NRG Oncology

Radiation Therapy Oncology Group

NRG-GU006

(ClinicalTrials.gov NCT #: 03371719)

A Phase II, Double-Blinded, Placebo-Controlled Randomized Trial of Salvage Radiotherapy With or Without Enhanced Anti-Androgen Therapy With Apalutamide in Recurrent Prostate Cancer (BALANCE*)

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A PHASE II, DOUBLE-BLINDED, PLACEBO-CONTROLLED RANDOMIZED TRIAL OF SALVAGE RADIOTHERAPY WITH OR WITHOUT ENHANCED ANTI-ANDROGEN THERAPY WITH APALUTAMIDE IN RECURRENT PROSTATE CANCER (BALANCE*)

** **B**iomarker trial of **A**pa**L**utamide and r**A**diation for recurre**N**t prostate **C**anc**E**r*

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.

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Protocol Agent

Agent	Supply	NSC #	IND #	IND Sponsor
Apalutamide	Janssen	794776	135824	NRG

Participating Sites

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

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A PHASE II, DOUBLE-BLINDED, PLACEBO-CONTROLLED RANDOMIZED TRIAL OF SALVAGE RADIOTHERAPY WITH OR WITHOUT ENHANCED ANTI-ANDROGEN THERAPY WITH APALUTAMIDE IN RECURRENT PROSTATE CANCER

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For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		

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SCHEMA (15-JUL-2019**)**

STEP 1 REGISTRATION
Submission of tissue for Decipher analysis
Note: Decipher analysis results must be completed before Step 2 randomization can occur. If Decipher results have already been obtained, in lieu of tissue, results must be submitted to GenomeDx for validation.

↓

STEP 2 REGISTRATION

STRATIFY
Surgical Margins: Positive vs. Negative
Pre-SRT PSA: <0.5 ng/mL vs ≥0.5-1.0 ng/mL
PAM50 Molecular Subtype (per Decipher analysis): Luminal B vs (Luminal A/Basal/Unknown)

Randomize 1:1

↓

Arm 1 (Blinded)*
External Beam Radiation:
64.8 to 70.2, 1.8-2.0 Gy/33-39 fractions
Plus

Blinded placebo daily for 6 months (~180 days) to start on Day 1 of radiation therapy (+/- 14 days)

vs.

↓

Arm 2 (Blinded)*
External Beam Radiation:
64.8 to 70.2, 1.8-2.0 Gy/33-39 fractions
Plus

Blinded apalutamide daily for 6 months (~180 days) to start on Day 1 of radiation therapy (+/- 14 days)

*See Section 5.1 for apalutamide/placebo treatment details and Section 5.2 for radiation therapy details.
Abbreviations: PSA, prostate specific antigen; SRT, salvage radiation therapy

1. OBJECTIVES

1.1 Primary Objective

To determine whether, in men with post-prostatectomy PSA recurrences, salvage radiation (SRT) with enhanced anti-androgen therapy with apalutamide will improve biochemical progression-free survival (bPFS) compared to SRT alone. A bPFS event is defined as a rise in PSA $\geq$ 0.2 ng/mL from nadir, confirmed by a second PSA measurement ; clinical or radiographic local, regional, or distant metastases; or death from any cause, whichever occurs first.

1.2 Secondary Objectives (14Jun2018)

1.2.1 To assess whether molecular stratification by the PAM50 gene expression clustering will identify subsets of prostate cancer (Luminal A or Basal, Luminal B) which derive the greatest benefit from anti-androgen therapy (PAM50 test will be run in conjunction with the commercial Decipher test from GenomeDx).

1.2.2 To assess overall survival

1.2.3 To assess cancer-specific mortality

1.2.4 To assess metastasis-free survival

1.2.5 To assess distant metastasis

1.2.6 To assess local-regional progression

1.2.7 To assess PSA nadir during first year of treatment and prior to initiation of any hormonal salvage therapy

1.2.8 To assess initiation of salvage hormonal therapy

1.2.9 To assess PSA with a non-castrate testosterone at 1 and 3 years post randomization: PSA < 0.1 ng/ml and testosterone ≥ 50 ng/dl

1.2.10 To assess acute and late physician-reported morbidity (per the CTCAE version 5.0) after SRT +/- apalutamide;

1.2.11 To assess acute and late patient-reported symptomatic adverse events morbidity (per the PRO-CTCAE) after SRT +/_apalutamide.

1.2.12 To assess testosterone levels at 3, 6, 9, 12, and 36 months post randomization.

1.3 Exploratory Objectives

1.3.1 To assess the prognostic and predictive value of the genomic classifier Decipher

2. BACKGROUND

The precise standard of care for men with a rising PSA post-prostatectomy is controversial and unclear. What is known is that SRT is recommended, but it is unclear whether the addition of ADT is necessary. Recently, the 12-year outcomes of RTOG 9601 were reported, and demonstrated that the addition of two years of a first-generation anti-androgen (bicalutamide) to SRT improved biochemical control, distant metastases, and overall survival compared to SRT alone (Shipley 2017). Notably, this trial was conducted in aggressive-risk patients (67% had T3 disease, 75% had a positive margin, 12% had a high persistently positive PSA post-RP of ≥0.5 ng/mL, and 17% had Gleason 8-10), with approximately 50% of patients with a pre-SRT PSA between 0.7-4.0 ng/mL, higher than seen in common practice today. Additionally, for the first 1/3 of the enrollment period men were required to have a pre-SRT PSA of at least 0.5 ng/mL, and current recommendations often recommend initiating SRT prior to reaching PSAs of this

level if possible. Furthermore, subset analyses demonstrated that for men with pre-SRT PSAs of ≤0.7 ng/mL, there was no benefit to the addition of first generation anti-androgen therapy in regards to both distant metastasis and overall survival.

The recently published GETUG-AFU-16 trial similarly demonstrated that there was an improvement in primarily biochemical control with the addition of 6-months of an LHRH agonist to SRT over SRT alone (Carrie 2016). Similarly, they found a greater benefit in biochemical control for men with high pre-SRT PSAs >0.5 ng/mL, compared to those with lower pre-SRT PSA. However, they did not demonstrate an improvement using this relatively mild form of hormone therapy in regards to distant metastasis or overall survival to date. Additionally, given that after LHRH analogue therapy testosterone is suppressed for numerous months (e.g. 3-12 months) post-treatment, the use of biochemical control (a measurement of PSA) as an endpoint is confounded in that the endpoint is dependent on the presence of testosterone and is of unclear clinical meaning. In contrast, anti-androgen therapy alone does not cause an analogous testosterone suppression and would be more informative of the benefit of short-term hormone therapy in this context.

We would argue that the standard of care for men with PSAs >1.0 ng/mL would consist of SRT plus hormone therapy, and that for more favorable men seen in modern practice with post-prostatectomy recurrences with a rising PSA up to ≤1.0 ng/mL, would be SRT alone. Therefore, *a phase II placebo-controlled randomized trial is warranted to test if the addition of a more potent next-generation anti-androgen would benefit this more favorable subset compared to SRT alone*. This phase II trial is also designed to determine if a molecular biomarker, which stratifies prostate cancers by luminal versus basal subtypes, can predict response to apalutamide, a novel, next-generation nonsteroidal anti-androgen in advanced clinical testing; if the biomarker is found to be predictive of treatment response, it would then be used for patient selection in the follow-up phase III trial.

2.1 The Importance of Salvage Radiation Therapy (SRT) for Post-Prostatectomy PSA Recurrences

Radical prostatectomy (RP) is a standard treatment option for patients with localized prostate cancer. However, greater than 30% of patients treated with RP will experience biochemical recurrence (BR), as represented by a rising PSA (Han 2001; Roehl 2004). A common option for initial management of patients with BR post-RP is SRT. While no randomized data exist comparing SRT to observation alone, many retrospective analyses have shown that SRT can provide long-term durable responses (Goenka 2012; Katz 2003; Stephenson 2007), and two large retrospective studies have suggested an improvement in prostate cancer-specific mortality as compared to observation for patients treated with SRT following BR (Cotter 2011; Trock 2008). Trock et al found that SRT was associated with a 3-fold decrease in risk of prostate cancer-specific mortality compared to observation, and that this was primarily true in patients with aggressive disease features (Trock 2008). Cotter et al similarly found that SRT improved all-cause mortality in both low- and high-risk patients, but that when controlling for patient comorbidities, this improvement was greatest in patients with high-risk features, with a 15% reduction in

actuarial all-cause mortality (Cotter 2011). Thus, SRT is a well-accepted standard practice for patients with post-prostatectomy PSA recurrences, including those with aggressive disease features.

2.2 The Need To Improve Outcomes for Patients With PSA Recurrences Post-Prostatectomy

While SRT has been shown to provide durable responses and a survival benefit for many patients experiencing BR post-RP, >50% of patients treated with SRT will experience disease progression (Goenka 2012; Katz 2003; Stephenson 2007). Previous studies have demonstrated that an even larger proportion of patients with aggressive pathologic and clinical features, such as a persistently elevated PSA post-RP, a higher pre-SRT, Gleason score 8-10, and seminal vesicle invasion, will have BR following SRT (Katz 2003; Stephenson 2007; Stephenson 2004; Song 2002).

2.3 The Rationale for Adding Hormone Therapy (HT) to SRT

Augmenting SRT with ADT represents one approach to improving long-term outcomes for post-prostatectomy patients treated with SRT for biochemical recurrence (BR). The addition of HT has resulted in significant improvements in rates of biochemical recurrence, metastasis-free survival, and overall survival in the context of definitive radiation therapy for localized prostate cancer (Bolla 2010; Horwitz 2008; Jones 2008; Lawton 2011). More recently, it was demonstrated that the addition of HT to SRT also confers a benefit (Shipley 2011). Long-term results from RTOG 9601, which randomized post-RP patients with biochemical recurrence to SRT + bicalutamide (a relatively weak first generation anti-androgen) for 24 months or SRT alone, have shown that the addition of bicalutamide provided a benefit in reducing PSA progression, decreased the incidence of metastatic disease, and improved overall survival (Shipley 2011). However, RTOG 9601 did not demonstrate a benefit in men with lower pre-SRT PSAs, and the cut point reported for benefit was ≥0.7 ng/mL in an overall high risk cohort.

RTOG 9601 assessed the addition of bicalutamide in a relatively unselected patient population with PSA recurrences following prostatectomy; in fact, the primary selection in RTOG 9601 allowed patients with a pre-radiation PSA of 0.2 to 4 ng/mL. Based on The Michigan Urological Surgery Improvement Collaborative (MUSIC), established in 2011, a physician-led quality improvement collaborative comprised of a consortium of urology practices in the state of Michigan, <10% of men with post-RP PSA recurrences in modern times have pre-SRT PSAs >1.0 ng/mL. This stands in stark contrast to the era in which RTOG 9601 was performed. Therefore, it is unclear how applicable the RTOG 9601 results are to modern populations of patients with post-prostatectomy PSA recurrence, the majority of which have pre-SRT PSAs much lower than the 0.7 ng/mL cut point.

A second randomized trial, GETUG-AFU-16 demonstrated that the addition of an LHRH agonist for 6 months with SRT improved primarily biochemical control over SRT. The benefit was greatest for men with pre-SRT PSAs >0.5 ng/mL. However, the use of an LHRH agonist confounds the results of bPFS (which is primarily a measure of PSA

recurrence) given that testosterone suppression can occur for months to years post-treatment.

We now propose to assess the benefit of the next-generation anti-androgen apalutamide in patients with a low pre-SRT PSA, defined as having a pre-SRT PSA of ≤1.0 ng/mL.

2.4 The Rationale for the Design of the Study Control Arm

To enhance the risk/benefit ratio in this trial, we will preselect for patients at moderate risk of disease recurrence following salvage radiation based on currently available data. Given that higher pre-SRT PSAs >1 ng/mL are associated with higher rates of distant metastases, we believe that the use of SRT alone in this population would not be justified given that SRT is given locally to the prostate bed. Therefore, based on RTOG 9601, which demonstrated that there was no benefit to the use of bicalutamide in men with a lower pre-SRT PSA, the control arm would receive SRT alone.

Our hypothesis is that the addition of apalutamide (see below for rationale) to SRT will intensify SRT, thus improving treatment efficacy while not compromising patient tolerance given the short duration (6 months) of apalutamide use.

2.5 The Rationale for Apalutamide in the Study Experimental Arm (14Jun2018)

Given that the first generation anti-androgen (bicalutamide) failed to demonstrate a benefit in men with lower pre-SRT PSAs, the question remains as to whether hormonal therapy will benefit these patients. To answer this question, we will use one of the most potent second next-generation anti-androgens available: apalutamide. Apalutamide is FDA approved for the treatment of non-metastatic castration resistant prostate cancer; however, apalutamide is still considered investigational in this trial setting. The use of next-generation anti-androgens provides a promising strategy for further intensifying short-course anti-androgen therapy with SRT patients. In particular, apalutamide is a next-generation anti-androgen that has a higher binding affinity for the androgen receptor (AR) when compared to the first-generation anti-androgen bicalutamide. As opposed to bicalutamide, apalutamide prevents binding of AR to DNA and to co-activator proteins. In addition, while bicalutamide has been shown to have agonist activity in the setting of AR overexpression, apalutamide acts as a pure antagonist. Importantly, enzalutamide (a highly related though less potent agent) improves overall survival for patients with metastatic castration-resistant prostate cancer (mCRPC) (Scher N Engl J Med 2012; Scher ASCO GU 2012). In the published study of enzalutamide in advanced mCRPC, more than half of patients experienced a greater than 50% reduction in serum PSA concentration and 25% had a greater than 90% decline from initial PSA as a result of treatment (Scher N Engl J Med 2012). In a phase II study of enzalutamide monotherapy in patients with castration-sensitive, systemic-therapy naïve patients an ≥80% reduction in serum PSA concentration in 62/63 (98.4%) was reported (Tombal 2013). Apalutamide has been shown to be more potent than enzalutamide, and as such we anticipate that when used earlier in the disease course, apalutamide will be highly effective.

Given the treatment setting, apalutamide is considered a more desirable agent than other anti-androgens due to its ease of administration and more favorable side-effect profile.

This will improve patient compliance in this setting. Therefore, the goal of this study is to determine if the addition of apalutamide to SRT can further improve outcomes for patients with low pre-SRT PSA.

2.6 PAM50 Predictive Biomarker to Predict Response to Hormone Therapy

PAM50 is an RNA expression based signature that was developed in breast cancer to molecularly subtype breast cancer patients into multiple subtypes, notably luminal and basal subtypes. Work led by the study Chairs analyzed the locked PAM50 subtyping, with the exclusion of the HER2 subtype, and applied this to prostate cancer leveraging the Decipher platform. This work (Zhao et al, JAMA Onc 2017) demonstrated that not only were the Luminal and Basal subtypes of prostate cancer very similar in expression pattern to that of breast cancer, but that Luminal B patients had the most unfavorable prognosis. Furthermore, using a matched cohort of patients that did and did not receive early post-operative hormone therapy, it was demonstrated that Luminal B patients significantly benefited from the addition of hormone therapy, while Luminal A and Basal patients (ie non-Luminal B) failed to derive benefit from hormone therapy. Although limited by the sample size and retrospective nature, this represents the foundational work that led to the present biomarker enhanced clinical trial to prospectively validate these findings in the appropriate manner.

To utilize the PAM50 in real-time and as part of the present trial, z-score parameters (mean and standard deviation) for each PAM50 gene were pre-calculated based on a large reference population of prostate cancer patients (n = 2829) from prospective testing with the Decipher assay. With these parameters precomputed, a single patient's gene expression can be standardized (z-scored) prior to application of PAM50, allowing the PAM50 subtype call to be used for patient stratification in this trial. This allows prospectively to make accurate calls to each additional patient analyzed and assign a molecular subtype. Additionally, analytical validation of the PAM50 assay on prostate cancer patients has been performed and demonstrated across 18 samples with 54 data points that the inter- and intra-assay lower bound reproducibility is approximately 90%. All samples will be analyzed on the same platform reported in the Zhao et al publication utilizing the Decipher platform on a Affymetrix HuEx Array 1.0 ST array (ThermoFisher, Carlsbad, CA).

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY 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 (see protocol cover page). For radiation therapy-related eligibility questions, please contact RTQA (see protocol cover page).

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.

3.1.2 Submission of tumor tissue sample from prostatectomy is required for all patients. **Investigators should check with their Pathology department (or site where surgery was done) regarding release of biospecimens before approaching patients about participation in the trial. If the pathology specimen cannot be obtained, the patient will be ineligible. If Decipher results have already been obtained, in lieu of tissue, results must be submitted to GenomeDx for validation.**

3.2 Eligibility Criteria (14Jun2018)

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 Pathologically (histologically) proven diagnosis of prostate adenocarcinoma. Prostatectomy must have been performed within 10 years prior to Step 1 registration and any type of radical prostatectomy is permitted, including retropubic, perineal, laparoscopic or robotically assisted.

3.2.2 Post-prostatectomy patients with a detectable serum PSA (≥0.1, but ≤1.0 ng/mL) at study entry (within 90 days of Step 1 registration) and at least one of the following:

- Gleason score 7-10 (ISUP grade group 2 to 5)*

  * ISUP grade group:
  a. Grade Group 1 = Gleason score ≤ 6,
  b. Grade Group 2 = Gleason score 3 + 4 = 7,
  c. Grade Group 3 = Gleason score 4 + 3 = 7,
  d. Grade Group 4 = Gleason score 8,
  e. Grade Group 5 = Gleason scores 9 and 10.
- ≥T3a disease
- Persistent elevation of PSA after prostatectomy measured within 90 days after surgery (PSA never became undetectable) of >0.04 but <0.2 ng/mL (PSA nadir)

3.2.3 pN0 or pNx

3.2.4 History/physical examination within 90 days prior to Step 1 registration;

3.2.5 Karnofsky performance status of 70-100 within 90 days prior to Step 1 registration;

3.2.6 Age ≥ 18;

3.2.7 Surgical FFPE specimen must be available for submission to GenomeDx for genomic analysis on Decipher GRID platform. Note: If Decipher results have already been obtained, in lieu of tissue, results must be submitted to GenomeDx for validation and for GenomeDx to provide the subtyping needed for stratification.

3.2.8 Prior androgen deprivation therapy (LHRH agonist and/or non-steroidal anti-androgen) is allowed if discontinued at least 90 days prior to Step 1 registration and given for ≤ 90 days duration.

- For example: Patients on prior LHRH analogs (post-prostatectomy), the discontinuation date should be calculated based on the expected duration of the sustained release injection, not simply the injection date of the drug. For instance, if a 22.5 mg sustained release dose of leuprolide acetate is given (3 month duration), then the expected duration of such a dose would be 90 days after the injection date. For a 7.5 mg leuprolide (1 month duration), the discontinuation date would be 30 days after the injection date.
- Please note: Finasteride or dutasteride must be stopped before treatment starts but prior usage will not affect eligibility.

3.2.9 Hemoglobin ≥9.0 g/dL, independent of transfusion and/or growth factors within 90 days prior to Step 1 registration

3.2.10 Platelet count ≥100,000 x 10^9/μL independent of transfusion and/or growth factors within 90 days prior to step 1 registration

3.2.11 Serum albumin ≥3.0 g/dL within 90 days prior to Step 1 registration

3.2.12 GFR ≥35 mL/min estimated by Cockcroft-Gault or measured directly by 24 hour urine creatinine within 90 days prior to Step 1 registration

- Cockcroft-Gault formula is as follows:
  https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation
  CrCl (eGFR) = Sex * ((140 - Age) / (SerumCreat)) * (Weight / 72)

3.2.13 Serum total bilirubin ≤1.5 × ULN (Note: In subjects with Gilbert's syndrome, if total bilirubin is >1.5 × ULN, measure direct and indirect bilirubin and if direct bilirubin is ≤1.5 × ULN, subject is eligible) within 90 days prior to Step 1 registration

3.2.14 Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) <2.5 × ULN within 90 days prior to Step 1 registration

3.2.15 Testosterone >50 ng/dL within 90 days prior to Step 1 registration

3.2.16 Concomitant medications known to lower the seizure threshold (see list under prohibited medications in section 5.3.2) discontinued or substituted at least 4 weeks (30 days) prior to Step 1 registration.

3.2.17 The patient must agree to use a condom (even men with vasectomies) and another effective method of birth control if he is having sex with a woman of childbearing potential or agree to use a condom if he is having sex with a woman who is pregnant while on study drug and for 3 months following the last dose of study drug.

3.2.18 The patient must agree not to donate sperm during the study treatment and for 3 months after receiving the last dose of study drug.

3.2.19 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry.

3.3 Ineligibility Criteria

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

Prior to Step 1 Registration

3.3.1 Definitive clinical, radiologic, or pathologic evidence of metastatic disease (M1) or lymph node involvement (N1).

3.3.2 Prior invasive malignancy (except non-melanomatous skin cancer, carcinoma in situ of the male breast, penis, oral cavity, or stage Ta of the bladder, or stage I completely resected melanoma) unless disease free for a minimum of 2 years;

3.3.3 Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable;

3.3.4 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;

3.3.5 History of any of the following:

- Seizure or known condition that may pre-dispose to seizure (e.g. prior stroke within 1 year prior to Step 1 registration).
- History of documented inflammatory bowel disease
- Transmural myocardial infarction within the last 4 months prior to Step 1 registration.
- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months prior to Step 1 registration
- History of any condition that in the opinion of the investigator, would preclude participation in this study

3.3.6 Current evidence of any of the following:

- Known gastrointestinal disorder affecting absorption of oral medications
- Active uncontrolled infection (eg, human immunodeficiency virus [HIV] or viral hepatitis)
- Uncontrolled hypertension
- Any current condition that in the opinion of the investigator, would preclude participation in this study

3.3.7 Prior whole gland ablative therapy [i.e. cryoablation or high intensity focused ultrasound (HIFU)] for prostate cancer is not allowed

3.3.8 HIV positive patients with CD4 count < 200 cells/microliter within 30 days prior to registration .

3.3.9 HIV patients under treatment with highly active antiretroviral therapy (HAART) within 30 days prior to registration regardless of CD4 count. (Note: HIV testing is not required for eligibility for this protocol as it is self-reported. This exclusion criterion is necessary because the treatments involved in this protocol may be immunosuppressive and/or interact with HAART.)

3.3.10 Patients must not plan to participate in any other clinical trials while receiving treatment on this study or being followed post-protocol therapy.

Prior to Step 2 Randomization (15-JUL-2019)

For patients who have not undergone prior Decipher analysis, submission of the specimen to GenomeDx should be as soon as possible after study registration (Step 1) as these results can take up 21 days after the specimen is received at GenomeDx. Step 2 registration must occur within 6 weeks (42 days) of Step 1 registration. If Decipher results have already been obtained, in lieu of tissue, results must be submitted to GenomeDx for validation.

GenomeDx will run the sample for the commercial test "Decipher" and simultaneously run the PAM50 test that will be used for biomarker stratification. For patients who have already previously undergone Decipher testing, a new sample is not needed and the prior sample can be used to run the PAM50 test. The PAM50 test will subtype patients into one of four subtypes, Luminal A, Luminal B, Basal, or Unknown. These results must be obtained prior to proceeding and completing Step 2 randomization.

NOTES: Results will be conveyed to NRG headquarters for patient stratification and randomization within 21 business days after GenomeDx receives sufficient material for analysis. Once results of the Decipher analysis are made known to NRG headquarters, the registering site will be contacted by NRG HQ with an email to proceed to step 2 randomization. Do not proceed to step 2 without this notification. If the specimen was inadequate for analysis GenomeDx will contact the site for more material and if none can be provided then the patient will be classified as "Unknown" molecular subtype but still deemed eligible for randomization. It is expected that <2% of the patients will fall into this category, but the rate will be monitored and if the number reaches 16 (approximately 5%), further accrual of these patients will be terminated.

Results of the PAM50 test will not be provided to patients or the enrolling center or treating physicians. Decipher results will be provided upon request by NRG to the treating physicians after completion of protocol therapy

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

(15-JUL-2019**)**

PRE-TREATMENT ASSESSMENTS*

Assessments	Prior to Step 1 Registration (calendar days)	Prior to start of radiotherapy (calendar days)
Prostatectomy	≤10 years	
History & physical	≤90 days	
Performance status	≤90 days	
Gleason score	At the time of prostatectomy	
PSA	≤90 days	
Hemoglobin	≤90 days	
Platelet count	≤90 days	
Serum albumin	≤90 days	
GFR	≤90 days	
Serum total bilirubin	≤90 days	
AST or ALT	≤90 days	
Total Serum Testosterone	≤90 days	
PRO-CTCAE*		≤90 days
Tissue for banking (for consenting patients)		See Section 10 for details.
Blood and urine for laboratory studies/banking (for consenting patients)		See Section 10 for details.

***** This study uses Medidata Patient Cloud ePRO. Remember to register the patient to the Patient Cloud ePRO. For instructions on registering the patients, please refer to Appendix III. The

study-specific PRO-CTCAE items for this protocol can be found on the CIRB tab of the CTSU protocol webpage and is titled "Participant Questionnaire (PRO-CTCAE)"

ASSESSMENTS DURING TREATMENT

Assessments	Timeframe
TSH*	Day 1 (+/- 5 days) of each apalutamide/placebo cycle (1 cycle = 30 days)
CBC and complete metabolic panel**	During the last week of radiotherapy (+/- 2 weeks)
Adverse Event assessment	During the last week of radiotherapy (+/- 1 week)
PRO-CTCAE***	During the last week of radiotherapy (+/- 1 week)
Blood for laboratory studies/banking (for consenting patients)	See Section 10 for details.

*With reflex to free T4; T3 only if clinically indicated afterwards.
**CBC and complete metabolic panel to be assessed and maintained in the patient record. Hgb, platelet count, albumin, AST or ALT, and total serum bilirubin to be reported on study-specific CRFs.
*** This study uses Medidata Patient Cloud ePRO. Remember to register the patient to the Patient Cloud ePRO. For instructions on registering the patients, please refer to Appendix III. The study-specific PRO-CTCAE items for this protocol can be found on the forms section of the CTSU protocol webpage and is titled "NRG-GU006 NCI PRO-CTCAE Item Library"

ASSESSMENTS IN FOLLOW UP

Assessments	From randomization: q3 mos. x 2 yrs; q6 mos. x 3 years; then annually (Note: first 6 months are on-treatment time points) (+/- 1 month)	As clinically indicated
PSA	**X**	
Total serum testosterone	At 3, 6, 9, 12, and 36 months post randomization or as clinically indicated	X
CBC and complete metabolic panel	At 3 months after RT only	X
TSH*	At 9 and 12 months post randomization only	
Adverse Event assessment	X	
PRO-CTCAE**	X At each follow-up in the first 2 years only	
CT, MRI, bone scan, and PET		X
Blood for laboratory studies/ banking (for consenting patients)	See Section 10 for details.	

* With reflex to free T4; T3 only if clinically indicated afterwards.

**The study-specific PRO-CTCAE items for this protocol can be found on the forms section of the CTSU protocol webpage and is titled "NRG-GU006 NCI PRO-CTCAE Item Library"

Definition of Disease Assessments

• Biochemical Progression-Free Survival (bPFS): Time from randomization to first event. Events for bPFS will be the first occurrence of biochemical failure by PSA ≥ 0.2 ng/ml PSA from nadir confirmed by a second equal or higher PSA than the first, recurrence (local, regional or distant), or death from any cause. If an event is identified, then the time of the event will be recorded as the first instance where any of the above situations occurs (e.g., the first instance where PSA ≥ 0.2 ng/ml, from nadir etc.).

•Initiation of salvage hormone therapy (LHRH analogues or non-study anti-androgens) will be recorded if it occurs after completion of SRT.

• Metastasis Free Survival (MFS): Time from randomization to first event. Events for MFS will be the first occurrence of distant metastasis or death from any cause. Subjects with biochemical failure should have a CT abdomen and pelvis and bone scan performed at least every 6 months. Patients without metastases with PSA ≥ 5 ng/ml and/or doubling time ≤ 6 months should have these scans performed at least every 4 months.

• Metastases will be defined based on radiographic findings with or without clinical correlation and/or pathologic confirmation. Nodes must be 1.5 cm short axis or more and above the iliac bifurcation. Equivocal bone scan findings should be confirmed by radiographic or pathologic methods. Locoregional recurrence and/or biochemical failure will be ignored for this endpoint. Metastases shall be classified as either castrate or non-castrate events.

• Overall survival (OS): Time from randomization to death from any cause.

• Time to locoregional progression: Time from randomization to local or regional recurrence ignoring biochemical failure and distant recurrence and censoring for death. Local or regional recurrence is defined as recurrence within the pelvis including lymph nodes below the iliac bifurcation. Lymph node recurrence is defined radiographically as any lymph node in the treatment field which measures at least 1.5 cm short axis dimension as measured by cross sectional imaging with CT or MRI. Biopsy confirmation of recurrence is strongly encouraged but not required.

• Undetectable PSA with a non-castrate testosterone at 1 and 3 years post randomization: PSA < 0.1 ng/ml and testosterone ≥ 50 ng/dl.

5. TREATMENT PLAN/REGIMEN DESCRIPTION (15-JUL-2019)

Arm 1 vs Arm 2 (Blinded)

Salvage Radiotherapy to 64.8-70.2 Gy at 1.8-2.0 Gy/33-39 fractions to the prostate bed*

AND

Blinded placebo or apalutamide daily for 6 months (180 days/ six 30-day cycles) initiated at start of radiotherapy

*Treatment of pelvic lymph nodes is allowed at the discretion of the treating physician.

5.1 Chemotherapy/Hormonal Therapy/Other Agent-Based Therapy (15-JUL-2019)

5.1.1 Apalutamide/Placebo: **To be initiated on day 1 of radiotherapy (+/- 14 days) after**

randomization.
Apalutamide/placebo will be given at a dose of 240 mg daily orally once daily for 6 months (180 days), at approximately the same time every day. 1 cycle = 30 days (total of 6 cycles).

5.2 Radiation Therapy (15-JUL-2019)

Protocol radiation therapy should start within 28 days following randomization. Placebo/apalutamide should begin the same day as radiotherapy treatment (+/- 14 days allowed). Radiotherapy should be delivered over approximately 7-8 weeks.

Radiation Therapy Schema

Arm 1, Prostate Bed Radiotherapy* Alone: 64.8-70.2 Gy (1.8-2.0 Gy per fraction) + placebo for 180 days, beginning day 1 of radiotherapy (+/- 14 days).

Arm 2, Prostate Bed Radiotherapy* + 6 months of apalutamide: 64.8-70.2 Gy (1.8-2.0 Gy per fraction) + apalutamide 240 mg daily for 180 days, beginning day 1 of radiotherapy (+/- 14 days)

*Treatment of pelvic lymph nodes is allowed at the discretion of the treating physician. The pelvic lymph nodes should be treated using 1.8-2.0 Gy per fraction to a total dose of 45-50 Gy over 25 fractions.

5.2.1 Treatment Technology

This protocol allows for photon treatment performed with 3D-CRT and, IMRT techniques, including Tomotherapy and VMAT. Treatments performed on MRLinac and CyberKnife treatment units are also allowed. Some form of image guidance is required (orthogonal planar imaging pairs, CBCT, electromagnetic transponders, etc).

5.2.2 Immobilization

Proper immobilization is critical for this protocol. Patient setup reproducibility must be achieved using appropriate clinical devices.

5.2.3 Simulation Imaging

A treatment planning CT scan will be required to define the clinical and planning target volumes, and the critical normal structures. The treatment planning CT will be acquired with the patient set up in the same position as for daily treatments. Each patient will be positioned preferably in the supine position. Prone positioning for treatment is not recommended, but is allowed. 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.

Use of contrast (IV, po, or rectal) is at the discretion of the treating physician. The placement of contrast in the rectum may cause the rectum to appear more anterior than it

will be during treatment.

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.

NRG-GU006 Structure Names for both Arms 1 and 2

Standard Name	**Description**	**Validation Required/Required when applicable/Optional**
CTV_xxxx (e.g. CTV_7020)	CTV (including prostatic fossa and seminal vesicle remnants if present)	**Required**
PTV_xxxx (e.g. PTV_7020)	PTV to receive 64.8-70.2 Gy	**Required**
OPTIONAL: Only if pelvic lymph nodes are treated:		
CTVn	Pelvic Lymph Nodes per the NRG Atlas	**Required when applicable**
CTVn_xxxx (e.g. CTVn_4500)	CTV_xxxx above **plus** pelvic lymph nodes (CTVn)	**Required when applicable**
PTVn_xxxx (e.g. PTVn_4500)	PTVn volume to receive 45 – 50 Gy	**Required when applicable**

Prostate Bed Planning for 3DCRT:

Prostate Bed Planning for 3D-CRT The definition of volumes will be in accordance with ICRU Report #62.

The PTV_xxxx margins from CTV_xxxx should be a minimum of 0.5 cm and a maximum of 1.5 cm in all dimensions. A posterior margin of < 0.6 cm will be considered an unacceptable deviation. Care should be taken to conform the prescribed dose as closely to the PTV_xxxx as possible, so as to avoid including the entire width of the rectum in the posterior blocked margin at the bladder neck-rectum interface. The planned dose between 64.8 to 70.2 Gy is determined after the patient is planned and all dosimetric parameters finalized.

Prostate Bed Planning for IMRT

Target volumes: The definitions of volumes will be in accordance with the 1999 ICRUReport#62.

The CTV_xxxx will be the same as for 3D-CRT. There is no need to add margin for penumbra. CTV_xxxx margin to PTV_xxxx should be between 0.5-1.5 cm. A posterior margin of 0.3-0.5 cm is acceptable if daily CBCT is being used. < 0.3 cm posterior margin is an unacceptable deviation.

Detailed Specifications:
CTV_xxxx: The CTV_xxxx will include the prostatic fossa and seminal vesicle remnants when present. Prostatic fossa CTV definition should follow guidelines as provided in the post-prostatectomy contouring atlas at https://www.rtog.org/CoreLab/ContouringAtlases.aspx. The prostatic fossa CTV will extend inferiorly from the top of the penile bulb (or one CT slice ≤ 0.3 cm above) to just above the pubic symphysis superiorly at a minimum (at least for the anterior-most portion of the bladder). Laterally, the prostatic fossa CTV will extend from the medial edge of one obturator internus muscle to the other. Anteriorly and posteriorly the prostatic fossa CTV will include the entire bladder neck until above the pubic symphysis, where a gradual reduction off the anterior bladder is made. The prostatic fossa CTV may be increased (not decreased) beyond these limits in order to encompass the entirety of the prostate based on pre-prostatectomy imaging information when available. In addition, the superior, lateral, and posterior extent of the prostatic fossa CTV should be increased as needed to cover any defined remnants of the seminal vesicles, which should be included in the prostatic fossa CTV.

PTV_xxxx: The PTV_xxxx will be a direct expansion of 0.5-1.5 cm beyond the CTV_xxxx. Additional expansion within this range is required to account for penumbra when 3D CRT is used. Reduction in posterior expansion to 0.3-0.5 cm beyond the CTV_xxxx is considered an acceptable variation when required to meet Rectum constraints or when daily CBCT is used.

Use of Cone Beam CT and Plan Adjustment: There may be cases in which the target and surrounding normal tissues are found not to be reproducible relative to the simulation CT and consequent plan. Replanning will invalidate the dosimetry and is considered a deviation. If all attempts to reproduce bladder and rectal filling by coaching the patient do not work and replanning is thought to be necessary, the patient should be replanned in the same supine position with the new contours drawn to reflect any changes in the anatomy.

Pelvic Lymph Node Irradiation Details:
Treatment of the pelvic lymph nodes is optional, and if performed should follow the NRG online contouring atlas (https://www.nrgoncology.org/Portals/0/Scientific Program/CIRO/Atlases/Prostate Pelvic Lymph Nodes.ppt with coverage of the internal and external iliac lymph nodes, presacral lymph nodes, and obturator lymph nodes. In general this begins at L5/S1, but coverage to the L4/L5 is acceptable.

CTVn should include pelvic lymph nodes per the atlas.

CTVn_xxxx should include the CTV_xxxx **plus** CTVn, relevant vascular structures with a 5-7 mm margin per the atlas, cropped away from muscle, bone, bowel, and bladder.

PTVn_xxxx should be a direct expansion of 0.5-1.5 cm beyond the CTVn_xxxx based on institutional standards. Typically a 0.7 cm PTV expansion is acceptable.

5.2.5 Definition of Critical Structures and Margins

Standard Name	Description	Validation Required/Required when applicable/Optional
Bladder	Entire bladder	**Required**
Bladder-CTV	Entire bladder minus CTV	**Required**
Rectum	anterior flexion of the rectosigmoid superiorly to the ischial tuberosities inferiorly	**Required**
Femur_Head_R	Outlined down to the region between the greater and lesser trochanters	**Required**
Femur_Head_L	Outlined down to the region between the greater and lesser trochanters	**Required**
Femurs	Femur_Head_R + Femur_Head_L	**Required**
PenileBulb	Entire penile bulb	**Required**
SeminalVes	Seminal Vesicle remnants if present	**Required when applicable**
Spc_Bowel	Small and large bowel in the pelvis and 1-2 cm superior to last slice of PTVn_xxxx (Bowel Bag).	**Required when applicable**
External	External contour	**Required**

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

Rectum: The rectum contour will include the rectum and anal canal and will be contoured on every slice from the rectosigmoid junction superiorly to the level of the ischial tuberosities inferiorly.

Bladder: The bladder contour will include the entirely of the bladder as defined on the simulation CT. The bladder should be moderately full as noted in Section 5.2.2 so that a portion lies outside the PTV (the patient should not be uncomfortable at simulation and probably will have more difficulty maintaining a full bladder during treatment).

Bladder-CTV: The bladder volume outside the CTV_xxxx as defined in Section 5.2.4.

Femurs: The femoral heads should be contoured down to the region between the greater and lesser trochanters.

SeminalVes: Seminal Vesicle remnants if present

Penile Bulb: The entirety of the penile bulb should be contoured. The penile bulb is the portion of the bulbous spongiosum of the penis immediately inferior to the GU diaphragm.

External: The body surface encompassing all CT slices from 1.5 cm inferior to superior of the radiation fields.
OPTIONAL:
Spc_Bowel: Bowel bag when covering pelvic lymph nodes: Small and large bowel in the pelvis and 1-2 cm superior to last slice of PTVn_xxxx.

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_xxxx	64.8 to 70.2	1.8-2.0	33 to 39	Covering 95% of PTV
If covering pelvic lymph nodes (optional):				
PTV_xxxx	45 to 50	1.8-2.0	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 95% of the PTV volume receives

prescription dose of 64.8 to 70.2 Gy.

Target Volume Constraints and Compliance Criteria

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
PTV_xxxx	D95%[%]	99-101	98-102
	D99%[%]	>=95	>=90
	D0.03cc[%]	<=107	<=111
PTV_ n_xxxx	D95%[%]	98-102	95-105

Per Protocol range is excluded from Variation Acceptable range. % is calculated with prescription dose.

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

Normal Structure Constraints and Compliance Criteria

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
Rectum	V64.8-70.2 Gy [%]	<=20	<=27.5
	V50Gy[%]	<=50	<=57.5
Bladder-CTV	V64.8-70.2 Gy [%]	<=40	<=47.5
	V50Gy[%]	<=60	<=67.5

Per Protocol range is excluded from Variation Acceptable range.

Recommended dose acceptance criteria for other normal tissue, but not to be used for plan score.

Structure	Recommended dose acceptance criteria
PenileBulb	Mean [Gy] <= 52.5 Gy
Femurs	V50 Gy [%]<= 20%
Spc_Bowel (if covering pelvic lymph nodes)	V45 Gy (cc) <=195 cc D0.1 cc (Gy) <= 50 Gy

Delivery Compliance criteria

	Per Protocol	Variation Acceptable
Apalutamide/placebo initiated on day 1 of radiotherapy	+/- 14 days	+/- 30 days
Interruptions	1-7 days	8-14 days

5.2.8 Treatment Planning Instructions

-Beam arrangement

Static gantry IMRT beam arrangements must be designed with a minimum of 5 gantry angles. If the beams are intercepted by a couch in the beam, the couch should be included in the treatment plan. For VMAT plans ≤3 arcs are suggested.

-Acceptable algorithms

For Convolution/Superposition type algorithms, dose should be reported as computed inherently by the given algorithm. For Monte Carlo or Grid Based Boltzmann Solver algorithms, conversion of Dm (dose-to-medium) to Dw (dose-to-water) should be avoided. Dm, computed inherently by these algorithms, should be reported.

-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 and AAPM task group report recommendations.

For IMRT/VMAT/proton plans, patient specific QA is highly recommended. The recommended patient specific QA criteria is for 90% of the comparison points to pass a ±3%/3mm Gamma Index analysis.

5.2.10 Daily Treatment Localization/IGRT

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 to focus on image-guidance at the time of radiation delivery to ensure its adherence to the planned treatment.

Daily image guidance using either 2D/2D or 3D methods is required. If any deviation is larger than 2 mm, correction should be performed. All image/signal-guidance data should be recorded and archived at the site and available for review if requested.

Management of Radiation Dose to the Patient from IGRT

NRG Oncology is concerned about the estimated doses given from IGRT, and is committed to limiting the imaging dose when IGRT is used in any of its protocols. This can be accomplished by avoiding the use of this technology to make small changes in patient positioning that are within the stated PTV margins. The imaging dose to the patient may become significant if repeated studies are done for patients with severe set up problems (e.g. requiring frequent corrections that are larger than the PTV margins). It is recommended that the institution sets their own limit of IGRT attempts before re-setting up the patient for better positioning. It is recommended that patients demonstrating severe set up problems during the first week of treatment be moved to a treatment with larger

margins.

5.3 General Concomitant Medication and Supportive Care Guidelines (15-JUL-2019)

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.

5.3.2 Prohibited Concomitant Medications

Non-protocol androgen deprivation therapy, 5-alpha reductase inhibitors, and/or chemotherapy are prohibited.

As a class effect, AR antagonists have been associated with seizures due to an off-target mechanism of action (gamma amino butyric acid chloride channel [$GABA_A$] inhibition). Drugs known to lower the seizure threshold or cause seizures are prohibited and a representative list is included below:

- Atypical antipsychotics (e.g. clozapine, olanzapine, risperidone, ziprasidone)
- Bupropion
- Lithium
- Meperedine and pethidine
- Phenothiazine antipsychotics (eg, chlorpromazine, mesoridazine, thioridazine)
- Tricyclic antidepressants (eg, amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine

Please see Appendix I for a more comprehensive list of medications prohibited while receiving apalutamide/placebo.

5.3.3 Restricted Concomitant Medications

Apalutamide is metabolized primarily by human CYP3A4, thus co-administration with strong inhibitors or inducers of CYP3A4 should be avoided as much as possible. Apalutamide may also induce CYP3A4; therefore, caution should be taken when administered in conjunction with CYP3A4 substrates that have a narrow therapeutic index. Examples of the strong CYP3A4 inhibitors and inducers include the following:

- Strong CYP3A4 inhibitors: itraconazole, clarithromycin, erythromycin, diltiazem, verapamil, delavirdine, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, grapefruit juice (or grapefruits); co-administration with any of these agents may increase apalutamide plasma concentrations.
- Strong CYP inducers: phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, efavirenz, tipranivir, St. John's wort; co-administration with any of these agents may decrease apalutamide plasma concentrations/

The potential for drug-drug interaction between apalutamide and warfarin (eg, Coumadin) is unknown at present. If a subject is taking warfarin, the prescribing physician should re-assess PT (prothrombin time)/international normalized ratio (INR) more frequently during the study protocol as clinically indicated or recommended by the prescribing physician for the specific indication of warfarin dose and adjust the dose of

warfarin accordingly.

5.3.4 Participation in Other Trials

Patients will not be allowed to participate in any other clinical trials while receiving treatment on this study or being followed post-protocol therapy.

5.4 Emergency Unblinding Procedure

The decision to break the unblinding code must be based on a serious adverse event unexpected for the study drug and related to the study drug or extraordinary clinical circumstance for which knowledge of drug assignment will affect clinical judgment.

Sites can call NRG Headquarters during business hours (8:30 AM to 5 PM ET), at 215-574-3150 and ask to speak to the Supporting Study Statistician. For after hours, weekends, and holidays, call 215-940-8902.

5.5 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 (14JUN2018)

Dose Modifications for Toxicity Attributed to Apalutamide

Dose modifications are provided as guidance and should not replace the investigator's own clinical judgment.

NOTE: PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol directed action.

Toxicity	Dose of apalutamide (assuming 240 mg/day dosing; four 60 mg tablets)
Grade 1 or 2	No change
≥Grade 3 or higher	Hold until Grade 1 or baseline, resume at full dose
First Recurrence ≥Grade 3	Hold until Grade 1 or baseline, resume at 180 mg (3 tablets)
Second Recurrence ≥Grade 3	Hold until Grade 1 or baseline, resume at 120 mg (2 tablets)
Third Recurrence ≥Grade 3	Discontinue
First occurrence of seizure of any grade or Grade 4 neurotoxicity	Discontinue

Thyroid Stimulating Hormone (TSH)
Changes in TSH from baseline have been observed both in subjects with and without a history of thyroid disorders, however, the largest numerical increases in TSH have been observed in subjects on thyroid hormone replacement. Increases in TSH are at times associated with decreases in T3 or T4 or both. Thyroid function should be monitored and doses of replacement hormones should be started or adjusted based on laboratory findings.

Rash
Dose modifications for rash related to study drug treatment are allowed for apalutamide/placebo and are summarized in below table.

The etiology of the rash remains unclear. Subjects commonly present with a maculo-papular rash with a localized or diffuse distribution, sometimes involving the entire body. Investigators have reported that the rashes improve with apalutamide interruption or treatment with various supportive medications (eg, anti-histamines and topical or systemic steroid therapy started sequentially or in combination) or both. Early medical intervention when subjects present with limited distribution may prevent extension/spreading of the rash. Once the subject's rash has improved, some investigators have re-started apalutamide at a reduced dose. No serious allergic/anaphylactic reactions have been observed after re-starting apalutamide. If the rash recurs, dose interruption, symptomatic management, and re-start with a further dose reduction may be considered. If rash recurs at the lowest allowable dose of 120 mg/day, apalutamide should be stopped permanently.

Severity	Intervention

Grade 1	• Continue apalutamide/placebo at current dose
	• Initiate dermatological treatment[a]
	  o Topical steroid cream AND
	  o Oral Antihistamines
	• Monitor for change in severity[a]

Grade 2 (or symptomatic Grade 1)[b]	• Hold apalutamide/placebo for up to 28 days
	• Initiate dermatological treatment[a]
	  o Topical steroid cream AND
	  o Oral Antihistamines
	• Monitor for change in severity[a]

	○ If rash or related symptoms improve, reinitiate apalutamide/placebo when rash is Grade≤1. Consider dose reduction at a 1 dose level reduction[c].
Grade ≥3[d]	• Hold apalutamide/placebo for up to 28 days • Initiate dermatological treatment[a] ○ Topical steroid cream AND ○ Oral Antihistamines AND ○ Consider short course of oral steroids • Reassess after 2 weeks (by site staff), and if the rash is the same or has worsened, initiate oral steroids (if not already done) and refer the subject to a dermatologist ○ Reinitiate apalutamide/placebo at a 1 dose level reduction[e] when rash is Grade≤1. ○ If the dose reduction will lead to a dose less than 120mg, the study drug must be stopped (discontinued) • If after 28 days, rash has not resolved to Grade≤1, contact the Medical Oncology Co-Chair, Edwin Posadas, MD, to discuss further management and possible discontinuation of study drug. • If a drug treatment recurrent Grade 3 toxicity occurs the study drug will be stopped (e.g. if one Grade 3 toxicity occurs followed by dose reduction and then the same Grade 3 toxicity occurs, the study drug must be stopped).

Note: Rash may be graded differently according to the type of rash and associated symptoms. For example, maculo-papular rash is graded by body surface area covered and not severity of the rash. Please consult NCI-CTCAE Version 5 for specific grading criteria for other types of rash.

[a] Obtain bacterial/viral cultures if infection is suspected
[b] Subject presents with other rash related symptoms such as pruritus, stinging, or burning
[c] 1 dose level reduction = decrease by 60 mg (1 apalutamide tablet) to 180 mg
[d] If there is blistering or mucosal involvement, stop apalutamide/placebo dosing immediately and contact the Medical Oncology Co-Chair, Edwin Posadas, MD
[e] If a subject previously started oral corticosteroids, continue for at least 1 week after resumption of reduced dose of apalutamide/placebo. If the proposed total oral steroid use will exceed 28 days, contact the Medical Oncology Co-Chair, Edwin Posadas, MD

7. ADVERSE EVENTS REPORTING REQUIREMENTS

Adverse Event reporting begins at the time a patient signs consent; please report all AEs that start after consent is signed. Report serious adverse events that meet expedited reporting criteria via CTEP-AERS.

7.1 Protocol Agents

Investigational Agents

The investigational agent administered in NRG-GU006, apalutamide**,** is being made available under an IND sponsored by NRG Oncology. For apalutamide, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in Section 7.4 of the protocol.

7.2 Adverse Events and Serious Adverse Events (15-JUL-2019)

7.2.1 This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

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 that apalutamide may have an effect on sperm, the impregnation of a study participant's partner must be reported via CTEP-AERS in an expedited manner.

Clinician graded CTCAE is the AE (adverse event) safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items but no protocol directed action will be taken. The specific PRO-CTCAE items for this protocol can be found on the forms section of the CTSU protocol webpage and is titled "NRG-GU006 NCI PRO-CTCAE Item Library. PRO-CTCAE is not intended for expedited reporting, real time review or safety reporting. PRO-CTCAE data are exploratory and not currently intended for use in data safety monitoring or adverse event stopping rules.

NOTE: PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol directed action.

7.2.3 Adverse Events and PRO-CTCAE

PRO-CTCAE

The PRO-CTCAE instrument will be used to assess patient reported toxicity outcomes.

PRO-CTCAE is a validated instrument developed by the National Cancer Institute to assess clinical trial toxicity outcomes by patient report; it complements information collected by physician-reported CTCAE. PRO-CTCAE is available in English and Spanish for this study. Patients participating on the electronic patient-reported outcome (Medidata Patient Cloud ePRO) will only have the option to complete the English language PRO-CTCAE. Spanish language PRO-CTCAE is not currently available on the Medidata Patient Cloud ePRO.

PRO-CTCAE assessments will be collected before the start of radiation ,during the last week of radiation treatment and in follow-up as specified in the Section 4 assessment tables.

The patient-reported AEs that will be assessed using PRO-CTCAE are listed in the table below. These adverse events, if reported, should also be clinician graded using the CTCAE per Section 7.2.1.

CTCAE Term	**PRO-CTCAE Items With Attributes**
Fatigue	Fatigue (severity, interference)
Breast pain; Gynecomastia	Breast swelling and tenderness (severity)
Hot flashes	Hot flashes (frequency, severity)
Concentration impairment	Concentration (severity, interference)
Memory impairment	Memory (severity, interference)
Nausea	Nausea (frequency, severity)
Diarrhea	Diarrhea (frequency)
Fecal incontinence	Fecal incontinence (frequency, interference)
Abdominal pain	Abdominal pain (frequency, severity, interference)
Dysgeusia	Taste changes (severity)
Anorexia	Decreased appetite (severity, interference)
Rash maculo-papular; Refer to Skin and subcutaneous tissue disorders for clinically accurate CTCAE term	Rash (presence/absence/amount)
Pruritus	Itching (severity)
Urinary tract pain	Painful urination (severity)
Urinary urgency	Urinary urgency (frequency, interference)
Urinary frequency	Urinary frequency (presence/absence/amount, interference)
Urinary incontinence	Urinary incontinence (frequency, interference)
Erectile dysfunction	Achieve and maintain erection (severity)
Ejaculation disorder	Ejaculation (frequency)
Libido decreased	Decreased libido (severity)
Delayed orgasm	Delayed orgasm (presence/absence/amount)
Anorgasmia	Unable to have orgasm (presence/absence/amount)

7.3 Adverse Events for Investigational Study Agents Provided by Janssen

(24-SEP-2020)

Refer to the Investigator Brochure for comprehensive information

Apalutamide

Very Common (>10%)	Common (1-10%)	Uncommon (< 1%)	Frequency unknown*
Fatigue	Itching	Seizure	Inflammation within the lungs that may lead to permanent damage (Interstitial lung disease)
Skin rash	Changes in thyroid function (Hypothyroidism)		Life-threatening rash with blisters and peeling over much of the body (Toxic epidermal necrolysis)
Joint pain (Arthralgia) or muscle spasms	Increase in cholesterol		
Weight Loss	Increase in triglycerides		
Fall	Change in experience of taste (Dysgeusia)		
Fracture	Reduced or blocked blood flow to the heart, including heart attack (Ischemic Heart Disease, including Myocardial Infarction)		
Increased blood pressure (hypertension)	Reduced or blocked blood flow to the brain, including stroke (Ischemic Cerebrovascular Disorders)		
Hot flush			
Diarrhea			
Decreased appetite**			

* this is information provided voluntarily by doctors using apalutamide in routine clinical practice; not from clinical trials, from a population of uncertain size; therefore, it is not possible to estimate frequency or exclude a causal relationship to apalutamide.

** this is information provided voluntarily by doctors using apalutamide in routine clinical practice where frequency cannot be estimated; however, frequency of this event can be estimated from clinical trials and is assessed as very common.

The following situations should be reported as adverse events on the case report form and if any of these events meet the criteria for seriousness, they should be reported expeditiously via CTEP-AERS:

- Overdose of the medicinal product
- Suspected abuse/misuse of the medicinal product
- Inadvertent or accidental exposure of the medicinal product
- Medication error, with or without patient exposure (e.g. name confusion)
- Suspected transmission of any infectious agent via administration of the medicinal product

7.4 Expedited Reporting of Adverse Events (15-JUL-2019)

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

Serious adverse events that begin after the patient signs consent but prior to the initiation of protocol treatment and meet expedited reporting criteria should be reported in CTEP-AERS by selecting the treatment assignment code, TAC-0, indicating prior to start of protocol treatment.

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 Oncology by phone at 1-215-574-3191. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

NOTE: PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol directed action.

7.4.1 Expedited Reporting Methods

- CTEP-AERS-24 Hour Notification requires that a CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS24-hour notification must be followed by a complete report within 5

days.

- Supporting source documentation is requested by NRG as needed to complete adverse event review. Supporting source documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page. Contact NRG Oncology at 1-215-574-3191 for source documentation assistance.
- 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.
- NRG Oncology reports serious adverse events to Janssen within 24 hours of awareness. Additionally, NRG Oncology reports applicable adverse events to FDA per 21 CFR 312.32

Pregnancy

Investigators must report a male participant's impregnation of his partner expeditiously as a grade 3 SAE coded in the CTCAE as "pregnancy, puerperium and perinatal conditions, other—pregnancy" in CTEP-AERS and also submit the Pregnancy Information Form found at this link: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf

The form should be submitted within 14 days of notification and then faxed to 301-230-0159 or 301-897-7404 **AND** the form should also be uploaded to the patient case file in RAVE in the source documentation upload folder at the same time. NRG Oncology will report the pregnancy to Janssen within 24 hours of notification of the event. Patients should be instructed to notify the investigator if it is determined after completion of the study that they have impregnated their partner, either during the treatment phase of the study or within 100 calendar days after the end of treatment. The pregnancy outcome for patients on study should be reported to NRG Oncology. NRG Oncology will report the status to Janssen.

7.4.2 Expedited Reporting Requirements for Adverse Events

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

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

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

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

Expedited AE reporting timelines are defined as:

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

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

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

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

Effective Date: May 5, 2011

Additional Protocol-Specific Instructions to Expedited Reporting Requirements
Not applicable

Clinician graded CTCAE is the AE safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items but no protocol directed action will be taken. The study-specific PRO-CTCAE items for this protocol can be found on the forms section of the CTSU protocol webpage and is titled "NRG-GU006 NCI PRO-CTCAE Item Library"

7.4.3 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.

7.4.4 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 AE reporting unless otherwise specified.

8. REGISTRATION AND STUDY ENTRY PROCEDURES (24-SEP-2020)

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
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 Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and

Additional information is located 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 Cancer Trials Support Unit Registration Procedures (24-SEP-2020)

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

IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRB Manager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the

network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements for Protocol NRG-GU006 Site Registration

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).
- IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC to begin the modality credentialing process.
- Enrolling site must be aligned to an RTI provider.

This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) credentialed provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. A primary role on any roster is required to update provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, please view the Person Roster Browser under the RUMS link on the CTSU website.

To complete protocol-specific credentialing the RT/I provider or enrolling site should follow instructions in protocol section 8.2 to submit documentation or other materials to the designated IROC Quality Control (QC) center. Upon the IROC QC center approving the RT/I provider for the study modality, IROC will automatically send the approval to the Regulatory Support System (RSS) to comply the protocol specific requirement. IROC will continue to copy the provider and/or enrolling site on modality approvals.

Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen, and may need to answer additional questions related to treatment in the eligibility checklist.

8.1.1 Additional Requirements for sites in Canada

Prior to clinical trial commencement, sites in Canada must also complete and submit via the Regulatory Submission portal on the CTSU website:

- Clinical Trial Site Information Form,
- Qualified Investigator Undertaking Form
- Research Ethics Board Attestation Form
- Protocol Signature Page
- Investigator Brochure Signature Page
- Delegation of Tasks (DTL) Log
- List of Laboratories
- SIV/Training Confirmation of Completion Form – Research Associate (please refer to the activation memo for details)
- SIV/Training Confirmation of Completion Form – Qualified Investigator (please refer to the activation memo for details)
- IRB/REB approved consent (English and native language versions*).

*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.

The following items are collected By NRG Oncology Regulatory on a yearly or biyearly basis:

- IRB/REB Membership Roster
- Laboratory Certificates and Normal Values
- CVs for Qualified Investigator and Sub-Investigators noted on the DTL log

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select *NRG Oncology* and protocol number NRG-GU006
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log on to the CTSU members' website, go to the → Regulatory section and select → Regulatory Submission.

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

Checking Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the sites 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

8.1.2 Pre-Registration Requirements for the Initial Shipment of Apalutamide

All pre-registration requirements must be met before registering the first case. All institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the CTSU website. Institutions must submit the SASF to the CTSU Regulatory Office via the Regulatory Submission Portal as soon as the individual responsible for the study agent has been identified.

8.2 RT-Specific Pre-Registration Requirements (15-JUL-2019)

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

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 and NRG Headquarters 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.

Credentialing Requirements	**Web Link for Procedures and Instructions: www.irochouston.mdanderson.org**	
	Treatment Modality	**Key Information**
	Photons	
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 Head and neck phantom irradiation 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 an institution, depending on its treatment delivery modalities, may be required to irradiate a phantom on different delivery machines such as ViewRay, TomoTherapy and CyberKnife
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

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:
Site staff that will be submitting images via TRIAD will need to register with CTEP and have a valid and active CTEP-IAM account.

- Must be registered as an Associate, Associate Plus, Non-Physician Investigator, or Investigator registration type. Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in Registration and Credential Repository (RCR).

To submit images, site staff must hold the TRIAD Site User role on an NCTN or ETCTN roster. Individuals requiring a TRIAD Site User role should contact the person holding a primary role at the site for their affiliated NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD, and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

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

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

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 (15-JUL-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)

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- 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.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

8.4 Medidata Patient Cloud ePRO Registration (Clinical Research Associates: Please review Appendix III) (24-SEP-2020)

This study includes the use of Medidata Patient Cloud ePRO (electronic patient-reported outcomes). After the patient is registered to the trial via OPEN, and if the patient is willing to participate in electronic data collection, the site staff will then complete a registration for the patient to the Patient Cloud ePRO through iMedidata. Note: Site staff must have already completed required eLearning for the Patient Cloud ePRO application

to register a patient and information about the training is in the ePRO Appendix. The registration to the Patient Cloud ePRO will create a unique patient registration code that the site staff will provide to the patient. The patient (with assistance from the site staff) should be instructed to download the Patient Cloud ePRO app onto his/her own device (IOS, Android, phone or tablet) and use the unique patient registration code to create an account. Once the patient's account is set up, the patient will be able to complete the submission of patient reported outcomes electronically for the trial.

There are MULTIPLE VERSIONS of the app available. The Patient Cloud ePRO App will be used on this study. Ensure that the patient downloads the correct version of the ePRO app. Note only 1 version of the app is active per protocol.

For sites providing a shared institutional device for use by multiple patients on site:

- The site staff should assist the patient with access and registration to the Patient Cloud ePRO app, and the patient can then complete the electronic data submission independently. Site staff may need to assist patients with logging on to the device at each visit.

8.4.1 CRA Patient Registration Instructions for ePRO

i. Please visit the CTSU website for reference information The subject registration process starts in iMedidata. Begin by selecting the Patient Cloud ePRO Registration link for your study

ii. The patient management app will display, select your STUDY and SITE from the drop downs and click Launch.

iii. Now you can register your first patient. Create a subject ID and select a Country / Language from the drop down, (these are the only required data fields). The subject initials are optional, but are helpful in identifying which subject ID maps with which activation code. When finished, click Add.

iv. The subject added and will include the date the patient was added, the subject ID, subject initials, (if included) and a unique auto-generated activation code. The activation code is unique for each patient and linked to the subject ID, it is not interchangeable. In addition, there is a status section, which indicates if the patient has registered. When the patient has registered the status will change from "invited" to "registered".

Reminder- site staff must have already completed the Medidata Patient Cloud training in order to register study participants . Please visit the Medidata Learning ToolCTSU website for reference information. on Patient Cloud ePRO for CRAs.
https://learn.mdsol.com/patient-cloud/en/video-library-for-providers-102101952.html

9. DRUG INFORMATION

9.1 Investigational Study Agent: Apalutamide (IND 135824) (15-JUL-2019)

To supplement the toxicity information contained in this document, investigators must obtain the current version of the Investigator Brochure for comprehensive pharmacologic and safety information. The Investigator Brochure can be obtained from the CTSU by completing the CTSU Request for Clinical Brochure form. This form can be found on the CTSU website under documents > site registration.

9.1.1 Adverse Events: See Section 7.3 and consult the investigator brochure for comprehensive information

9.1.2 Dosage Selected, Preparation, and Schedule of Administration

Apalutamide/placebo is administered orally on a continuous once daily dosing schedule. The therapeutic dose is 240mg (4 x 60mg tablets) once daily. Apalutamide/placebo can be taken with or without food.

9.1.3 Supply, Packaging, Accountability, and Drug Ordering

Apalutamide 60 mg and Matching Placebo will be distributed by a vendor, Clinical Research Services, a division of RxCrossroads by McKesson. Apalutamide/placebo 60-mg tablets will be packaged in 120-count, 160 cc high-density polyethylene (HDPE) bottles with child-resistant closures and include desiccant and should at all times be kept in the original packaging. Apalutamide/placebo must be stored in a secure area and administered only to subjects enrolled in the clinical study in accordance with the conditions specified in this protocol. Participants should return all pill bottles at the 3 month and 6 month visits, regardless of whether the bottle is empty.

Janssen will supply apalutamide and placebo free of charge to subjects on study in the U.S. and Canada. The investigator, or responsible party designated by the investigator, must maintain a careful record of the receipt, distribution, and return of all drugs received from Clinical Research Services according to good clinical practices. Sites are encouraged to use the NCI Investigational Agent Accountability Record available on the CTEP website or their institutional drug accountability log.

At the completion of the study, unused supplies will be destroyed at the site according to the institution's policy for drug destruction. Sites should complete the drug destruction form located on the CTSU website under protocol-specific page and send the form to Clinical Research Services (see contact information for submission on the form).

The Study Agent Shipment Form (SASF), available on the CTSU website, under the NRG-GU006 study page must be completed and submitted to the CTSU Regulatory Office via the Regulatory Submission Portal as soon as the individual responsible for the study agent has been identified.

The drug supply will not be shipped by Clinical Research Services until the subject has been registered (Step 1) and randomized (Step 2). NRG Oncology will notify Clinical

Research Services to initiate each of these shipments after registration and randomization of the subject. Clinical Research Services will ship drug for subjects randomized to **Arm I and Arm II**. A six month supply of Apalutamide or Placebo will be sent per subject to complete six cycles of treatment. Apalutamide or Placebo will be supplied as 60 mg tablets (120-ct bottles). Apalutamide or Placebo must be stored at room temperature 15-30°C.

Upon notification of a new subject enrollment, Clinical Research Services will call the site contact to confirm that the site's shipment is being processed. Clinical Research Services' distribution team will monitor packages throughout the duration of transit via the FedEx website and FedEx One Call Solution (live support). Real-time monitoring enables Clinical Research Services to mitigate potential delivery delays.

Clinical Research Services will ship drug to sites in the U.S. and Canada, according to the following schedule:

NRG GU006 Shipment Schedule				
Subject Randomized (Step 2)	Initial e-order sent by NRG	Initial e-order received by CRS (before 2 p.m. ET)	Initial order shipped by CRS	Initial order received at site
Monday	Monday	Monday	Monday	Tuesday
Tuesday	Tuesday	Tuesday	Tuesday	Wednesday
Wednesday	Wednesday	Wednesday	Wednesday	Thursday
Thursday	Thursday	Thursday	Thursday	Friday
Friday	Friday	Friday	Monday	Tuesday

For orders intended for sites in the U.S., Clinical Research Services will ship the order "same day" for all orders received before 2 p.m. ET, Monday through Thursday, via FedEx Priority Overnight/FedEx International Priority. Orders received after 2 p.m. ET, Monday through Wednesday, will be processed and shipped the next business morning.

Drug deliveries are restricted during weekends and holidays. Clinical Research Services observes the following holidays: New Year's Day, Memorial Day, Independence Day, Labor Day, Thanksgiving Day, the Friday following Thanksgiving Day, Christmas Eve, and Christmas Day. Sites should plan ahead to accommodate subjects being treated during restricted times.

Please contact the program manager listed below directly for shipment tracking information and for anticipated delivery dates or if a shipment has not been received by the expected date.

Questions about supply and delivery should be directed to:

Elliott Lee, Program Manager
Clinical Research Services, a division of RxCrossroads by McKesson
845 Regent Blvd.

Suite 100B
Irving, TX 75063
Email: clinicalresearchservices@mckesson.com

Toll Free 800-693-4906

10. PATHOLOGY/BIOSPECIMEN

10.1 Biospecimen Submission Tables (15-JUL-2019)

10.1.1 Mandatory Specimen Submissions

GenomeDx Decipher Analysis (see Appendix II for details) Subtyping via the PAM50 and other classifiers (mandatory study)
To subtype prostate cancers into luminal versus basal subtypes via the PAM50 classifier, gene expression in prostate cancer specimens (from prostatectomy blocks) will be assessed using high-density oligonucleotide microarrays (Affymetrix Human Exon (HuEx) 1.0 ST GeneChips) in a CLIA-certified laboratory in collaboration with GenomeDx Biosciences.

As these arrays allow for a transcriptome-wide analysis, the prognostic and predictive value of other previously published classifiers in addition to PAM50, such as Decipher (Karnes 2013; Young 2012) or PORTOS (Zhao 2016) will also be assessed using the array data. These subtypes will be used as a stratification variable; therefore sites must submit tissue specimens for all cases or the patient will not be eligible.

Forms to include with tissue submission: 1) GU006 Study Specific P4 Form and 2) redacted pathology report. Please note: if the patient has already had Decipher analysis of his tumor specimen then a copy of the original report and the completed P4 form must be emailed to GenomeDx (RUO@genomedx.com) for validation and for GenomeDx to provide the subtyping needed for stratification. Please be sure this form is redacted as only the GenomeDx ID # is necessary along with the study/case number as an identifier. Please be sure to review the 'study specific specimen transmittal form (P4) completion instructions' posted on the CTSU website.

For patients who consent to banking: After generation of all the array data and QC analysis, GenomeDx will ship remaining tissue and tissue derivatives (ie, RNA) to the NRG Oncology Biospecimen Bank- San Francisco along with a copy of the tissue submission form (P4) and redacted pathology report (**Please note**: if unstained slides are sent for Decipher analysis these are **not acceptable** for banking and additional material will need to be sent to NRGBB if the patient agrees to banking)..
For patients who do not consent to banking: Genome Dx will return received pathology materials to site directly.

Genome Dx FFPE RUO (research use only kit—**do not use a commercial kit**) collection/shipping kits are available with frozen specimen kits from the NRG Biospecimen Bank - San Francisco (NRGBB@ucsf.edu). GenomeDx FFPE RUO Kits can be requested from the NRG Biospecimen Bank- San Francisco along with the banking kits via an email to: NRGBB@UCSF.edu

See detailed specimen collection/processing/shipping instructions for the GenomeDx samples on **the protocol-specific page of the CTSU website. See also Appendix II.**

For questions about mandatory FFPE specimen submission, contact:
GenomeDx Biosciences Laboratory
Department of Clinical Development
10355 Science Center Drive, Suite 240
San Diego, California 92121
Email: RUO@genomedx.com
Phone: 1-888-520-8718

Specimen Type	Collection Time Points	Collection Information	Shipping

		and Requirements/Instructions for Site	
FFPE Block from primary tumor from	Pre-treatment	Using a Genome Dx RUO kit provide: FFPE Block OR One 1.5mm punch for all patients. See Appendix II	Ship ambient or with cold pack in special kit to Genome Dx

10.1.2 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.

Circulating tumor cells to translate PAM50 findings into blood-based assay (optional study)

1) Circulating tumor cells (at pre-treatment, at completion of therapy, and at time of recurrence; see collection timepoints below) will be collected into ACD Tubes, enumerated, and profiled to translate the PAM50 findings into a non-invasive blood-based assay.
2) Special CTC kits available for CTC sample processing will be shipped upon request from the NRGBB-SF (NRGBB@ucsf.edu)
3) Forms: Study Specific ST form for CTC shipments (posted on the CTSU website protocol page).
4) Shipping days: To Cedars Sinai Monday-Wednesday (US Sites), Monday-Tuesday (Canada). Please email the testing lab GroupHem-OncologyPosadasLabSpecimenCollection@cshs.org and Edwin.Posadas@csmc.edu with a tracking number on the day of shipment to notify them of an incoming sample. **Specimens must be received within 4 days of collection** and should be kept at 4 degrees C until shipping with a cold pack (provided)**.**
5) Shipping costs- One time use prepaid labels will be provided with the kits from the NRGBB-SF

Ship all CTC specimens to:
Uro-Oncology Laboratories: Posadas Lab
Cedars-Sinai Medical Center
100 N George Burns Rd
Davis Building Room 5094C
Los Angeles, CA 90048
ATTN: NRG-GU006 study specimen team

For questions, please contact the Posadas Lab
Email: Edwin.Posadas@csmc.edu
GroupHem-OncologyPosadasLabSpecimenCollection@cshs.org
(Voice 1/laboratory) 310-423-1510 (Voice 2/office) 310-423-7600 fax 310-967-3841

Specimen Type	Collection Time Points	Collection Information and Requirements/Instructions for Site	Shipping
Circulating tumor cells (extracted from whole blood)	A. Pre-Treatment: Prior to start of apalutamide/placebo	Two (2) yellow top ACD (acid citrate dextrose) tubes. Should be collected and put on ice then	Specimens should be shipped by priority overnight courier with a

	B. Post-Treatment: Completion of apalutamide/placebo (+/- 2 weeks) C. At recurrence	stored at 4 degrees until shipping Please label specimens with patient ID and draw index (A, B, or C) and date/time of draw.	frozen cold pack on the day of or after collection to Cedars-Sinai. Do **NOT** ship to the NRG bank.

Analysis of SNPs associated with androgen deprivation therapy response (optional study)

1) Whole blood pre-treatment will be collected for analysis of SNPs associated with androgen deprivation therapy response (Hearn 2016)
2) **Forms**: ST Form- can be same one as used for banking samples when shipping
3) **Whole Blood Kits:** Will be included with the banking kits. These can be requested from the NRGBB-SF at NRGBB@ucsf.edu. Allow 5-10 business days for kits. Sites must have IRB approval before requesting kits.
4) **Shipping:** One prepaid return label provided for each case for batch shipping frozen biospecimens only

Ship all specimens to:
NRG Oncology Biospecimen Bank – San Francisco
UCSF – Dept of Radiation Oncology
2340 Sutter Street- Room S341
San Francisco, CA 94115

For questions, please contact the San Francisco Bank at:
Email: NRGBB@ucsf.edu
Phone: 415-476-7864/Fax 415-476-5271

Specimen Type	Collection Time Points	Collection Information and Requirements/Instructions for Site	Shipping
DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix	Pre-treatment: Prior to start of apalutamide/placebo *Note: If site missed this collection, they may collect at any other time but must note this on the ST form when submitting*	Frozen whole blood samples containing minimum of **1.5 mL** per aliquot in 2 mL cryovials (three cryovials). Store frozen at -80°C until ready to ship	Whole blood sent frozen on dry ice via overnight carrier in batch shipment to NRGBB-San Francisco

Specimen Collection for Biobanking for Potential Future Research (optional study)
Forms: ST Form, pathology report with accession number and date of procedure visible. All other PHI information should be redacted.
Kits: Frozen Specimen and Punch kits can be requested from the NRGBB-SF at NRGBB@ucsf.edu. Allow 5-10 business days for kits. Sites must have IRB approval before requesting kits.
Shipping: One prepaid return label provided for each case for batch shipping all frozen biospecimens only
Processing: Instructions for processing and shipping are included with the protocol documents included on the CTSU website, www.ctsu.org.

Ship all specimens to:
NRG Oncology Biospecimen Bank – San Francisco
UCSF – Dept of Radiation Oncology Box 1800
2340 Sutter Street- Room S341
San Francisco, CA 94115

For questions, please contact the San Francisco Bank at:
Email: NRGBB@ucsf.edu
Phone 415-476-7864/Fax 415-476-5271

Specimen Type	**Collection Time Points**	**Collection Information and Requirements/Instructions for Site**	**Shipping**
Representative H&E stained slides of the primary tumor taken from the prostatectomy	Pre-treatment	H&E stained slide can be a duplicate cut slide (does not have to be the diagnostic slide). Slide will be stored at the bank for all patients	Slide shipped ambient to NRGBB-San Francisco.
A corresponding paraffin-embedded tissue block of the primary tumor from the prostatectomy	Pre-treatment	Paraffin-embedded tissue block (must match the H&E slide being submitted). The block can be the same block submitted for the Decipher testing, or it can be an additional block. For sites unable to provide the block then two 3 mm or one 5 mm punch taken from the block is an acceptable alternative. FFPE specimens will be stored at the bank for all consenting patients.	Block or punch shipped ambient to NRGBB-San Francisco. Use of a cold pack is recommended during warm weather.
SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge	Pre-Treatment: Prior to start of apalutamide/placebo Post-Treatment: Within 7 days after completing apalutamide/placebo At recurrence, if applicable.	Process serum and aliquot a minimum of **0.5 mL serum** per aliquot into five (5) 1 mL cryovials. Freeze and store: -80°C and ship frozen.	Batch ship on dry ice by Priority Overnight Courier to NRG BB-San Francisco
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube (purple/ lavender top) and centrifuge	Pre-Treatment: Prior to start of apalutamide/placebo Post-treatment: Within 7 days after completing apalutamide/placebo At recurrence, if applicable.	Process plasma and aliquot a minimum of **0.5 mL plasma** per aliquot into five (5) 1 mL cryovials. Freeze and Store: -80°C and ship frozen.	Batch ship on dry ice by Priority Overnight Courier to NRG BB-San Francisco
Urine	Pre-treatment: Prior to start of apalutamide/placebo	One **10 mL** urine aliquot in one sterile 15 ml polypropylene centrifuge tube. Store frozen at -80°C. (-20° C is allowed for short term storage).	Batch ship on dry ice by Priority Overnight Courier to NRG BB-San Francisco.

11. SPECIAL STUDIES (NON-TISSUE)

Not applicable to this study.

12. MODALITY REVIEWS

12.1 Radiation Therapy Quality Assurance Reviews

The Principal Investigator, Dr. Felix Feng, and the Radiation Oncology Co-Chairs will perform an RT Quality Assurance Review after IROC Philadelphia-RT has received complete data in TRIAD. The RT reviews will be ongoing and performed remotely. 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, Variation Acceptable, and Unacceptable Deviation**.

12.2 Medical Oncology Modality Quality Assurance Reviews

The Medical Oncology Co-Chair will perform a Hormone Therapy Assurance Review of all patients who receive or are to receive apalutamide/placebo in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of hormone treatment data. The scoring mechanism is: **1) Per Protocol, 2) Unacceptable Deviation, and 3) Not Evaluable**.

The Medical Oncology Co-Chair will perform a Quality Assurance Review after NRG Headquarters has received complete data for cases enrolled. The reviews will be ongoing and performed remotely. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as NRG Headquarters has received complete data for all cases enrolled, whichever occurs first.

13. DATA AND RECORDS

13.1 Data Management/Collection (24-SEP-2020)

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata:

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section 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 for information about expedited and routine reporting. PRO-CTCAE is not intended for expedited reporting, real time review, or safety reporting. PRO-CTCAE data are exploratory and not currently intended for use in data safety monitoring or adverse event stopping rules.

Summary of Data Submission: Refer to the protocol page on CTSU website.

See Section 8.3 for TRIAD account access and installation instructions.

13.3 Data Quality Portal (15-JUL-2019)

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered

queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

13.4 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).

14. STATISTICAL CONSIDERATIONS

14.1 Study Design

14.1.2 A biomarker-stratified, randomized, double-blind, placebo-controlled design was selected for this phase II trial to evaluate the safety and efficacy of adding apalutamide to SRT and to assess whether molecular stratification using the PAM50 gene expression test will identify subsets of prostate cancer patients who derive the greatest benefit from anti-androgen therapy. If the treatment is sufficiently promising, the results of this study will be used to design a follow-up phase III trial.

Stratification will be:

1. Surgical margin status (positive or negative)
2. Pre-SRT PSA <0.5 vs ≥0.5-1 ng/mL
3. Molecular subtype (Luminal B vs Luminal A/Basal/Unknown)

14.2 Study Endpoints

14.2.1 Primary Endpoint

Biochemical progression-free survival (bPFS). bPFS is defined as the time from randomization to the first occurrence of either:

- A rise in PSA ≥0.2 ng/mL from nadir PSA, confirmed by a second PSA measurement equal to or higher than the first
- Clinical or radiographic local, regional, or distant metastases
- Death from any cause

14.2.2 Secondary Endpoints

- Overall survival

- Cancer-specific mortality (death from prostate cancer)
- Metastasis-free survival (distant metastasis or death from any cause)
- Distant metastasis (see Section 4 for definition)
- Local-regional progression (see Section 4 for definition)
- PSA nadir during first year of treatment and prior to initiation of any hormonal salvage therapy
- Initiation of salvage hormonal therapy
- Undetectable PSA with a non-castrate testosterone (PSA < 0.1 ng/ml and testosterone ≥ 50 ng/dl at 1 and 3 years after study enrollment)
- Acute & late physician-reported morbidity (per the CTCAE version 5)
- Testosterone levels every 3 months until 6 months post anti-androgen/placebo treatment
- Acute and late patient-reported morbidity symptomatic adverse events (per the PRO-CTCAE)

14.3 Primary Objectives Study Design

14.3.1 Primary Hypothesis and Endpoint

The primary question addressed in this study is whether SRT in combination with apalutamide will improve biochemical progression-free survival (bPFS) compared to SRT alone in men with post-prostatectomy PSA recurrences. In addition, we will assess whether molecular subtype is predictive of treatment benefit. The primary endpoint is bPFS, as defined above. If an event is identified, then the time of the event will be recorded as the first instance where any of the above occurs (e.g., the first instance where the PSA rise is ≥ 0.2 ng/ml, etc.). If no such event occurs, the patient will be censored as of the date of the last negative evaluation, i.e., the last examination documenting no PSA rise and no local, regional, or distant progression.

14.3.2 How Primary Endpoint Will Be Analyzed

We will employ the design strategy described in Freidlin et al (2012) for phase II trials incorporating biomarkers. This design involves a two-step process in which the efficacy of the experimental treatment is first evaluated in the biomarker- positive subgroup. If the treatment is deemed effective in the biomarker-positive subgroup, evaluation of the effect of the treatment in the biomarker-negative subgroup is undertaken, leading to a recommendation as to whether the phase III trial should be conducted using a biomarker-enrichment design (i.e., enroll biomarker-positive patients only), a biomarker-stratified design (continue to enroll both types of patients), or as a standard phase III trial (eliminate the biomarker from consideration). If a significant difference is not found in the biomarker-positive patients, the data are pooled over the two biomarker subgroups and an overall comparison of the treatment arms is performed, leading to a recommendation to either perform a standard phase III design or to conduct no further study of the new therapy.

Under this design strategy, we will first analyze the luminal B subgroup. bPFS curves will be estimated by the Kaplan-Meier (1958) method and compared between the two treatment arms using a one-sided logrank test at the α=0.12 significance level. Letting $S_{1+}(t)$ and $S_{2+}(t)$ denote the bPFS curves in the control (SRT alone) and combination treatment (SRT plus apalutamide) arms in the biomarker-positive subgroup, the null and

alternative hypotheses are:

$$H_{01}: S_{1+}(t) = S_{2+}(t) \text{ vs. } H_{A2}: S_{2+}(t) > S_{1+}(t).$$

If H_{01} is rejected, an 80% confidence interval (CI) will be constructed for the hazard ratio (control/combination) in the luminal A/Basal/Unknown subgroup by fitting a Cox (1972) regression model. If the upper limit of the CI is less than 1.3, the new therapy will considered insufficiently active in the luminal A/Basal/Unknown subgroup and a phase III enrichment trial will be proposed. If the whole CI exceeds 1.5, there is evidence that apalutamide is beneficial in both subgroups, and a standard phase III design ignoring the biomarker will be proposed. If neither of these conditions holds (i.e., the whole CI includes 1.3 or 1.5, or lies entirely within 1.3 to 1.5), the results will be deemed inconclusive and a phase III biomarker-stratified design will be recommended**.**

If H_{01} is not rejected, then the two biomarker groups will be pooled and the overall bPFS curves between the two treatment arms compared using a logrank test at the one-sided α=0.05 significance level. Letting $S_1(t)$ and $S_2(t)$ denote the bPFS curves in the control and combination treatment arms for all randomized patients, the null and alternative hypotheses are:

$$H_{02}: S_1(t) = S_2(t) \text{ vs. } H_{A2}: S_2(t) > S_1(t).$$

If H_{02} is rejected, a standard phase III design will be proposed, whereas if H_{02} is not rejected, the trial results will be interpreted as negative and no further studies of apalutamide will be recommended. Further details of the design, including sample-size considerations, are given in Section 14.3.3 below.

In addition to the above analyses, a multivariable Cox regression model will be fit in the pooled study population incorporating the three stratification factors used in the randomization (surgical margins, pre-SRT PSA, and molecular subtype) as covariates to estimate the adjusted hazard ratio (HR) between the two treatment groups. Additional regression models will be fit including other pretreatment characteristics as covariates. The goodness-of-fit of the proportional hazards assumption will be evaluating using graphical methods (Kay, 1977), residual plots, and the global test proposed by Grambsch and Therneau (1994). Missing covariates will be handled using multiple imputation as described in White and Royston (1982).

14.3.3 Sample Size and Power Calculations

We have used updated data from RTOG 0534: A Phase III Trial of Short Term Androgen Deprivation With Pelvic Lymph Node or Prostate Bed Only Radiotherapy in Prostate Cancer Patients with a Rising PSA After Radical Prostatectomy, to project the rate of bPFS for the SRT alone arm of this study. RTOG 0534 used the same endpoint definition of a PSA rise $\geq$ 0.2 ng/mL, the occurrence of local, regional, or distant metastases or death from any cause. Based on the information for patients from the RT alone arm of RTOG 0534 whose baseline PSA was less than 1.0, we assume that the 3-

year bPFS rate for Arm 1 of this study will be 0.67. Zhao et al (2017) reported a hazard ratio (HR) of 0.69 between luminal A/Basal patients relative to luminal B patients for bPFS. Assuming two-thirds of patients are luminal A/Basal/Unknown and one-third luminal B, we assume a 70% 3-year bPFS rate for luminal A/Basal/Unknown patients in the control arm and a 60% 3-year bPFS rate for the luminal B subgroup within the control arm.

To determine sample-size, we conducted simulations under several scenarios with the results summarized in the table below. The first scenario assumed a beneficial treatment effect in both the luminal B (HR=2.0) and luminal A/Basal/Unknown (HR=1.5) molecular subtypes, with greater benefit in luminal B. Under this scenario, a targeted sample size of 292 patients (approximately 100 luminal B and 192 luminal A/Basal) will provide 85% power to detect a HR of 2.0 in the luminal B subgroup and 91% power for the pooled, overall comparison (note: weighted average of the two HRs equals 1.67). The probability that the trial results will lead to a recommendation to conduct a phase III biomarker-enrichment design (BE), a biomarker-stratified design (BS), or a standard design (STD) is 1.8%, 74.4%, and 19.2%, respectively. The probability that no further testing would be indicated is 4.5%. Logistically, patients will be enrolled until there are 100 luminal B patients or 196 luminal A/Basal/Unknown patients, whichever comes first. If the 196 luminal A/Basal/Unknown patients are accrued first, accrual will be closed in this subgroup but will continue in the luminal B group until 100 luminal B patients are enrolled. If 100 luminal B patients are enrolled first and at least 176 luminal A/Basal/Unknown patients have been entered, recruitment will end. Otherwise, enrollment of both cohorts will continue until a maximum of 120 luminal B or 176 luminal A/Basal/Unknown patients is reached. The average total number of patients enrolled is N=291.5. The calculation assumes 42 months of accrual; follow-up will continue until 41 events have been observed in the luminal B subgroup, which is projected to occur 30 months after the last patient is enrolled. (The total number of expected events is 105.) With a rate of 10% for patients with issues regarding eligibility, insufficient tissues, consent among others, **the final targeted accrual for this study will be 324 patients (162 per treatment arm).**

Under the same design (i.e., a target of 100 luminal B patients and 192 luminal A/Basal/Unknown patients), scenario 2 assumes equivalent beneficial effects (HR=1.67) in both molecular subgroups. Here a BS design would be recommended 52.3% of the time and a standard design 40.9% of the time, while the probability of a negative result is 6.2%. Rarely would a BE design be proposed (0.5%). Scenario 3 assumes a HR of 2.0 in the luminal B patients and no effect in the luminal A/Basal/Unknown subgroup. The ideal recommendation would be a BE design although a BS design would be acceptable. The probabilities for a BE and BS recommendation are 48.3% and 36.6%, respectively, with a small 1.2% probability of recommending a STD design and a 13.8% chance of a negative study. Finally, scenario 4 is the null case, i.e., no treatment effect in either biomarker subgroup. The chance of recommending further testing ("type I error") is just under 15%.

Scenarios and Phase III Trial Recommendation Probabilities.

	Biomarker-Pos			Biomarker-Neg			Recommendation (%)			
Scenario (Avg. N)	$S_{2+}(3)$	$S_{1+}(3)$	HR	$S_{2-}(3)$	$S_{1-}(3)$	HR	BE	BS	STD	Neg
1 (291.5)	0.77	0.60	2.0	0.79	0.70	1.5	1.8	74.4	19.2	4.5
2 (291.5)	0.74	0.60	1.67	0.82	0.70	1.67	0.5	52.3	40.9	6.2
3 (291.5)	0.77	0.60	2.0	0.70	0.70	1.0	48.3	36.6	1.2	13.8
4 (291.5)	0.60	0.60	1.0	0.70	0.70	1.0	6.3	5.7	2.4	85.6

BE: enrichment design; BS: biomarker-stratified design; STD: standard design; Neg: negative study (no further testing)

14.4 Study Monitoring of Primary Objectives

14.4.1 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 reports will be prepared twice per year until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase, compliance rate of treatment delivery with the distributions of important prognostic baseline variables, and the frequencies and severity of adverse events by treatment arm. Aside from adverse events, the interim reports will not contain the results of treatment comparisons with respect to the primary endpoint and secondary endpoints, with the following exception: Two interim futility analyses will be performed after 50% of the required number of events in the biomarker positive (Luminal B) subgroup have occurred, i.e., 21 events. (At this point in time, the expected number of events in the biomarker negative [Luminal A/Basal/Unknown] subgroup under Scenario 1 is 32.) . The analyses will be performed on an intent-to-treat basis with all eligible cases included in the treatment arm to which they were randomized regardless of what treatment the patients actually received. If the estimated HR for the treatment effect is >1 in favor of the control arm in the biomarker negative subgroup, a recommendation will be made to the DMC to continue the trial only in biomarker positive patients. If the HR is >1 in favor of the control arm in the biomarker positive patients, a recommendation will be made to terminate the entire trial. This stopping rule will result in only a small power loss on the order of 2% (Wieand et al., 1994).

14.4.2 Reporting the Initial Treatment Analyses

The analysis reporting the treatment results will be carried out once the required number of events has been observed. The report will include tabulation of all cases entered and those excluded from the analyses; the distribution of the important prognostic baseline variables; safety treatments; treatment compliance; and observed results with respect to the primary and secondary endpoints. All eligible patients will be included in the comparison and will be analyzed according to the arm to which they were randomized regardless of what treatment the patient actually received, under a (modified) intent-to-treat principle. (Randomized patients who were subsequently deemed to have been ineligible will be excluded.)

14.5 Accrual/Study Duration Considerations (15-JUL-2019)

Based on patient accrual in previous NRG Oncology/RTOG randomized prostate studies, it is expected that there will be no patient accrual during the initial 6 months while institutions are obtaining IRB approval. The accrual rate is estimated to be 7-8 patients per month, and the study is projected to finish accrual in 50 months after study activation, with an additional 30 months for follow-up. The total duration of the study is therefore expected to be 6.7 years from the time the study opens to the time of the final analysis.

14.6 Secondary or Exploratory Objectives (including correlative science aims) (20Jul2018)

14.6.1 Secondary Hypotheses and Endpoints: We hypothesize that SRT+apalutamide will lead to improvements on a number of secondary endpoints compared to SRT alone and that it will have an acceptable toxicity profile. The endpoints are listed in Section 14.2.2 above and include overall, prostate cancer-specific, and metastasis-free survival; local, regional, and distant recurrences; initiation of salvage hormonal therapy; PSA nadirs and levels at 1 and 3 years; physician and patient-reported symptoms and adverse events; and testosterone levels. Comparisons of all secondary endpoints will be performed at the two-sided, α=0.05 significance level. We also hypothesize that the effects of anti-androgen treatment on the secondary endpoints will be greater in patients in the Luminal B subgroup relative to those in the Luminal A/Basal/Unknown subgroup.

14.6.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

Overall survival (OS) will be defined as the time from randomization until death from any cause. Patients who have not died will be censored as of the date last known alive. Cancer-specific mortality (CSM) will be measured from the date of randomization to the date of death due to prostate cancer. Patients dying from other causes will be censored as of the date of death. Metastasis-free survival (MFS) will be defined as the time from randomization until distant metastasis (clinical and/or radiographic appearance of disseminated disease) or death from any cause. OS, CSM, and MFS will be estimated by the Kaplan-Meier method and compared between treatment arms via the logrank test. Cox regression will be used to obtain HRs for these outcomes, both unadjusted and adjusted for covariates. A competing risks analysis will be performed treating death from prostate cancer as the event of interest and death from all other causes as a competing risk. Cumulative incidence curves will be generated (Gooley et al., 1999; Dignam et al., 2004) along with 95% confidence intervals and compared between the two treatment arms using Gray's method (Gray, 1988). In addition, multivariable analysis will be conducted using Fine and Gray's regression model (Fine and Gray, 1999) to derive covariate-adjusted (subdistribution) HRs and confidence intervals. Time to local-regional progression, time to distant metastasis, and time to initiation of salvage hormonal therapy will also be analyzed under a competing risks framework (each analyzed separately), treating death without experiencing the event in question as a competing risk.

The mean PSA nadir during the first year of treatment (or until initiation of hormonal salvage therapy) will be compared between the two groups using a two-sample t-test. The proportion of patients with an undetectable PSA level and testosterone $\geq$ 50 ng/dl at

1 and 3 years after randomization will be compared using chisquare tests.

Adverse events will be scored according to the NCI's Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0. For each type of adverse event, counts and frequencies will be provided for the worst grade experienced by the patient by treatment arm. The proportion of patients with grades ≥1 and ≥3 will be compared between groups using a chi-square test, or Fisher's exact test if cell frequencies are < 5, at the two-sided 0.05 significance level. An *acute* adverse event will be defined as one occurring within 30 days after the completion of RT. Logistic regression, both univariate and multivariate, will be used to model the probability of grade 3+ acute adverse events as a function of treatment arm and covariates. Both unadjusted and adjusted odds ratios and the respective 95% confidence intervals will be computed. Late grade 3+ adverse events will be defined as grade 3+ adverse events occurring more than 30 days after the completion of RT. The time to late grade 3+ adverse events will be measured from the time protocol treatment started to the time of the first recorded late grade 3+ adverse event. If no such late adverse event is observed, the patient will be censored at the time of the analysis. Death without late adverse event will be considered as the competing risk for late adverse events and the distribution of time to late grade 3+ adverse events will be estimated using the cumulative incidence approach and Fine and Gray's regression model.

Adverse events will also be assessed using PRO-CTCAE items. The PRO-CTCAE is a patient-reported outcome measurement system developed to characterize the frequency, severity and interference of 78 symptomatic treatment toxicities (Basch et al., 2014). These include symptomatic toxicities such as pain, fatigue, nausea, and cutaneous side effects such as rash and hand-foot syndrome. Items are scored on a Likert scale (e.g., for severity, 0=none, 1=mild, 2=moderate, 3=severe, and 4=very severe). The specific symptoms to be evaluated for this study are listed in Section 7.2.3 above. Assessments will be collected before and at the end of radiotherapy treatment and in follow-up as specified in the Section 4 assessment tables. For each symptom and each domain (i.e., frequency, severity, and interference), counts and frequencies will be provided for the worst score experienced by the patient by treatment arm. The proportion of patients with scores ≥1 and ≥3 will be compared between groups using a chi-square test, or Fisher's exact test if cell frequencies are < 5. Analysis of changes in patient reported outcomes over time will analyzed by fitting GEE models using a logit link (dichotomizing the symptom scores as 0 vs. ≥1 and 0-2 vs. 3-4) with time of assessment, treatment arm, and treatment-by-time interaction terms in the model.

14.7 Exploratory Hypothesis and Endpoints

Exploratory analyses will be performed to assess the prognostic and treatment-predictive value of the 22-marker genomic classifier Decipher (GC). The primary outcome variable for these analyses will be bPFS; OS and MFS will be secondary endpoints. Cox regression models will be fit, including treatment arm, GC, and a treatment-by-GC interaction term. The GC score is a continuous marker ranging from 0 to 1 that has been found to be associated with the incidence of metastasis in prostate cancer (Karnes et al, 2013). We will analyze GC both as a continuous measure and categorized as <0.4, .4-.6, and >.6 as in Karnes et al.

14.8 Gender/Ethnicity/Race Distribution

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	N/A	1	N/A	0	1
Asian	N/A	4	N/A	0	4
Native Hawaiian or Other Pacific Islander	N/A	1	N/A	0	1
Black or African American	N/A	38	N/A	0	38
White	N/A	223	N/A	23	246
More Than One Race	N/A	2	N/A	0	2
Total	N/A	269	N/A	23	292

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	N/A	1	N/A	0	1
Asian	N/A	5	N/A	0	5
Native Hawaiian or Other Pacific Islander	N/A	1	N/A	0	1
Black or African American	N/A	2	N/A	0	2
White	N/A	19	N/A	3	22
More Than One Race	N/A	1	N/A	0	1
Total	N/A	29	N/A	3	32

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APPENDIX I

MEDICATIONS PROHIBITED WHILE ON ACTIVE TREATMENT WITH APALUTAMIDE

Generic Name	Brand Name*
aminophylline	Aminocont; Aminomal; Diaphyllin; Filotempo; Neophyllin; Norphyl; Phyllocontin; Syntophyllin; Tefamin; Truphylline; Xing You Shan;
aminophylline in combination	Asmeton; Cha Xin Na Min; Emergent-Ez; Fufang Dan An Pian; Ke Zhi
amitriptyline	Amirol; Amitrip; Amixide; Deprelio; Diapatol; Elatrol; cElatrolet; Elavil; Endep; Enovil; Emitrip; Klotriptyl; Laroxyl; Levate; Limbitrol; Limbitryl; Mutabase; Mutabon; Nobritol; Novo-Triptyn; Pertriptyl; Redomex; Saroten; Sarotex; Sedans; Syneudon; Teperin; Triptizol; Triptyl; Tryptizol
amitriptyline in combination	PMS-Levazine
bupropion	Aplenzin; Buproban; Contrave; Elontril; Forfivo; Fortivo XL; Le Fu Ting; Prexaton; Quomem; Voxra; Wellbutrin; Wellbutrin XL; Wellbutrin SR; Yue Ting; Zyban
chlorpromazine	Aminazin; Chlorazin; Hibernal; Klorproman; Largactil; Megaphen; Ormazine; Plegomazin; Solidon; Taroctyl;Thorazine; Vegetamin; Wintermin; Zuledin Note: in Ireland also called "Clonazine" – very easy to confuse with clozapine.
Clozapine	Azaleptin; Clopine; Closastene; Clozaril; CloZAPine; Denzapine; Elcrit; Fazacio ODT; Klozapol; Lanolept; Leponex; Lozapine; Nemea; Ozapim; Synthon, Versacloz; Zaponex
desipramine	Deprexan; Norpramin; Nortimil; Pertofrane
Doxepin	Adapin; Anten; Aponal; Deptran; Gilex; Li Ke Ning; Quitaxon; Silenor; Sinepin; Sinequan; Zonalon
Imipramine	Impril; Melipramin; Mipralin; Norfranil,; Novo-Pramine; Persamine; Pertofram; Pryleugan; Talendep; Tofranil; Tolerade
Lithium	Arthriselect; Camcolit; Carbolith; Carbolithium; Eskolith; Hypnorex; Li-Liquid; Licarbium; Limas; Liskonum; Litarex; Lithane; Lithicarb; Lithioderm; Lithionit; Lithobid; Liticarb; Litiomal; Lito; Maniprex; Neurolepsin; Plenur; Priadel; Quilonorm; Quilonum; Saniquiet; Sedalit; Teralithe
lithium in combination	Boripharm No 23; Emser Salz; Girheulit HOM; Helidonium-Plus; Heweurat N; rheuma-loges; Rhus Toxicodendron Compose; Rhus-Plus; Ricinus Compose
Maprotiline	Cronmolin; Deprilept; Ludiomil; Mapromil; Melodil; Neuomil; Psymion
meperidine/pethidine	Alodan ; Atropine and Demerol; Centralgine ; Demerol ; Dolantin ; Dolantina,; Dolantine ; Dolargan,; Dolcontral,; Dolestine ; Dolosal ;

	Dolsin; Fada; Hospira; Liba; Mepergan ; Meprozine,; Mialgin,; Opystan; Pethidine ; Petigan Miro ; Psyquil compositum
meperidine/pethidine in combination	Pamergan P100
mesoridazine	Serentil, Mesorin
mirtazapine	Arintapin; Avanza; Axit; Combar; Esprital; Mi Er Ning; Miro; Mirta TAD; Mirtabene; Mirtachem; Mirtadepi; Mirtagamma; Mirtalan; MirtaLich; Mirtamylan; Mirtaron; Mirtaz; Mirtazelon; Mirtazon; Mirtazonal; Mirtel; Mirtin; Mirtor; Mirzaten; Norset; Noxibel; Paidisheng; Psidep; Remergil; Remergon; Remeron; Remirta; Rexer; Yarocen; Zispin
Olanzapine	Anzorin, Arenbil; Arkolamyl; Atyzyo; Bloonis; Clingozan; Egolanza; Lansyn; Lanzek; Lazapix; Nolian; Nykob; Olafid; Olanzaran; Olanzep; Olanzin; Olanzine; Olapin; Olasyn; Olazax; Olpinat; Olzapin; Olzin; Ou Lan Ning; Ozilormar; Parnassan; Ranofren; Sanza; Stygapon; Synza; Ximin; Zalasta; Zamil; Zappa; Zapris; Zerpi; Zolafren; Zolaxa; Zonapir; Zopridoxin; Zylap; Zypadhera; Zypine; Zyprexa; Zyprexa Relprew; Zydis
olanzapine in combination	Symbyax
Risperidone	Aleptan; Apo-Risperid; Arketin; Calmapride; Diaforin; Doresol; Hunperdal; Jing Ping; Ke Tong; Leptinorm; Lergitec; Orizon; Ozidal; Perdox; Ranperidon; Resdone; Ridal; Ridonex; Rileptid; Ripedon; Risepro; Rispa; Rispaksole; Rispefar; Rispemylan; Rispen; Rispera; Risperanne; Risperdal; Risperdalconsta; Risperdaloro; Risperigamma; Risperon; Rispolept; Rispolux; Rispond; Rispons; Risset; Rixadone; Rorendo; Ryspolit; Si Li Shu; Sizodon; Speridan; Suo Le; Torendo; Zhuo Fei; Zhuo Fu; Ziperid; Zoridal
theophylline	Aerolate; Afonilum; Aminomal; An Fei Lin; Apnecut; Apo-Theo; Asmalix; Asmalon; Bi Chuan; Bronchoparat; Bronchoretard; Cylmin; Diffumal; Elixifilin; Elixophyllin; Etipramid; Euphyllin; Euphyllina; Euphylline; Euphylong; Frivent; Gan Fei Lin; Nuelin; Protheo; Pulmophylline; Quelesu; ratio-Theo-Bronc; Respicur; Retafyllin; Shi Er Ping; Slo-Bid; Slo-Phyllin; Telbans; Teotard; Terdan; Teromol; Theo-24; Theo-Dur; Theo; Theochron; Theodur; Theofol; Theolair; Theoplus; Theospirex; Theostat ; Theotard; Theotrim; Theovent; Tromphyllin; Unicon; Unicontin; Unifyl; Uniphyl; Uniphyllin Continus; Uniphyllin; UniXan; Xanthium; Xi Fu Li; Yan Er
theophylline in combination	Antong; Baladex; Bi Chuan; Binfolipase; Broncho-Euphyllin; Broncomar; Do-Do ChestEze; Elixophyllin-GG; Elixophyllin-KI; Insanovin; Marax ; Neoasma; Theofol Comp; Theophedrinum-N; Xu Hong; Yi Xi Qing
Thioridazine	Detril; Elperil; Melleril; Ridazin; Ridazine; Thiodazine; Thioril; Sonapa
Ziprasidone	Geodon; Li Fu Jun An; Pramaxima; Si Bei Ge; Ypsila; Zeldox; Zipwell; Zypsila; Zypsilan

**** Note: This document is intended as an aid in identifying prohibited medications, but may not be all inclusive.**

APPENDIX II (14JUN2018)
INSTRUCTIONS FOR SUBMITTING TISSUE TO GENOMEDX FOR DECIPHER ANALYSIS

DECIPHER PROSTATE RP

GenomeDx Biosciences
10355 Science Center Drive, Suite 240
San Diego, CA 92121
Tel: 1 (888) 520-8718 | RUO@genomedx.com
www.genomedx.com

SPECIMEN REQUIREMENTS - RADICAL PROSTATECTOMY
FOR RESEARCH USE ONLY

Block Selection:

Select one (1) formalin fixed paraffin embedded (FFPE) tissue block with the highest Gleason score and at least 0.5cm^2 of tumor tissue by area, and a minimum of 60% tumor (by surface area).

Please select one of the following options below when submitting specimens for Decipher® testing

Option 1: Block Submission (Preferred):

1. Select the best appropriate FFPE block for punching.

Option 2: Punch Submission:

1. Identify an H&E slide that closely matches the block face.
    a. If multiple sections have already been cut from the block, then cut and create a new H&E stained slide.
2. Circle the area with the highest Gleason grade on the corresponding H&E slide.
3. Using the punch tool provided in the specimen kit, take two (2) x 1.5 mm diameter punches from the FFPE block which corresponds to the area circled on the H&E slide.
    a. Two (2) x 1.5mm diameter cores are required.
4. Place each core in a separate micro-centrifuge tube, close the caps and seal each tube with Para-film.
    a. Note: If the tissue gets stuck in the punch tool, then wrap the punch tool in foil and ship.
5. Document that each punched core contains ≥ 60% tumor content on the Specimen Profile Form.
6. Number each tube to correspond with the Specimen Profile Form.

Option 3: Slide Submission:

1. Submit one (1) H&E slide and five (5) 5µm thick serially sectioned unstained slides ***or*** six (6) 5 µm thick serially sectioned unstained slides.
2. Label the serial sectioned slides (1-6) in the order in which they were cut for scraping.

If you have any questions about specimen submission, please contact
1 (888) 520-8718 or email RUO@genomedx.com

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DECIPHER PROSTATE

GenomeDx Biosciences
10355 Science Center Drive, Suite 240
San Diego, CA 92121
Tel: 1 (888) 520-8718 | RUO@genomedx.com
www.genomedx.com

SHIPPING REQUIREMENTS

FOR RESEARCH USE ONLY

Blocks:

1. After appropriate block selection, place the selected FFPE block into the small resealable bag provided.
2. Place the small sealed bag containing the block on top of the foam insert.

Slides:

1. Place slides into the two (2) slide holders (up to 5 slides each).
2. Place the slide holder(s) back into the foam insert.

Punches:

1. Number each tube containing the punch specimen to correspond with the Specimen Profile section of the Test Requisition Form.
2. Place the labeled specimen tubes back into the foam insert.

---

3. Verify that the Specimen ID on the Test Requisition Form matches the labeling on the sample.
4. Keep a completed COPY of all forms and email a copy to RUO@genomedx.com to order the Decipher test.
5. Fold (a) Test Requisition Form and (b) Pathology Report (if applicable) and place all paperwork into the specimen kit, between the dividing flap and the foam insert.
6. Fold down the dividing flap, place the provided frozen cold pack on top of the flap, and close the specimen kit.
7. Place the closed specimen kit into the FedEx® Clinical Lab Pak and apply the shipping label provided.
8. Ship to GenomeDx laboratory via your regular FedEx® pickup or email RUO@genomedx.com to inquire about how to schedule a FedEx® pick up.

For specimen requirements, please contact your GenomeDx research team at
1 (888) 520-8718 or email RUO@genomedx.com

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APPENDIX III (24-SEP-2020)
Medidata Patient Cloud ePRO Operational Instructions

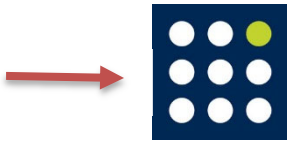
Introduction

Electronic collection of patient-reported outcomes (ePRO) through Medidata Patient Cloud ePRO is preferred but not mandatory. Traditional paper submission is the other option. Patients who will be submitting PRO data via Patient Cloud ePRO must be registered to Patient Cloud ePRO by an authorized site user after the patient has been registered to the study. Patients may use their own device or one provisioned by the site.

Sites can use a site-specific tablet for multiple study participants. If a site-specific tablet is used, CRAs need to setup the tablet for multiple users. Multi-user mode lets multiple study participants log in to Patient Cloud ePRO with their passwords or their PIN codes on the same device.

ePRO Application Download

Note that there are multiple versions of the Medidata Patient Cloud ePRO Application. Patients should be instructed to download the version chosen by the study team for the protocol. The patient will receive an error if the wrong version is downloaded.



Patient Cloud ePRO

CRA Site Users

Site users of Patient Cloud ePRO require the same access as Rave. Access to the trial in the Patient Cloud ePRO is granted through the iMedidata. Site users will receive an invitation to Patient Cloud ePRO and the site user must accept the invitation to begin patient registration. Users who have not previously activated their iMedidata/Rave account at the time of initial approval of site registration will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Please note, site users will not be able to access the study in the Patient Cloud ePRO until all required Rave and study specific trainings are completed.

Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

CRA Instructions for Setting the Patient Cloud ePRO App to Multi-User Mode

Sites conducting studies entirely on-premise, where participants travel to the sites to fill out

questionnaires, can use multi-user mode. Multi-user mode lets multiple study participants log in to Patient Cloud with their passwords or their PIN codes on the same device. . If patients will be using devices supplied by the institution, site staff will need to help the patient to access the device if the device is locked.

The study provider will download the Patient Cloud ePRO app to the device and set the Patient Cloud ePRO App to multi-user mode if applicable.
To switch from personal mode (default setting) to multi-user mode:

1. Tap **About** at the bottom of the log in screen.
2. Scroll to the bottom and tap **Advanced User**.
3. Tap **Mode**, then select **Multi-User**.
4. Tap **Yes** to confirm.
5. Tap the back arrows to return to the log in screen.

Note: If enabling multi-user mode on a device, it is highly recommended that completion reminders are turned off on that device.

For a video demonstration, see Show Me How to Switch to Multi-User Mode.

Patient Users
To use the Patient Cloud ePRO, patients will need to use their own device (IOS, Android phone or tablet). Short term data will only appear on the patient's device until responses are completed and submitted. The patient data will import directly into the database once the patient selects the "Submit" button and will no longer be visible on the patient's device.

Sites can provide a site-specific tablet for multiple study participant use on site. If a site-specific tablet is used, study staff need to setup the tablet for multiple users. Multi-user mode lets multiple study participants log into Patient Cloud ePRO with their passwords or their PIN codes on the same device. **Refer to Appendix E on Setting the Patient Cloud ePRO App to Multi-User Mode.**

Patient Instructions for Accessing the Patient Cloud Using Your Personal Device
Downloading the Patient Cloud ePRO App
If you are using your personal device, and you do not have the Patient Cloud ePRO app, use the following instructions. When downloading the app, you must use the Apple ID or Google account associated with the device. If the Patient Cloud ePRO app is already on the device, or if you are using a provider's device, you can skip this section.

You will need an email address that you agree to use for this purpose. The e-mail address is needed to identify you on the Patient Cloud Application and for you to receive notifications to let you know when forms are due. Your e-mail address will only be used for this survey study, and will not be used for mail or marketing purposes.

If you decide to use the electronic method to complete the questionnaires, and do not have an e-mail address, you may sign up for one at no charge at many different websites. A few sites that are commonly used and will allow you to create an email address very easily are Yahoo, Gmail, and Outlook.

For iOS:

1. An Apple ID is required for downloading the Patient Cloud ePRO app.
2. Tap the *App Store* icon.
3. Search for *Medidata Patient Cloud* and follow the installation instructions.

Note: Patient Cloud ePRO is listed as an iPhone App in the App store. When using an iPad, please view the search results under iPhone apps.

For Android:

1. A Google account is required for downloading the Patient Cloud ePRO app
2. Tap the *Play Store* icon.
3. Search for *Medidata Patient Cloud* and follow the installation instructions.

Registering

You must register in order to complete and submit your study forms. When you register, you will create a username, which is your email address, and a password that allows you to log in to the Patient Cloud ePRO app.

Note**:** You must have an activation code to begin this process. If you do not have an activation code, please contact your provider.

There are two possible ways to register. Your provider may have sent you a link to a web address where you may register from any web browser, including the one on your device. The other way to register is on the Patient Cloud ePRO app.

1. If registering from the Patient Cloud app, tap Register on the bottom of the log in page. If registering on the web, open the URL shield.imedidata.com on a web browser.
2. Enter your activation code and tap Activate.
3. On the next page, read the instructions and tap Next.
4. Read the privacy notice and tap I agree. Then tap OK to confirm.
5. Enter and confirm your email address. Tap Next.
6. Enter and confirm your password. Tap Next.
7. Choose a security question by scrolling through the dropdown menu to display the question of your choice.
8. Enter your security question response.
9. Tap Create my account to complete your registration.

If you registered on the Patient Cloud ePRO app, it automatically logs you out. If you registered on the web, you are presented with the option to download the Patient Cloud ePRO app. You can then proceed to log in with the credentials you created.

Logging in to the App

1. Enter your Email and Password that you created during the registration process. (If you previously set a PIN code, just enter your four-digit PIN.)
2. Tap Log in.

Note: If you do not remember your password, tap **Forgot Password**, and follow the instructions provided.

Setting a PIN Code

The first time you log in to the Patient Cloud ePRO app, you are given the option to create a PIN code. A PIN code allows you to bypass the step of entering your email and password every time you need to log in to the Patient Cloud ePRO app. Instead, you can enter a four-digit PIN.

1. If you wish to set a PIN code the first time you log in, tap Yes when prompted.
2. Note: You can also set your PIN at a later time by tapping the options menu on the top left of most pages and selecting Set PIN.
3. Enter a four-digit PIN.
4. Re-enter the four-digit PIN to confirm.

If you forget your PIN code, tap **Forgot PIN** and you can access the app using your email and password. You may reset your PIN by tapping the options menu on the top left of most pages and selecting Set PIN.

Resetting Your Password

You can reset your password by using the options menu at the top left of most pages.

1. Tap the options menu icon.
2. Tap Reset Password.
3. Follow the instructions to reset your password.

Completing and Submitting Forms

Once logged in, forms related to your study display on the Tasks page. If you are enrolled in multiple studies, select the appropriate study first, and then select a form. New forms can appear on the Tasks page at any time, depending on how the study is designed.

There are two types of forms displayed on the Task List page:

- *Scheduled Forms* (with a  icon): These forms have a "Due Date" indicator in them so you are aware of the last day by which you will need to complete the form. If the form is due in less than one day, you will see the due time in hours.
- *Anytime Forms* (with a  icon): These forms have "Last Completed Time" indicator on them which tells the most recent date or time when you

completed the form. If you start a form, but do not complete it, you will see an 'Incomplete" status beneath the form name, along with a half-moon icon.

1. Select the appropriate form.
2. Follow the on-screen instructions until you reach the end of the form where you are given the opportunity to review and change your responses prior to submitting.
3. Review your responses by scrolling down the list.
4. If you need to change an answer, tap the question to go back and change the answer.
5. When you are ready to submit, tap Submit Your Data.

Note: Once a form is submitted, you will be unable to edit any of your responses. In some cases, you may be asked to acknowledge your submission by entering your password.

Patient Compliance

The patient data imports directly from a device into the Rave database. There are no documents to audit. The patient-submitted electronic responses are the source documentation.

Security

All data is encrypted on the device (256 bit encryption and Hyper Text Transfer Protocol Secure [https]) and the app requires each user to have a unique username and password for access. If the user is idle for too long (5 minutes inactivity time), the app will time out and the user will need to log in again.

The data will only reside on the device for a short period of time. Once the user clicks "Submit," the data is securely transferred over HTTPS between the device and internal relay to the Rave database. Except for the patient's email address, no identifying information is stored in iMedidata. The email address is stored for what purpose? The patient's email links the device (used) and (ePRO) account to where the data is stored. The patient's email is not visible to anyone in the system.

The Patient information (email/password) does not reside in Medidata Rave EDC and the patient accounts are hidden in iMedidata from sites and LPOs.

The Patient Cloud ePRO application is 21 CFR Part 11 compliant and acts as a gateway between the device and Medidata Clinical Cloud (MCC).

Messages and information communicated to and from the Patient Cloud ePRO are encrypted and therefore this information cannot be read if intercepted while in transit.

Site checklist for activities prior to consenting a patient

Site staff must have already completed required eLearning for the Patient Cloud ePRO application. See last bullet with hyperlink to training video library. Contact the LPO to request appropriate Rave access to register patients in Patient Cloud ePRO

Accept study invitation at iMedidata.com

- Note: you must be rostered in RSS and have received an invitation to Patient Cloud ePRO

Verify the IOS or Android operating system is using the most current version

Verify Patient Cloud ePRO app is using the most current version

If using institutional shared devices, first patient only: Verify Patient Cloud ePRO app is in Multi-User mode

Refer to Review Quick Reference Guides for videos and other procedural information

Patient withdraws study consent or withdraws consent from participating on ePRO
CRA must instruct the patients that are participating on ePRO who decide to withdraw consent to delete the App from their smart phones. This will prevent QOL reminders from being sent to the patient.