CASE COMPREHENSIVE CANCER CENTER

Study Number:	CASE10814
Clinicaltrials.gov#:	NCT02681614
Study Title:	Pilot Study Evaluating the Role of Histopathology Correlation in Treatment Planning
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Sponsor:	Case Comprehensive Cancer Center
Support:	Invivo, Gainesville, FL, Philips Medical Systems, Cleveland, OH
Supplied Device:	Uronav biopsy guidance system
IDE#:	[redacted]
Protocol Date:	06 February 2018

SUMMARY OF CHANGES

Protocol Date	Section	Change
10.07.2015		Initial IRB approval
03.17.2016	Cover page	Updates to cover page
	4.3	Changed Treating physician to Enrolling physician
	7.0	Removed 3 month post MRI
06.04.2016	4.3	Update clinical stage to be consistent with section 3.1
	6.1	Update to virtual fiducial markers
		Remove reference to biopsy charge
	7.0	Remove SOC items from study procedures
	7.1	Add "routine treatment data" to information collected
01.04.2017	Cover page	Changed PI to Bryan Traughber, removed list of co-investigators
	4.3.3	Replaced "hormonal therapy, radiotherapy, surgery" with "prostate cancer"
3.9.2017	7.0	Change screening from 15 days to 60 days.
	7.0	Add "blood pressure and pulse rate" to vitals
	7.1	Clarified follow-up times
	9.1	Clarified safety assessment times
4.18.2017	Cover Page	PI changed from Traughber to Kumar
2/6/2018	Cover page/ footer	PI Change: Kumar back to Traughber Footer date revised to 02.06.2018

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1.0 Introduction

1.1 Study Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB), and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB according to its policies and procedures.

1.2 Background

Despite many advances in imaging and therapy, prostate cancer remains the second most common cause of cancer-related death of men in the United States (1). Over one million men undergo prostate biopsies annually in the US. These biopsies have routinely been blind bilateral biopsies of the gland based on transrectal ultrasound guidance to assess tissue from representative section of the gland. The standard practice continues to evolve, and has progressed biopsies from unlabeled location of the right and left gland to routine biopsy of up to 12 labeled regions of the prostate including both medial and lateral locations from the base, mid, and apical regions(2, 3). By obtaining an increased number of biopsy locations, the percentage of detected cancers has been shown to increase. The potential disadvantages to increasing the number of biopsies however include increased patient discomfort and risk of complications as well as increased cost. It may also increase the number in clinically insignificant cancers that are detected, thus placing the patient at an increased risk of harm from treatment of tumors with a low risk of becoming life threatening such as low volume low grade disease (4). Most recently the introduction of MRI to guide and track biopsy location has been developing.

The use of MRI imaging has become increasingly more prevalent in the guidance of prostate biopsies both in the United States and internationally. Studies have confirmed that the use of MRI imaging to help direct the location of biopsies has increased both the frequency of diagnosing cancer, but even more importantly diagnosing clinically significant higher grade disease (5, 6). Several commercially available devises have come to market that aid in the ultrasound guidance of prostate cancer in patients that have had an MRI obtained prior to the biopsy (7). These devises may be designed for either transrectal or transperineal guided biopsy. Almost all of these manufactures have relied on the ability to use image fusion to align a real time transrectal ultrasound image of the prostate to the previously acquired MR image. By using segmentation tools to define high risk volumes likely to harbor cancer, these systems aid in the placement of a biopsy needle to the site of a suspected tumor foci. One such system, Uronav, developed by a subsidiary of Philips Medical, InVivo, has been FDA approved for routine use in transrectal guided biopsies of the prostate gland using an electromagnetic (EM) sensory system to help guide the biopsy needle tip to within 2 mm of the desired biopsy target defined by MRI. They have developed an additional version for transperineal biopsy as well and seek a validation trial to assess this platform.

Routinely all patients at University Hospitals schedule to receive prostate brachytherapy treatment undergo a 3T MR imaging of the pelvis and prostate to plan prostate brachytherapy. At the time of the brachytherapy procedure a transrectal ultrasound probe is used to image the prostate, and a commercially available computer planning system, Symphony (MIM Software, Beachwood,

Ohio) is used to align the MR image to the live ultrasound image to assist in needle placement and brachytherapy source delivery. During the procedure typically 20 to 35 needles are placed transperineally to deposit the brachytherapy sources per the computerized plan. Regions that are found to be suspicious for harboring cancer within the prostate volume are routinely planned to received a higher dose of radiation than the whole gland by placing additional radioactive sources at these locations at the time of the implant, however without a biopsy confirming the image findings it is unknown if these radiographic findings represent the biopsy proven disease site within the patients, or if these lesions may harbor higher grade disease or are false positive findings.

Hypothesis: Multiparametric MRI with histopathological correlation will improve the segmentation of the target volumes to treat sub-volumes of the prostate with focal dose escalation in low- and intermediate-risk patients beyond the use of imaging alone using standard T1 and T2 MRI and the addition of functional MRI sequences.

1.3 Preclinical Data

The use of the electromagnetic guidance system employed by Uronav was developed at the NCI. Funding was partially supplied by Philips to develop the system platform originally labeled Percunav. Non-animal phantom studies were followed by animal studies to provide the initial validation and safety profile for FDA approval in human subjects (8).

1.4 Clinical Data to Date

The NCI went on to complete a human trial using the electromagnetic guidance system to compare MRI directed biopsies versus routine sextant biopsies in a series of 101 patients with a known diagnosis of prostate cancer. The data confirmed the transrectal ultrasound guided biopsy of the fused ultrasound and MR images yielded a higher rate of positive biopsies and also increased the yield for positive biopsies of high Gleason grade disease than routine ultrasound imaging directed biopsy alone (6). Limitations for the transrectal system include difficulty in placement of biopsy needles into regions seen in the anterior gland or transitional zone, as well as the increasingly prevalent risk of post procedural infections or rectal bleeding presumably related to the transrectal needle placement (9, 10).

2.0 Study Objectives

Specific Aim 1: Evaluate final pathology post-operatively for histopathology confirmation of multiparametric MRI targets detected during treatment planning. This will be accomplished by using transperineal biopsies obtained prior to interstitial brachytherapy during the procedure, while under anesthetic just prior to the placement of the brachytherapy needles and sources.

Specific Aim 2: Evaluate the ability of the Uronav system in a transperineal setting to guide biopsy needle placement using the electromagnetic guidance system and transperineal ultrasound probe stabilization device and stepper.

3.0 Study Design

3.1 General Design

This 1-year pilot study will include 6 patients with a clinical diagnosis of prostate cancer (clinical stage T2a or T1cN0M0), Gleason score ≤7 (4+3), with a PSA ≤15ng/mL and routine pelvic screening with MRI of the prostate and pelvis for staging and treatment planning who have elected to undergo prostate brachytherapy as definitive treatment.

Only patients who have clinically detectable intraprostatic findings on the MRI will be eligible to participate, and will be screened from the routine population of patients undergoing prostate brachytherapy at University Hospitals.

3.2 Primary Study Endpoints

The primary endpoint will be to report correlation of biopsy tissue histopathology with intraprostatic MRI findings. A total of 12 to 15 tissue samples will be obtained from each subject using standard sextant biopsies in addition to targeted biopsies of intraprostatic MRI findings. Assuming 14 specimens are sent for histopathology analysis in 6 subjects we will use the 84 biopsy sites to report sensitivity and specificity for the MRI findings along with positive and negative predictive values.

3.3 Secondary Study Endpoints

3.3.1 We will report the post-operative radiation dose coverage for the prostate, organs at risk, and targeted lesion for each case. The coverage for the brachytherapy implant will be reported for the V100, V150, and V200, i.e. volumes of the prostate receiving 100, 150, and 200% of the prescribed dose. The dose delivered to the targeted lesion or lesions will be reported as a V100, V150, V200 as well to evaluate the ability to target the dose escalation prospectively, though again is per routine and not as part of a therapeutic trial design at this time. Additionally, the D90, i.e. dose to 90 percent of the prostate volume will be reported. Doses to the bladder, rectum and urethra will also be calculated for evaluation in the study.

3.3.2 An additional secondary endpoint for the study will be to report the incidence of successful completion of the transperineal biopsy procedure using the Uronav system which is provided by Philips Medical as part of the support for this study. The Symphony biopsy system will be available in the operating room (OR) as a back-up to complete the biopsies if needed. It is, however, anticipated that the combined DynaCAD computer for processing the MR images and Uronav systems supplied for the study to integrate with our standard transperineal ultrasound system will be 100% successful in obtaining the required biopsies. We will also report on any unanticipated complications or infections. It is anticipated that the risk of infection should be substantially diminished by avoiding transrectal biopsies. However, the risk for prostate edema and urinary obstruction may be increased due to the additional transperineal needle placement as the biopsy will be followed by routine prostate brachytherapy. Patients may therefore be asked to maintain a Foley catheter overnight to allow edema to resolve, and avoid acute obstruction the following day. Assuming the Uronav system is capable of completing biopsies on all patients and no more than 1 patient acquires a post-operative infection this pilot study will be deemed a success, and further investigation may be warranted.

3.4 Primary Safety Endpoints
The primary safety endpoint for the study will be the rate of infection or hospital admission within 30 days that are felt to be directly related to the procedure.

4.0 Subject Selection and Withdrawal

4.1 General Characteristics of the Proposed Subject Population
The subject population will be screened from males with low to intermediate risk prostate cancer Gleason score $\leq$ 7(4+3) with PSA below 15 ng/mL who are consented for prostate low dose rate brachytherapy. They will qualify for the study if the planning MRI used for screening and brachytherapy source planning shows at least one region within the prostate that is reported as probable for malignancy by a Diagnostic Radiologist. Treatment planning will be preformed per routine, and thus this trial is deemed non-therapeutic as it will not alter treatment. The patient's Urologist will consent them if desired for this study, and will perform the biopsies in the OR prior to proceeding with the prostate brachytherapy procedure as routinely preformed with Radiation Oncology and the biopsy locations will be tracked with virtual fiducial markers using the Uronav system in addition to gold fiducial markers. The cost for the additional histopathology will be covered by the study along with required supplies.

The goal for this pilot study is to show feasibility to track histopathology location correlated to standard and functional MR imaging with the possible implication to translate to a therapeutic trial design in subsequent studies to use the combined histopathology data and imaging correlation to direct radiotherapy using either brachytherapy of other forms of radiotherapy such as intensity modulated photon or proton therapy. Post-operative dosimetry will be reported for the whole gland as well as the targeted lesions per routine. The standard goal is to provide 150% of prescribed dose to the region defined as high probability for containing tumor at the time of the brachytherapy implant. As many patients do undergo a combination of both external beam radiation and brachytherapy as a boost dose, the implications could yield a secondary therapeutic trial in higher risk patients where the brachytherapy implant could be completed prior to the external beam therapy, and image guided intensity modulated radiotherapy (IMRT) could be designed to paint dose on the prostate gland following the implant to optimize target coverage. For example if the histopathology confirms cancer, but the post operative dosimetry defines a region that was not fully escalated to 150% of prescribed dose, one can envision using dose painting to target further dose to that region, or conversely if the implant post operative dosimetry shows high doses near any organ at risk such as the rectum or bladder, this area could be dose de-escalated in the additional 25 routine fractions of IMRT.

4.2 Anticipated Number of Research Subjects
The pilot study is designed to include only 6 subjects for testing of feasibility to obtain transperineal tissues and report correlation to MRI image findings.

4.3 Inclusion Criteria

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. The checklist must be completed for each patient and must be signed and dated by the treating physician.

Patient's Name _____

Medical Record # _____

Research Nurse /
Study Coordinator Signature: _____ **Date** _____

Enrolling Physician [Print] _____

Enrolling Physician Signature: _____ **Date** _____

Patients must meet <u>all</u> of the following inclusion criteria to be eligible for enrollment:

_____4.3.1 Patients must have histopathology confirmed prostate cancer that is Gleason score ≤7(4+3) clinical stage ≤ T2aN0M0 with a PSA below 15 ng/mL.

_____4.3.2 Patients must have MRI findings reporting intraprostatic lesions suspicious for malignancy**.**

_____4.3.3 Patient must not have had any prior treatment for prostate cancer

_____4.3.4 Age ≥18 years.
Because no dosing or adverse event data are currently available on the use of *Uronav* in patients <18 years of age, children are excluded from this study.

_____4.3.5 ECOG Performance status ≤ 2 [See Appendix A].

_____4.3.6 Subjects must have an International Prostate Symptom Score of ≤ 15.

_____4.3.7 Subjects must have the ability to understand and the willingness to sign a written informed consent document.

4.4 Exclusion Criteria

The presence of <u>any</u> of the following will exclude a patient from study enrollment.

_____4.4.1 Gleason score of ≥ 8(4+4)

_____4.4.2 PSA ≥ 15 ng/mL.

_____4.4.3 Clinical stage >T2b or evidence of nodal

_____4.4.4 Patients who are on anticoagulants or high dose aspirin therapy that cannot be safely stopped for greater than 10 days prior to treatment should be excluded to limit

increased risk for urinary obstruction.

_____4.4.5 Patients with uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

_____4.4.6 HIV-positive patients on combination antiretroviral therapy are ineligible because of the unlikely risk of prostate cancer being life threatening in this population.

4.5 Subject Recruitment and Screening
Subject will be screened from the practice of the Principle Investigator in men who have consented for prostate brachytherapy.

4.6 Inclusion of Women and Minorities
Women are excluded from participating in this study. Men of all races and ethnic groups are eligible for this trial.

5.0 Registration
All subjects who have been consented are to be registered in the OnCore Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

All subjects will be registered through University Hospitals Cleveland Medical Center and will be provided a study number by calling the study coordinator listed on the front page.

5.1 Early Withdrawal of Subjects

5.1.1 Criteria for Removal from Study
Subjects may withdraw from the study at anytime prior to the procedure. They will be replaced by an additional subject to maintain 6 subjects in the cohort.

5.1.2 Follow-up for Withdrawn Subjects
Subjects who withdraw from the study will be followed per departmental routine policy if they proceed with the prostate brachytherapy or elect external beam radiation. They may otherwise elect to be followed by their urologist. As noted above, subject may be replaced to maintain adequate cohort numbers to complete the study.

6.0 Study Biopsy Procedures

6.1 Description biopsy procedure
All biopsies will be completed in the outpatient setting in the ambulatory OR prior to routine prostate brachytherapy under general anesthesia. Patients will be prepped in a dorsal lithotomy position with insertion of a Foley catheter. The perineum will be shaved as needed, and cleansed with antiseptic solution, and the scrotum will be elevated with a towel roll to expose the perineum. The FDA approved DynaCAD and Uronav system will be used to localize the diagnostic MRI findings within the prostate. The 510K approved tranperineal Uronav system will

be used to perform transperineal biopsy with electromagnetic alignment of the transrectal probe and stepper system attached to the perineal biopsy guide 17 gauge template.

Specimens will be sent to anatomic pathology office of:
Dr. MacLennan in separate cassettes at room 215A institute of pathology
2085 Adelbert Rd
Cleveland Ohio 44106

They will be received by Liwei Jia, MD, PhD.

Each specimen will be sent separately and identified by location in the prostate (1-12 a or p to identify the involved portion of the gland divided in 12 sextants and either anterior or posterior to midline of the coronal plane) along with PIRADS classification of the lesion in MRI report. The proximal and distal end of the sample will be dyed for orientation in the OR at the time of acquisition of each sample, or at a minimum noted if it is from the proximal, mid or distal 1/3 portion of the biopsy cavity to correlate with the same region of the virtual fiducial marker placed at the site of the biopsy.

Standard stains will be used to identify tumors within the specimen with photos taken after processing is completed to allow localization relative to the virtual fiducial marker placed at the site of the biopsy using the Uronav system. The pathology evaluation will be provided through Greg MacLennan, MD.

Biopsy samples will be obtained by hand using direct visualization of the live transrectal ultrasound image with fusion to the mapping MRI obtained preoperatively. The Urologist and Radiation Oncologist will obtain the tissue samples using either an 18 gauge biopsy gun with a 25 cm needle, or additionally may use a FDA approved 17 gauge needle as a trocar to be placed across the perineum and allow for readjustment between biopsies to reduce the number of needle placements and acquire additional biopsy samples using this trocar to reposition the tip to the desired biopsy location (note this step is per part of a pending patent application applied for by UH and the managing PI). The preoperative MRI images obtained prior to the procedure will be reviewed by the investigators, including Radiology, Urology, and Radiation Oncology, to determine the target volume for biopsy using the DynaCAD system, with transfer of the DICOM RT dataset and images to the Uronav system for image guided biopsy. The Uronav and its associated electromagnetic guidance system will be positioned adjacent to the patient in the operating room while the patient is in a dorsal lithotomy position under general anesthesia. The stepper/stabilizing devise associated with the Uronav system will be attached to the B&K Flexfocus ultrasound unit after placing the biplanar transrectal probe into position to visualize the prostate gland. Calibration of the encoders on the stabilization unit with the electromagnetic guidance system will be commissioned and maintained by Radiation Physics.

7.0 Study Procedures

Study Procedures	Screening (within 60 days of biopsy)	Biopsy	Visit 3 ~2 weeks Post	Visit 4 1 month Post	Visit 5 3 months Post
Informed consent	X				
Demographics	X				
Medical History	X			X	X
Height and Weight	X			X	X
Vitals[1]	X			X	X
Concomitant Med Assessment	X			X	X
ECOG Status	X		X	X	X
Adverse events assessment	X	X	X	X	X
Uronav Guided Biopsy		X			
Pathology		X			

1. Including blood pressure and pulse rate

7.1 Follow-up Procedures

Patients will be followed for safety assessments at post-operative day 1, and at visits 3, 4, and 5. Data collection will include routine treatment data, assessment of urinary obstruction requiring Foley catheter placement as well as signs or symptoms of infection requiring additional antibiotics or hospital admission felt to be directly related to the procedure.

8.0 Correlative/Special Studies

N/A

9.0 Safety and Effectiveness Assessments

9.1 Safety Assessments

Laboratory values obtained as part of the routine pre-surgical evaluation for prostate brachytherapy will be assessed prior to the procedure including: Basic Metabolic panel, CBC, Glomerular Filtration Rate, Coagulation Screen, and Urinalysis. Any abnormal labs will be reviewed by the Urologist and/or the Radiation Oncologist to determine clinical significance and the possible need for a reasonable delays or cancellation of the procedure. Any abnormal laboratory values will be repeated prior to proceeding with the procedure in such an event.

9.2 Effectiveness Assessments

Effectiveness will be analyzed by the rate of urinary obstruction beyond 7 days or infection directly related to the procedure, in addition to the analysis for the correlation of the biopsy samples with preoperative MR imaging. Statistical analysis of effectiveness is not anticipated due to the limited number of subjects in this exploratory initial analysis.

9.3 Other Response Parameters

The dose to the targeted lesion will be planned to be 150% of the prescribed peripheral dose to the prostate gland. The post-operative dosimetry and intraoperative dosimetry values will be recorded. In addition we will report the biopsy results for each targeted lesion to confirm correlation of the imaging with histopathology. There however will not be any therapeutic treatment alteration to be made based on the results for this study.

10.0 Statistical Plan

10.1 Sample Size Determination

Sample size justification: This is a hypothesis-generating pilot study with enrollment of 6 patients. Each patient is expected to have 12 to 15 tissue samples using standard sextant biopsies in addition to targeted biopsies of intraprostatic MRI findings. Assuming 14 specimens are sent for histopathology analysis in 6 subjects we will use the 84 biopsy sites. Based on the report in the literature [6], we expect the cancer lesion detection rate of 22% using multiparametric MRI/US fusion vs. 11% under current standard care. Ignoring the potential correlation of multiple lesions from the same patient, 6 patients (84 lesions) will have 82% power to detect in 11% improvement of detection rate using 2-sided one-sample chi-square test with a significance level of 0.05.

10.2 Statistical Methods

Statistical analysis: The correlation of biopsy tissue histopathology with intraprostatic MRI findings will be estimated using binomial evaluation for True Positive, False Positive, True Negative, False Negative values to report Sensitivity, Specificity, and Positive as well as Negative Predictive value for parametyric MRI findings relative to correlated histopathology. These data will be used for reporting the study results in regards to Specific aim 1, The infection rate and hospitalization rate within 30 days due to the procedure will be collected for expected acute events (AE's) and these data will be used for reporting the study results for specific aim 2 evaluation the transperineal use of Uronav to determine if the transperineal biopsy approach results in a reduced rate of infection or hospitalization compared to standard transrectal biopsies.

Any deviations from the previously described statistical plan will be described and justified in a protocol amendment.

10.3 Interim Analysis

Patients will be continuously monitored for safety and toxicity as we enroll up to 6 patients for the study. A stopping point will be enforced if 2 or more subjects develop infections requiring IV antibiotics or require hospitalization.

11.0 Risk Analysis

Clinical information from subjects will be recorded onto Case Report Forms and subsequently transferred into OnCore. Patients who additionally consent to a separate Urology Registry will have their data added to the Urologic Oncology & Minimally Invasive Therapies Database for UHHS Faculty.

Should any unanticipated adverse events occur during the course of the study, the clinical research coordinator will ensure that they are documented by the investigator and reported to the appropriate IRB per its then-current guidelines. If the determination is made that an unanticipated adverse event presents an unreasonable risk to subjects, the clinical evaluation will be paused, or if deemed appropriate (to enable further investigation), the subject will be withdrawn as soon as safely possible.

Adverse events, grade 2 and above, will be captured in OnCore and will be reported in accordance with the Data and Safety Monitoring Plan (DSMP) that is approved by the Cancer Center Protocol

Review and Monitoring Committee (and aligned with the NCI-approved plan). All monitoring and reporting will be compliant with policies presented in the most current version of the CCCC Clinical Trials Operations Manual, so that an independent assessment can be made of study activities. The study will be updated to remain compliant with any changing rules/policies of the CCCC.

Accrual reports will be provided to the PRMC and Cancer Center leadership. In addition, all active patients will be assessed for toxicity, SAE reports, completeness of data collection, and protocol violations. Early stopping toxicity endpoints, accrual goals and safety, and whether consent form modifications need to be made will also be reviewed.

11.1 Anticipated Risks

The Phillips Medical's Uronav device poses no significant risk, however, any unanticipated complications or infections will be reported as stated below. The risk for prostate edema and urinary obstruction may be increased due to the additional transperineal needle placement as the biopsy will be followed by routine prostate brachytherapy. In this event, patients will be asked to maintain a Foley Catheter overnight to allowed edema to resolve, and to avoid acute obstruction the following day.

11.2 Adverse Event Definitions

An adverse event (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

11.3 Expectedness

Adverse Events can be Expected or Unexpected.

An expected adverse event is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol. Expected acute events in this study would be an infection requiring additional antibiotic treatment beyond the standard postoperative antibiotic given for the prostate seed implant, or readmission to the hospital for pain, infection, or obstruction as a result of the biopsies.

An unexpected adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

11.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study devise or procedures.
- Probable – The AE is likely related to the study devise or procedures.
- Possible – The AE may be related to the study devise or procedures.
- Unlikely – The AE is doubtfully related to the study devise or procedures.
- Unrelated – The AE is clearly NOT related to the study devise or procedures.

11.5 Reporting Procedures for All Adverse Events

All participating investigators will assess the occurrence of AEs throughout the subject's participation in the study. Subjects will be followed for adverse events for 3 months after the Uronav guided biopsy or until death, whichever occurs first. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the subject's case report form, subject's medical records, and/or any other institutional requirement. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study), requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event.

The investigator will provide the following for all adverse events:

- Description of the event
- Date of onset and resolution
- Grade of toxicity
- Attribution of relatedness to the investigational devise or procedures
- Action taken as a result of the event
- Outcome of event

In this study, descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 available at http://ctep.cancer.gov will be utilized for AE reporting.

Serious Adverse Events

A **serious adverse event** (SAE) is any adverse experience occurring that is attributed to the research devise that results in any of the following outcomes:

- Results in **death.**
- Is a **life-threatening** adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of

the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.

- Requires **inpatient hospitalization or prolongation of existing hospitalization**. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:
    - The admission results in a hospital stay of less than 24 hours OR
    - The admission is pre-planned (e.g., elective or scheduled surgery arranged prior to the start of the study) OR
    - The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

  However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependant on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.
- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. The development of a new cancer is always considered an important medical event.

SAE Report Form

SAEs will be recorded on the FDA Form 3500A (MedWatch) but should only be reported as instructed below. The electronic FDA SAE reporting forms should not be used.

Reporting Procedures for Serious Adverse Events

For the purposes of safety reporting, all adverse events will be reported that occur on or after Biopsy through Visit 5. Adverse events, both serious and non-serious, and deaths that occur during this period will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). Related AEs will be followed until resolution to baseline or grade 1 or stabilization.

SAE Reporting Requirements

- The Site Principal Investigator will review the SAE and report the event to the FDA, external collaborator(s), and IRB as applicable.
- It is the Sponsor-Investigator's responsibility (e.g. lead site PI) to ensure that ALL serious adverse events that occur on the study (e.g. ALL SAEs that occur at each enrolling institution) are reported to all participating sites.

Institutional Review Board Reporting Requirements:

- Investigative sites will report adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

SAEs and OnCore

- All SAEs will be entered into OnCore.
- A copy of the SAE form(s) submitted to the sponsor-investigator is also uploaded into Oncore.

11.6 Data Safety and Toxicity Committee

It is the responsibility of each site PI to ensure that ALL SAEs occurring on this trial (internal or external) are reported to the Case Comprehensive Cancer Center's Data and Safety Toxicity Committee. This submission is simultaneous with their submission to the sponsor and/or other regulatory bodies.

The sponsor-investigator is responsible for submitting an annual report to the DSTC as per CCCC Data and Safety Monitoring Plan.

11.7 Data and Safety Monitoring Plan (DSMP)

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI guidelines.

11.8 Stopping Rules

A stopping point will be enforced if 2 or more subjects develop infections requiring IV antibiotics or infections that require hospitalization if felt to be related to the procedure (i.e for example gram negative sepsis) within 30 days of the procedure.

12.0 Data Reporting

The OnCore Database will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. OnCore is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. OnCore properly used is compliant with Title 21 CFR Part 11. Access to data through OnCore is restricted by user accounts and assigned roles. Once logged into the OnCore system with a user ID and password, OnCore defines roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore Administrator at oncore-registration@case.edu.

OnCore is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. This study will utilize electronic Case Report Form completion in the OnCore database. A calendar of events and required forms are available in OnCore.

13.0 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

13.1 Written Informed Consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject.

13.1.1 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

13.1.2 Retention of records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with national and international regulations.

14.0 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Research Quality Assurance Office, IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the center to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

15.0 Ethics

This study will be conducted in compliance with the protocol approved by the IRB, the relevant federal regulations, and IRB policies and procedures and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB according to its policies and procedures.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this

study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of all subjects will be sought using the IRB-approved consent form. Before a subject undergoes any study procedure, an informed consent discussion will be conducted and written informed consent obtained with a consent form signed by the subject or legally acceptable surrogate if applicable. An investigator-designated research professional will obtain written informed consent from subjects.

16.0 Conflict of Interest

One or more of the Investigators conducting this study serve as consultants for *Philips*, the company that makes *the Uronav system*, which is the device being used in this study. These financial interests are within permissible limits established by the Case Conflict of Interest Policy.

17.0 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study will be obligated to provide the sponsor with complete test results and all data derived from the study. An abstract and/or manuscript is anticipated to be reported as a result of the completion of the study, and images are to be provided to the sponsor for their use in research or marketing of the device.

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Appendix A

ECOG Performance Status Scale	
Grade	Description
0	Normal activity. Full active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% if waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.