

**Assessing the Detection of Clinically  
Significant Prostate Cancer using Magnetic  
Resonance Imaging-Guided Transperineal  
Targeted Biopsy Compared to Standard  
Transrectal Biopsy Outcomes Study: The  
ASTROS Trial (NCT03044197)**

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## SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Site Investigator:\*

Stephen B. Williams M.D.

Signed: \_\_\_\_\_ Date: \_\_\_\_\_

*Name Stephen B. Williams M.D.*

*Title: Assistant Professor*

*\* The protocol should be signed by the local investigator who is responsible for the study implementation at his/her specific site; i.e., if Investigational New Drug study, the individual who signs the Form FDA 1572.*

## 1.0 Background

Prostate cancer (PCa) is the most common non-cutaneous malignancy and the second leading cause of death among men.<sup>1</sup> Transrectal ultrasound guided prostate biopsies are currently the gold standard for the diagnosis of PCa which can be categorized as clinically significant or indolent PCa. Clinically significant prostate cancer (csPCa) is deemed cancer which warrants treatment and is defined according to previously published studies as biopsy Gleason score  $\geq 7$  or maximum cancer core length  $\geq 5$ mm.<sup>2</sup> Indolent PCa is considered cancer which does not require treatment with patients placed on active surveillance and is defined by the modified Epstein criteria as biopsy Gleason score  $\leq 6$ , PSA density  $\leq 0.15$ ,  $\leq 2$  positive cores, and unilateral cancer).<sup>2,3</sup> Given concerns regarding the overtreatment of indolent PCa, efforts to improve the diagnosis of csPCa and limit diagnosis of indolent disease are needed.<sup>4</sup>

Standard in-office prostate biopsies using transrectal ultrasound guidance are random, non-diagnostic and imprecise in detecting PCa. Moreover, standard biopsies may miss csPCa. With multi-parametric magnetic resonance imaging (mpMRI), we now have a way of increasing the detection of csPCa while decreasing the detection of indolent disease. Using the mpMRI and scoring methodology called the prostate imaging reporting and data system (PIRADS v2), lesions suspicious for PCa and csPCa can be categorized as: 1: very low, 2: low, 3: intermediate, 4: high, and 5: very high risk of csPCa.<sup>5</sup> Studies using mpMRI recommend prostate biopsy of mpMRI lesions with PIRADS  $\geq 3$ .<sup>2,5,6</sup>

The Division of Urology has introduced a powerful new solution for analysis, planning and targeted biopsy of the prostate. This consists of using DynaCAD for Prostate mpMRI and the UroNav fusion biopsy system- a comprehensive solution which offers a cutting edge imaging option for many patients with clinical suspicion for harboring PCa mainly by elevated and/ or rising prostate specific antigen (PSA) levels. Targeted MRI/Ultrasound biopsy is poised to become the new standard in PCa diagnosis at UTMB.

Presently at UTMB, if patients have a mpMRI and region of interest identified (usually mpMRI obtained after prior negative biopsy or in patients deemed to have indolent disease by standard prostate biopsy and to be placed on active surveillance) then they are referred for consideration of targeted biopsy with UroNav.

No study has compared UroNav transperineal mpMRI-targeted versus standard transrectal ultrasound guided prostate biopsy in the detection of prostate cancer. A recent trial compared transperineal/transrectal mpMRI-targeted versus TRUS systematic biopsy in biopsy naïve men and noted improved detection of csPCa.<sup>7</sup> Specifically, the overall (50.5% vs 29.5%,  $p=0.002$ ) and csPCa (43.9% vs 18.1%,  $p<0.001$ ) detection rates were significantly higher in the targeted versus the standard transrectal ultrasound guided prostate biopsy group, respectively.<sup>7</sup> While this trial provided the first level one evidence in support of mpMRI-targeted biopsy in biopsy naïve men, the study used a device not

commercially available in the United States and allowed both transperineal or transrectal mpMRI-targeted prostate biopsies to be performed in the targeted biopsy arm of the study.

In this prospective randomized trial, the investigators will assess the detection rates of csPCa diagnosis of standard transrectal ultrasound guided prostate biopsy compared to computer targeted system (UroNav - InVivo corp) to sample suspicious areas (PIRADS  $\geq 3$ ) identified on mpMRI.

The hypothesis being tested is that computerized fusion guided biopsy (UroNav) will increase detection of csPCa compared to standard transrectal ultrasound guided prostate biopsy alone.

## **2.0 Rationale and Specific Aims**

Transrectal prostate biopsy with multiple samples using a standardized template under transrectal ultrasound (TRUS) guidance is the current standard diagnostic approach in suspicion of PCa as recommended by the European Association of Urology (EAU) and American Urological Association (AUA).<sup>8,9</sup> With the introduction of mpMRI we now have an effective way to localize cancer and direct our biopsies more effectively.<sup>6</sup> mpMRI guided biopsies have shown to have high negative predictive values, especially in men with prior negative mapping results.<sup>10,11</sup> mpMRI-targeted biopsy and systemic biopsies are comparable in their detection rates of PCa, with mpMRI showing increasing csPCa detection in biopsy-naive patients, thus decreasing the detection of indolent PCa.

The mpMRI-targeted biopsy system UroNav allows for the fusion of mpMRI images with live TRUS feed to target lesions noted on mpMRI. Studies have demonstrated men undergoing biopsy for suspected PCa, targeted MR/ultrasound fusion biopsy (using the transrectal UroNav prostate biopsy device), compared with standard extended-sextant TRUS-guided biopsy, was associated with increased detection of high-risk PCa and decreased detection of indolent disease.<sup>6</sup>

The mpMRI-targeted devices used in prior studies have been either the UroNav transrectal machine or used a combination of transrectal and transperineal techniques using devices not available in the United States.<sup>6,7</sup> Based on these prospective studies and limited randomized trials there is increasing support of the utility of using mpMRI-targeted prostate biopsy in the detection of PCa.

The present study will assess a transperineal device (UroNav) currently available in the United States and thus will not only directly assess the impact of transperineal prostate detection of csPCa but provide the first United States trial assessing the utility of this platform. UTMB has the *only* commercially available UroNav transperineal mpMRI-targeted device in the state of Texas. Thus, this trial has the leverage of a large academic primary care referral network combined with a novel device to provide important clinical

information discerning the improved detection of csPCa in a relatively short period of time (approximately one year).

The UroNav fusion biopsy system until recently *only* allowed targeted prostate biopsy to be performed transrectally. With over 200 devices sold in the United States, UroNav is the most commonly used targeted biopsy system and has been extensively studied by the National Institutes of Health (NIH). UroNav requires pre-biopsy mpMRI for lesion(s) delineation, real-time TRUS registered to the mpMRI and electromagnetic tracking of biopsy needles for precise guidance. The actual working elements of the UroNav fusion biopsy system includes the UroNav mobile workstation cart, ultrasound cart and the electromagnetic field generator which connects to the patient bed by a mobile arm. The electromagnetic field generator in combination with a navigation sensor mounted to the TRUS transducer merges the mpMRI images with live TRUS guidance to accurately biopsy the prostate. As previously mentioned, UroNav provides support for transrectal biopsy procedures but *now* has the capability to perform biopsy via a transperineal approach. The UroNav fusion-guidance for transperineal biopsy requires the transperineal stepper which holds the TRUS probe and a standard biopsy grid plate equipped with UroNav universal sensors to precisely perform biopsies. Invivo supports both UroNav and DynaCad which UTMB has recently acquired and the Department of Radiology currently has been working with for many years, respectively. DynaCad is a software used in the radiology suite which exports diagnostic 3D information from a prior mpMRI exam to discern the prostate gland and MR-suspicious lesions. The transperineal approach (skin halfway between scrotum and anus) essentially eliminates the risk of sepsis and/or infection associated with transrectal prostate biopsy samples obtained through feces and rectal mucosa. Sepsis occurs in up to 3% of patients who undergo transrectal prostate biopsy (Table 1).<sup>12</sup>

**Table 1. Signs and Symptoms of Sepsis<sup>12</sup>**

<p><b>General</b> Fever (&gt;38.3°C) Hypothermia (&lt;36°C) Tachycardia &gt;90/min Tachypnea Hypotension (SBP&lt;90 mmHg) Altered mental status Significant edema or positive fluid balance Oliguria Ileus Altered mental status/lethargy</p> <p><b>Laboratory</b> Normal WBC with &gt;10% immature forms Creatinine increase &gt;0.5 mg/dL INR &gt;1.5 or aPTT &gt;60 secs</p>
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Thrombocytopenia (platelet count <100,000/mm<sup>3</sup>)  
Hyperglycemia (plasma glucose >120 mg/dL) in the absence of diabetes  
Hyperlactatemia (>1 mmol/L)

No study has compared UroNav transperineal mpMRI-targeted versus standard transrectal prostate biopsy in the detection of prostate cancer.

The **hypothesis** being tested is that computerized fusion guided biopsy (**UroNav**) will increase detection of csPCa compared to standard biopsy (SB) (transrectal) alone. The primary end point will be the comparison of detection rates csPCa between arm A mpMRI+ and arm B (refer to figure on page 9). csPCa will be defined according to the Standards of Reporting for MRI-targeted Biopsy Studies (START) criteria for targeted biopsy Gleason Score  $\geq 7$  or maximum cancer core length (CCL)  $\geq 5$  mm and the updated Epstein criteria for SB (Gleason score  $\geq 7$ , PSA density  $\geq 0.15$ , Gleason score  $\geq 2$  positive cores, and bilateral cancer).<sup>2,3</sup> The secondary end points will be (1) comparison of the overall detection rate of PCa and csPCa between arm A mpMRI+, arm A mpMRI-, and arm B and (2) comparison of complication rates (Table 2) between arm A mpMRI+ and arm B.

Considering 10% of patients will be lost to follow-up, the total sample size needed will be 80 patients (See Section 9.1 Statistical Considerations). The clinical trial is enrolled in clinicaltrials.gov (**ClinicalTrials.gov Identifier NCT03044197**).

If the primary end point is reached, the study will continue and remain ongoing to examine the remaining secondary end points.

#### **Specific Aims:**

1. Determine if UroNav increases the detection of csPCa between arm A mpMRI+ than arm B standard transrectal biopsy.
2. Determine if UroNav increases the overall detection of PCa between arm A mpMRI+ versus arm A mpMRI- and arm B standard transrectal biopsy.
3. Determine if UroNav decreases rates of complications between arm A mpMRI+ than arm B standard transrectal biopsy.

### **3.0 Inclusion/Exclusion Criteria**

**Subjects must meet all of the inclusion criteria in order to be eligible to participate in the study.**

1. Males aged 18-75 years old
2. PSA >1 ng/ml but <15 ng/ml
3. Negative DRE

4. Subject has provided informed consent in a manner approved by the IRB and is willing and able to comply with the trial procedures.

**Subjects meeting any of the exclusion criteria at baseline will be excluded from study participation.**

1. Previous prostate biopsy or prostate surgery
2. Previous prostate mpMRI
3. Contraindication to mpMRI: Patient has implanted metal clips or wires of the type which may concentrate radiofrequency fields or cause tissue damage from twisting in a magnetic field. Examples include: aneurysm clip, implanted neural stimulator, implanted cardiac pacemaker or autodefibrillator, cochlear implant, ocular foreign body (e.g., metal shavings), any implanted device (pumps, infusion devices, etc), shrapnel injuries.
4. Patients in the Texas Department of Criminal Justice (prisoners)
5. Patients with acute urinary symptoms including urinary retention and urinary tract infection
6. Patient has dialysis dependent renal failure or baseline serum creatinine level > 2.0mg/dL

#### **4.0 Treatment Assignment/Randomization**

Enrollment into the study is defined as following randomization. Patients who fulfill all eligibility criteria and have provided written consent will be randomized to undergo mpMRI followed by targeted biopsies (arm A mpMRI+) or TRUS transrectal biopsy (arm-B) by the PI and authorized study collaborators. [REDACTED], study coordinator, will have access to randomization, generated by an electronic randomization system provided by REDCap.

##### Sequence generation

Patients will be randomly assigned to arm A or arm B following a 1:1 simple randomization procedure according to a computer-generated randomization list provided by REDCap. [REDACTED] [REDACTED] study coordinator, and a designated back-up will be the only persons to have access of the REDCap randomization list.

#### **5.0 Study Procedures**

##### **Study population and design:**

Eligible patients referred to the Division of Urology will be randomly assigned to one of the following arms: **arm A (mpMRI+ group)**, mpMRI prior to transperineal mpMRI-targeted prostate biopsy; **arm B (Standard group)**, TRUS-guided transrectal 12-core prostate biopsy.

In arm A, all patients with positive mpMRI evidence of lesions suspicious for PCa, i.e. PI RADS  $\geq 3$  will be submitted to transperineal MRI-targeted prostate biopsy (arm A mpMRI+). In cases of negative mpMRI results i.e. PI RADS < 3, arm A patients will

undergo TRUS-guided transrectal 12-core prostate biopsy (arm A mpMRI-)(refer to figure on page 9).

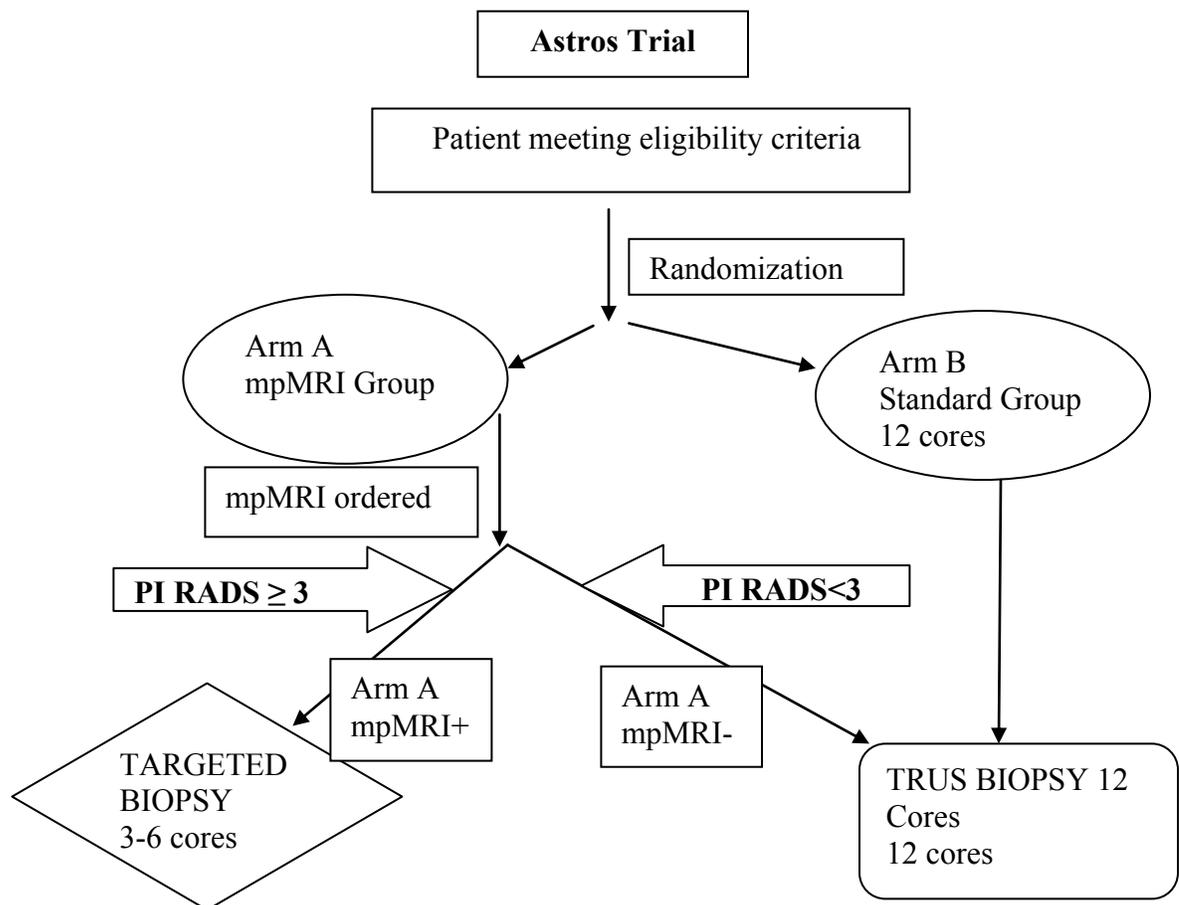
The present randomized clinical trial will compare the outcomes between the two arms.

**Primary End-Points:** The primary end point will be the comparison of detection rates csPCa between arm A mpMRI+ and arm B. csPCa will be defined according to the Standards of Reporting for MRI-targeted Biopsy Studies (START) criteria for targeted biopsy Gleason Score  $\geq 7$  or maximum cancer core length (CCL)  $\geq 5$  mm and the updated Epstein criteria for standard biopsy (Gleason score  $\geq 7$ , PSA density  $\geq 0.15$ , Gleason score  $\geq 2$  positive cores, and bilateral cancer).<sup>2,3</sup> Patients will be enrolled in an intention to treat trial (See Section 9.1 Statistical Considerations).

**Secondary End-Points:** The secondary end points will be:

- i. Comparison of the overall detection rate of PCa and csPCa between arm A mpMRI+, arm A mpMRI-, and arm B and
- ii. Comparison of complication rates (Table 2) between arm A mpMRI+ and arm B.

If the primary end point is reached, the study will continue and remain ongoing to examine the remaining secondary end points.



Patients will be consented by Urology providers (IRB approved Co-Investigators and collaborators).

Randomization and data collection will be done by [REDACTED] [REDACTED] (study coordinator) into a REDCap generated case form (SEE APPENDIX). Study coordinator will provide de-identified data for statistical data analysis and will have master file, in password protected computer, which will link the PHI to subject ID (will be assigned by the study coordinator). After the completion of statistical analysis the master file will be deleted permanently.

Data analysis will be done by Yong Shan (Department of Surgery analyst) supervised by Dr. Stephen Williams (PI) and statistical analysis collaborators (Dr. Yong-Fang Kuo, IRB approved). Data to be analyzed will be de-identified will have no protected health information (PHI) including patient name, medical record number or date of birth.

### **PRE-PROCEDURE EVALUATION (within 2 months from study enrollment)**

Patients are going to be evaluated at the time of office appointment by the PI and Study Collaborators

- Screening-Patients with elevated level of Prostate-specific antigen (PSA >1 ng/ml but <15 ng/ml), will be screened for research study participation by the urology providers (Co-Investigators) and Stephen B. Williams, MD (PI).
- Inclusion/ Exclusion Criteria
- Consent- Patient having all the inclusion and no exclusion criteria for eligibility will be approached with research consent for participation by the urology providers (Co-Investigators) and Stephen B. Williams, MD (PI).
- Demographics
- Medical History
- Surgical History
- Clinical Stage/ Digital Rectal Exam
- Vital Signs
- Physical Exam
- MRI PI-RAD Score (Grade System to classifying prostate cancer , using Pre-Procedure MRI (within 2 months from consenting & randomization))- only required for arm A
- Gland Volume (Calculated from the mpMRI and/or Ultrasound -within 2 months from consenting & randomization)
- Prostate specific antigen (PSA)

### **PROCEDURE EVALUATION (Surgical procedure)**

Patient will undergo prostate biopsy in arm A or arm B as assigned by the randomization card

- A. Transperineal mpMRI-targeted prostate biopsy (arm A mpMRI+) (Procedure will be performed in operating room):** mpMRI-targeted prostate biopsy is standard of care and will be performed using the UroNav transperineal fusion system by a single urologist (Stephen Williams, MD). Dr. Williams has >1 yr experience in performing mpMRI-targeted prostate biopsies. All patients will receive one dose of Ancef intravenous antibiotic at time of surgery (Vancomycin 1gm intravenous for penicillin/cephalosporin allergies or prior history of orthopedic hardware implanted within 2 years) to cover skin flora and may add additional antibiotic if prior documented UTI(s) in past then antibiotic may be tailored according to those culture(s) sensitivities) to cover enteric flora as well. All patients will receive an enema until result to be performed the morning of prostate biopsy.

The gland and the regions of interest will be contoured, and the prostate contour will be fused in real time with the TRUS image. Biopsies will be performed via a transperineal approach in the operating room. The patient will be placed in dorsal lithotomy position. mpMRI-targeted biopsies will be performed on regions of interest, and three to six cores will be obtained for biopsy from each lesion and is standard of care according to START criteria for targeted biopsy.

**Multiparametric magnetic resonance imaging (mpMRI)**

All of the patients in arm A will undergo mpMRI according to the European Society of Urogenital Radiology guidelines. The Prostate Imaging–Reporting and Data System (PI-RADSv2) classification (1-5) will be used to describe the lesions found: 1: very low, 2: low, 3: intermediate, 4: high, and 5: very high risk of csPCa. <sup>5</sup> The mpMRI will be performed at two centers with a 3-T scanner using a 32-channel phase array coil or four-channel phase array coil. Two experienced radiologists will analyze the mpMRI findings. Lesions with a PI-RADS score of  $\geq 3$  will be considered suspicious for PCa.

In cases of negative mpMRI results, arm A patients will undergo TRUS-guided transrectal 12-core prostate biopsy (arm A mpMRI–) in an identical fashion as described in arm B. Urologists (PI and Co-Investigators) will obtain SOC informed consent and perform the TRUS biopsies.

Dr. Williams will collect the biopsy sample in case of positive mpMRI results (arm A mpMRI+) and it will be sent out to pathology lab at UTMB for analysis, as SOC.

Please Note: Patients having positive mpMRI results will be referred to Dr. Williams, by their primary urology (Co-Investigators and collaborators) providers, only after patients provide written consent to participation. Primary Urology (Co-Investigators and collaborators including Dr. Williams) providers will consent the patients.

- B. TRUS-guided transrectal prostate biopsy (arm B) (Procedure will be performed in Clinic):** TRUS-guided transrectal prostate biopsy will be performed using a disposable 18-gauge biopsy gun with a specimen size of 18–22 mm (Bard Medical, Covington, GA, USA) by Urology providers (Co-Investigators and Dr. Williams

(PI). All patients will receive one dose fluoroquinolone antibiotic to be taken the morning of prostate biopsy (if fluoroquinolone allergy then may substitute Bactrim DS, if prior documented UTI(s) in past then antibiotic may be tailored according to those culture(s) sensitivities) to cover enteric flora. All patients will receive an enema until result to be performed the morning of prostate biopsy.

Urologists will obtain SOC informed consent and perform the TRUS biopsies.

The 12 cores will be obtained from 12 separate anatomical regions of the prostate which is standard practice in performing TRUS-guided transrectal prostate biopsy: left medial apex, left lateral apex, left medial midgland, left lateral midgland, left medial base, left lateral base, right medial apex, right lateral apex, right medial midgland, right lateral midgland, right medial base and right lateral base.

For arm A and arm B biopsy, [REDACTED] (the study research coordinator) , Stephen B. Williams, MD and Eduardo Orihuela, MD (Chairman, Division of Urology and study co-investigator), will monitor safety and any possible Unanticipated Adverse Device Events (UADEs). Serious Adverse Events (SAEs), Adverse Events (AEs) and UADEs assessment will be done by Eduardo Orihuela, MD.

For Arm A and Arm B biopsy, the procedure will be performed and the sample will be sent to the Pathology lab for analysis. Dr. Williams and other urology providers will not be involved with the sample analysis and biopsy report data and results. Once the report / data is available on Epic for review, the study coordinator will extract data from patient records/ Epic into an electronic data sheet (REDCap case form, SEE APPENDIX) on which the patient will be identified by a subject ID assigned to them, no PHI information will be present. The data analysis will be performed in aggregate. A master file linking the patient to Subject ID will remain with the study coordinator for data entry purposes and once the data analysis is complete, the master file will be securely stored and password protected.

- Adverse event assessment (Tables 2 and 3)

**POST-PROCEDURE EVALUATION/ END OF STUDY- (Follow-up can be done by telephone or clinical visit)**

- Diagnosis of csPCa- Based on the biopsy report will be available 2-4 weeks post-procedure
- Gleason score ((Grade System to classifying PCa)- Based on the biopsy report will be available 2-4 weeks post-procedure
- Total cancer core length (mm)- Based on the biopsy report will be available 2-4 weeks post-procedure
- Maximum cancer core length (mm)- Based on the biopsy report will be available 2-4 weeks post-procedure
- Adverse event assessment- Can be done by telephone or clinical visit, usually 2-4 weeks post biopsy procedure

**Table 2. Schedule of Events**

Variables (Both Arm A and Arm B)	Pre-Study (within 2 months from consent and randomization)	Biopsy	Post-Biopsy Follow-up/Study End (within 2-4 wks from biopsy) <b>Follow-up can be done by telephone or clinical visit)</b>
Informed consent*	X		
Demographics	X		
Medical History	X		
Surgical History	X		
Clinical Stage/digital rectal exam	X		
Vital signs	X		
Height	X		
Weight	X		
PSA	X		
MRI PI-RADS ( Arm A)	X	X	
Gland volume (MRI- Arm A or US- Arm B)	X	X	
Diagnosis of Prostate Cancer			X
Serum creatinine***	X		
Diagnosis of Clinically Significant Prostate Cancer**			X
Gleason score			X
Total cancer core length (mm)			X
Maximum cancer core length (mm)			X
UADE*		X	X

\* Indicates study-only activity.

All other procedures/tasks are standard of care. Prostate specific antigen (PSA), Digital rectal examination (DRE), Prostate Imaging Reporting and Data System (PI-RADS), transrectal ultrasound (TRUS), Unanticipated Adverse Device Event

\*\*Clinically significant PCa defined as targeted biopsy Gleason Score  $\geq$  or maximum CCL  $\geq$  5 mm and the updated Epstein criteria for SB.

\*\*\* The serum creatinine assessment will be performed no more than one month prior to randomization.

## 6.0 Study Product Description

The actual working elements of the UroNav fusion biopsy system includes the UroNav mobile workstation cart, ultrasound cart and the electromagnetic field generator which connects to the patient bed by a mobile arm. The electromagnetic field generator in combination with a navigation sensor mounted to the TRUS transducer merges the mpMRI images with live TRUS guidance to accurately biopsy the prostate. As previously mentioned, UroNav provides support for transrectal biopsy procedures but *now* has the capability to perform biopsy via a transperineal approach. The UroNav fusion-guidance for transperineal biopsy requires the transperineal stepper which holds the TRUS probe and a standard biopsy grid plate equipped with UroNav universal sensors to precisely perform biopsies. Invivo supports both UroNav and DynaCad which UTMB has recently acquired and the Department of Radiology currently has been working with for many years, respectively. DynaCad is a software used in the radiology suite which exports diagnostic 3D information from a prior mpMRI exam to discern the prostate gland and MR-suspicious lesions.

A detailed UroNav Brochure is attached with IRB submission for review and will be provided to patients (SEE APPENDIX).

## 7.0 Adverse Events or Unanticipated Problems involving Risk to Participants or Others

**Table 3. Complications associated with prostate biopsy**

Common (greater than 1 in 10)	Occasional (between 1 in 10 and 1 in 50)	Rare (less than 1 in 50)
<ul style="list-style-type: none"> <li>•Blood in your urine for up to 10 days.</li> <li>•Blood in your semen for up to 6 weeks; this is harmless and poses no risk to you or any sexual partners.</li> <li>•Bruising in your perineal area.</li> <li>•Urinary infection (10% risk).</li> <li>•Sensation of discomfort due to bruising.</li> <li>•Haemorrhage(bleeding) preventing you from passing urine (2% risk).</li> </ul>	<ul style="list-style-type: none"> <li>•Blood infection (septicaemia) needing hospitalisation (2% risk).</li> <li>•Haemorrhage (bleeding) needing hospitalisation (1% risk).</li> <li>•Failure to detect a significant cancer of the prostate.</li> <li>•The procedure may need to be repeated if the biopsies are inconclusive or your PSA level rises further.</li> <li>•Inability to pass urine (retention of urine).</li> </ul>	<ul style="list-style-type: none"> <li>•Hospital-acquired infection</li> <li>•Colonisation with MRSA (0.9% - 1 in 110).</li> <li>•MRSA bloodstream infection (0.02% - 1 in 5000).</li> <li>•Clostridium difficile bowel infection (0.01% - 1 in 10,000).</li> </ul> <p><b>Please note:</b> The rates for hospital-acquired infection may be greater in “high-risk” patients. This group includes, for example, patients with long-term drainage tubes, patients who have had their bladder removed due to cancer, patients who have had a</p>

		long stay in hospital or patients who have been admitted to hospital many times.
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**Complications associated with MR-Gadolinium:**

The contrast material used in MRI called gadolinium is less likely to produce an allergic reaction than the iodine-based materials used for x-rays and CT scanning. Very rarely, patients are allergic to gadolinium-based contrast materials and experience hives and itchy eyes. Reactions usually are mild and easily controlled by medication. Severe reactions are rare.

Nephrogenic systemic fibrosis (NSF), a thickening of the skin, organs and other tissues, is a rare complication in patients with kidney disease that undergo an MR with contrast material. Gadolinium-based contrast material may be withheld in some patients with severe kidney disease.

**Adverse Event:**

For the purposes of this study, pre-planned interventions noted at baseline are not considered AEs.

Adverse Events (AEs) collected in this study will be limited to death post biopsy procedure, serious injury (life threatening, results in permanent impairment of body functions or permanent damage to a body structure, or necessitates medical or surgical intervention to preclude permanent impairment of body functions),

Any unanticipated adverse device event will be recorded and reported to the IRB within 10 business days.

AE/SAE information must be collected up until subject's completion of the study. In the case of death or serious injury, Investigator or study coordinator must report to IRB as soon as possible within 10 business days after first learning the event.

Collection of all AEs, to be reported as follows:

- i) all serious adverse events and/or unanticipated problems involving subjects will be reported as required per the UTMB IRB Policies and Procedures, Section 8; and
- ii) All other adverse events will be recorded on an excel spreadsheet and submitted with each continuing review.

**Serious Adverse Event (SAE):**

An SAE is defined as an AE that meets one of the following conditions:

- Death during the period of protocol defined surveillance
- Life-threatening event (defined as a subject at immediate risk of death at the time of the event)
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance
- Results in congenital anomaly or birth defect
- Results in a persistent or significant disability/incapacity
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All SAEs will be:

- recorded on the appropriate SAE CRF
- followed through resolution by a study clinician
- reviewed and evaluated by a study clinician

#### **Unanticipated Adverse Device Events (UADEs):**

An UADE is “any serious adverse effect on health and safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or protocol., or any other unanticipated serious problem associated with a device that relates to the right, safety, or welfare of subjects. (21 CFR 812.3(s)).”The principal investigator will submit to the reviewing IRB a report of any UADE occurring during an investigation as soon as possible, but in no event later than ten (10) days after the investigator learns of the effect. All UADEs must be documented by the investigator including the date of consent, a complete description of the event, possible reason(s) for the event, severity, duration, concurrently with appropriate CRF.

## **Reporting Procedures**

Any AE considered serious by the PI (Dr. Williams) or Co-PI (Dr. Orihuela) or which meets the aforementioned criteria must be submitted on the SAE form to the IRB in accordance with IRB policies and procedures.

The study PI (Dr. Williams) or Co-PI (Dr. Orihuela) will complete Serious Adverse Event Assessment Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the Serious Adverse Event Form within 72 hours of awareness.
- Serious adverse events other than death and immediately life-threatening events, regardless of relationship, will be reported within 10 days of becoming aware of the event.

All SAEs will be followed until satisfactory resolution or until the PI (Dr. Williams) or Co-PI (Dr. Orihuela) deems the event to be chronic or the patient to be stable.

**Study related risks include loss of confidentiality.**

## **8.0 Study Withdrawal/Discontinuation**

A study subject will be discontinued from participation in the study if any of the following occur:

- Unacceptable adverse event (AE)
- Intercurrent illness, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject in the opinion of the treating investigator
- Development of any exclusion criteria
- Subject withdraws consent to continue in the research for any reason

## **Handling of Withdrawals**

Subject will be followed as per standard of care, after withdrawal from study.

## **Termination of Study**

Possible reasons for discontinuation of the study include poor study accrual and/or IRB request for study closure after review of reported adverse event(s) in the required timeline as above.

## **9.0 Statistical Considerations**

This is an un-blinded, single center, randomized controlled trial. The associations between categorical variables and the arms will be analyzed with Fisher's exact test; Mann-Whitney and Kruskal-Wallis tests for continuous variables. p values will be obtained by the two-sided exact method at the conventional 5% significance level. Using an intention to treatment power analysis for Aim 1, a sample size of 62 patients (31 per arm) will be required to detect a 30% absolute increase in the detection rate of csPCa, with a one-sided 0.05 significant level, a type II error of 0.20, and the rate of csPCa being 18.1% from standard biopsy,<sup>7</sup> based on two-sample test for proportions. For Aim 2, assuming about 25% of Arm A is MRI- and rate of csPCa was 4% in MRI- and 48% in MRI+ (based on the results from paper published by Porpiglia et al<sup>7</sup>) and using one-way ANOVA test, it will require 72 patients (36 per arm) to detect this difference with power of 80%. Considering 10% of patients will be lost to follow-up, the total sample size needed will be 80 patients. No interim analyses will be planned, and all procedures will be performed on an intention-to-treat basis for Aim 1 as our main analyses. Non-intent to treat analyses under Aim 2 will be treated as sensitivity analyses. All analyses will be performed with SAS version 9.4 (SAS Institute, Cary, NC).

## **10.0 Ethics and the Protection of Human Subjects**

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

The investigator must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate independent ethics committee (IEC) or IRB registered with the OHRP. Any amendments to the protocol or consent materials must also be approved before they are placed into use. In the United States and in other countries, only institutions holding a current US Federalwide Assurance issued by OHRP may participate.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product. Consent forms will be IRB-approved and the subject will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. The subjects will sign the informed consent document prior to any procedures being done specifically for the study. The subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to

participate. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

### **Privacy/Confidentiality Issues**

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal investigator.

Individuals authorized to view study records will be identified to the study subject on the informed consent but may include a study monitor or other authorized representatives of the sponsor or funding agency or federal or local agencies that regulate research including representatives from the Food and Drug Administration, Office of Human Research Protections, or the Institutional Review Board. Study records may also be made available for internal compliance reviews and quality assurance representatives.

These individuals may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

In accordance with the Food and Drug Administration Amendment Act of 2007 (FDAAA) and The International Committee of Medical Journal Editors (ICMJE) member journals trials-registration policy as a condition for publication, this study will be registered in the public trials registry [ClinicalTrials.gov](http://ClinicalTrials.gov), which is sponsored by the National Library of Medicine. Results will be published to [clinicalTrial.gov](http://clinicalTrial.gov) when available but will not identify individual subjects.

### **11.0 Record Retention**

Consent forms and other study related documents will be retained for a minimum of 6 years from study closure with IRB,

- *The specific location of the data and where/how the data will be stored*

The gathered data will be stored on an IBM General Parallel File System (GPFS) in our institution. GPFS is a high-performance, shared-disk file management system that can provide faster, more reliable access to a common set of file-based data. The GPFS allows multiple applications or users to share access to a single file simultaneously while maintaining file-data integrity. Currently, our department in the Sealy Center for Aging

has 78 terabytes of storage space on the GPFS, and it can be expanded to 2 petabytes if needed. All the data can be accessed through an SAS server. This SAS server is a Red Hat Enterprise Linux server configured with two 8-core 2.9-GHz processors and 160 GB of DDR3 RAM memory. Both the GPFS and the SAS server are housed in a tier-4 data center located on the institution's main campus.

- *How the data will be protected from unauthorized access*

Clinical research staff will have access to the GPFS and SAS server is password protected. The passwords are created by the information technology (IT) team in our institution. The IT team manages the passwords through Active Directory Group Policies. The principal investigator (PI), Dr. Stephen Williams, will not have access to any knowledge of the participants in the study, however, authorized co-investigators, and authorized statistical analysts can access the data via desktop computers provided by our institution. Only investigators and analysts who are approved and working directly on the projects will be provided access. All the co-investigators and statistical analysts who are authorized by the PI to have access to the data will need to sign an internal data use agreement (DUA). The PI will store those signed DUAs in the office and keep a list of all staff members who have access to the data. The password will be updated every three months. If a staff member leaves the project or our institution, he or she will be removed from the server and will no longer have access to the data. All the desktop computers are located in offices that can be locked to prevent unauthorized access. The computers log off and enter a screensaver mode after a period of inactivity to protect the data. Several of our analysts have home computers provided by our institution. They can use these personal computers with the supported institution's VPN to link to their desktop computers to work with the prospectively gathered data saved on the server from home. All data generated using the gathered data will be stored on the GPFS in our institution's server behind the institutional firewall.

- *Information on the storage/protection of the media you receive containing the original files*

The media received containing the original files will be stored in a locked file cabinet in a locked office, Room 6.622 of Rebecca Sealy Building on The University of Texas Medical Branch campus. The office building is secured by police and/or security guards, and off-hours access to the building is available only to staff with a The University of Texas Medical Branch badge who work within the building.

- *Assurances that no attempt will be made to identify individual patients, hospitals, or physicians*

We will educate/train our co-investigators and statistical analysts to not attempt to identify patients, their physicians, or the treating hospital.

- *Assurances that publications and presentations of the data will not allow identification of patients, hospitals or physicians.*

We will make sure that all the results reported in the publications or presentations contain no information that can be used to identify patients, hospitals, or physicians.

## 12.0 References

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4. Chamie K, Williams SB, Hu JC. Population-Based Assessment of Determining Treatments for Prostate Cancer. *JAMA oncology*. 2015;1(1):60-67.
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