method (Kaplan & Meier 1958) and compared with the log-rank test (Mantel 1966). Cox regression (1974) will be used to obtain hazard ratios (HRs) for OS and TTP. Fine and Gray's regression (1999) will be used for the endpoints with competing risks. Adjusted HRs and the respective 95% confidence interval will be computed. Baseline PSA, stratification variables (baseline EPIC score and ADT status), and, as appropriate, age, race, and other covariates (Gleason, T-stage), will be adjusted for in this analysis. Statistical power will be limited for these analyses.

Adverse Events

Adverse events (AEs) will be graded with CTCAE v4. Counts of all AEs by grade will be provided by treatment arm. Counts and frequencies will be provided for the worst grade AE experienced by the patient by treatment arm. A Chi-square test will be used to compare the number of patients with at least 1 grade 3 or higher AE between the treatment arms. A comparison of grade 3 and higher GU and GI events related to treatment (separately) between treatment arms will also be tested using a Chi-square test.

14.7 Exploratory Endpoints

14.7.1 Exploratory Hypotheses and Endpoints

- Measured utilities and cost-effectiveness for health outcomes using the EQ5D.
- Paraffin-embedded tissue block, serum, plasma, whole blood, and urine for future translational research analyses for predictors of toxicity following hypofractionated or conventionally fractionated post-prostatectomy radiotherapy. Note: Testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

14.7.2 Definitions of Exploratory Endpoints and How These Will Be Analyzed

Cost effectiveness

The VAS and index scores from the EQ-5D-5L will be calculated at each time point (baseline, end of RT, 6 months, and 1, 2, and 5 years from the start of RT) and compared between treatment arms using a t-test with a 2-sided significance level of 0.05. If there are significant differences, then a cost analysis will be conducted.

Quality-adjusted life years (QALY) is defined by the weighted sum of different time episodes added up to a total quality-adjusted survival time. A Markov model will be used

to model cost for this analysis. The Medicare reimbursement in dollars/QALY will be calculated as a function of the monetary cost per relative value of each health state and its duration. The EQ-5D-5L index score at 6 months and 5 years will be used for the cost-utility analysis. The z-test will be used to test the hypothesis that the cost-utility in the two treatment arms is the same with significance level of 0.05. The cost-utility using the Medicare reimbursement in dollars/QALY between the two treatment arms after adjusting for the baseline and stratification variables.

14.8 Gender/Ethnicity/Race Distribution (26-APR-2019)

No differences across the patient subsets below are anticipated.

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	2	0	1	3
Asian	0	2	0	0	2
Native Hawaiian or Other Pacific Islander	0	1	0	1	2
Black or African American	0	40	0	3	43
White	0	139	0	10	149
More Than One Race	0	1	0	1	2
Total	0	185	0	16	201

Racial Categories	INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	0	1	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	2	0	0	2
White	0	70	0	8	78
More Than One Race	0	0	0	0	0
Total	0	73	0	8	81

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