Comparative Analysis of Transperineal versus Transrectal Approaches for MRI-US Fusion-Targeted Biopsy of the Prostate for the Detection and Characterization of Prostate Cancer

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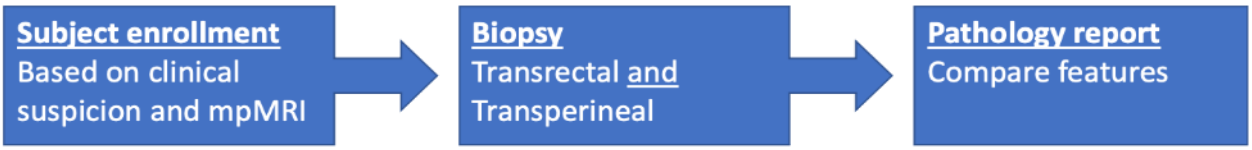
1. SUMMARY OF TRIAL DESIGN

This is a prospective, open-label, single-center trial to compare the efficacy of two different standard care approaches for MRI-ultrasound fusion-targeted prostate biopsy in men with high-suspicion lesions demonstrated on multi-parametric magnetic resonance imaging (mpMRI).

Subjects are enrolled on the basis of elevated clinical suspicion for prostate cancer and area of high suspicion on mpMRI. Subject participation includes one standard care biopsy session during which both transperineal and transrectal biopsies will be obtained using ultrasound/MRI fusion guidance to sample suspicious lesions identified on MRI. A follow-up visit after one week will be in accordance with current post-biopsy management practices, and further clinical management will proceed as per standard of care following the biopsy results.



The purpose of this study is to determine whether image-guided transperineal prostate biopsy can better characterize suspicious lesions in the prostate than transrectal biopsy. Accurate characterization of possible cancer foci is dependent on adequate targeting of suspicious lesions. Thus, the primary endpoint of the trial will be to determine the comparative efficacy of both approaches to accurately sample target lesions, which will be inferred from measuring the core-cancer length (CCL) in each positive core. Larger CCL when targeting the same lesion corresponds to better target sampling and will allow comparison of the relative ability of each biopsy approach to characterize lesions within the prostate.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective:

1. To assess the comparative efficacy of image-guided transperineal versus transrectal biopsy in characterizing prostate cancer.

Secondary Objectives:

1. To demonstrate the feasibility and investigate the cancer detection rate (CDR) of targeted transperineal biopsy, which has been shown to have a lower risk of infectious complications than transrectal prostate biopsy.

Additional Observations:

1. Occurrence of adverse events.
2. Time spent in performing each biopsy technique.
3. Correspondence of MRI suspicion score to presence of clinically significant cancer detected on biopsy

2.2 HYPOTHESIS

We will test the hypothesis that transperineal targeted biopsy will result in larger core-cancer length than transrectal biopsy when targeted to the same cancerous lesion in the prostate.

3. BACKGROUND and OVERVIEW OF THE STUDY

3.1 Background and rationale

Prostate cancer is the most common malignancy and the second most common cause of cancer death in men in the Western hemisphere.[1] When suspicion for prostate cancer is sufficiently raised by a combination of increased prostate-specific antigen (PSA) level and abnormal digital rectal examination, definitive diagnosis is reliant on biopsy of the prostate gland. Today, expert recommendations from the American Urological Association (AUA) propose transrectal ultrasound (TRUS)-guided prostate biopsy involving 10-12 cores for diagnosis in men with adequate suspicion for prostate cancer.[2] This recommendation is based on optimizing the balance between adequate detection of clinically significant disease while minimizing detection of clinically insignificant disease, which has the potential to lead to overtreatment and increased morbidity.

Transrectal access to the prostate is the most common approach for systematic biopsy. However, a concerning limitation of this approach is the rising rate of infectious complications, which is the leading cause of hospitalization after biopsy despite antimicrobial prophylaxis.[3] Additionally, impeded access to the anterior and apical regions of the prostate from the rectum has lead to undersampling of this region and reported false-negative rates as high as 30%.[4] Poor sampling of regions of the prostate which may harbor cancer foci leads to misdiagnosis or mischaracterization of disease.

Transperineal biopsy of the prostate does not perforate the rectal wall, and thereby minimizes the risk of Gram-negative infection and rectal bleeding associated with transrectal biopsy. Because transperineal biopsy requires incision of the skin, the procedure presents a risk of infection and is often performed using local or regional anesthesia. Despite this, a 2012 meta-analysis concluded that transperineal biopsies do not have added risk of complications in comparison to transrectal biopsy, including infection.[5] Additionally, a transperineal approach allows better access to the anterior region of the prostate. For patients with previously negative biopsies who still have an elevated risk of prostate cancer based on rising PSA, there is evidence to suggest that transperineal biopsies may be of clinical value in detecting previously undiagnosed disease.[6] Improved sampling of cancer foci within the prostate can lead to more accurate characterization of disease, which ultimately serves as a major determinant in clinical decision-making. Finally, transperineal prostate biopsy follows the same physical approach as most modalities of focal therapy. Identification of cancers using this approach can thus optimize planning for focal therapy application in eligible patients.

Recently, the emergence of targeted biopsy using multi-parametric magnetic resonance imaging (mpMRI) to identify foci of potentially malignant disease prior to biopsy has raised the potential for selective target sampling. By using a combination of MRI sequences to evaluate the prostate, including T2, diffusion weighted, and dynamic contrast-enhanced images, a 5-point Likert scale is used to grade lesions based on suspicion for prostate cancer. This technique has demonstrated superior diagnostic power for clinically significant prostate cancer, with sensitivity exceeding 80% for detecting 0.2 cm^3 of Gleason 4 + 3 or above and 0.5 cm^3 of ≥ Gleason 3 + 4 in one study.[7] As a result, transrectal biopsy using MRI-targeting has demonstrated improvement in selectively identifying clinically significant cancer and reduced overdetection of low-risk disease.[8]

However, the current practice of transrectal needle placement still carries the same risks of undersampling of the anterior prostate and infection. Because a transperineal approach to the prostate allows improved sampling of the anterior region, it is reasonable to expect that an MRI-targeted biopsy using a transperineal approach may facilitate more accurate characterization of prostate cancer while also inherently limiting the risk of infection associated with transrectal biopsy.

The purpose of this study is thus to examine whether a transperineal approach to prostate biopsy using MRI-targeting can provide improved characterization of prostate cancer compared to a transrectal approach.

3.2 MRI-US Fusion Biopsy (Artemis)

Computerized targeting of MP MRI lesions in our institution is routinely performed using Artemis™ software system. The Artemis-Profuse software requires an initial transrectal ultrasound measurement of the prostate in order to obtain a 3D image of the prostate on ultrasound. The computerized co-registration is then performed by software within the Artemis™ system and will fuse the MR imaging with real-time ultrasound imaging (this will require approximately 10 minutes). Upon completion of co-registration, the Artemis™ system will be used to target suspicious lesions identified by MP MRI and these biopsies and locations will be mapped within the Artemis software. A total of four computerized targeted biopsies per MP MRI lesion will be made using the Artemis™ system.

4. STUDY DESIGN

Subjects are enrolled on the basis of elevated clinical suspicion for prostate cancer and identifiable area of suspicion on routine mpMRI. Subjects will initially be identified from the population of men undergoing outpatient management for suspected or known prostate cancer at NYU Smilow Prostate Cancer Center (SPCC) by members of the patient's treatment team or members of the investigational team. An investigator will screen the patients for eligibility in the study, and all information will be obtained either directly from the patient and/or their medical record. Initial screening will be based on suspicion for prostate cancer demonstrated by mpMRI of the prostate obtained as part of

the standard of care at NYU SPCC. Screening will be followed by evaluation of exclusion criteria for enrollment into the study.

Inclusion Criteria

1. Men 40-85 years of age
2. No contraindication to prostate biopsy (e.g. coagulopathy, medical condition prohibiting abstinence from anti-platelet or anticoagulation therapies, anatomical considerations)
3. Area of suspicion or known cancer focus on previously obtained mpMRI of the prostate (at least one lesion with MRI suspicion score > 2/5)

Exclusion Criteria

1. Prior pelvic radiotherapy
2. Evidence of urinary tract infection or significant urinary retention
3. Prostate instrumentation (e.g. prostate biopsy, transurethral prostate procedure) within 2 months prior to mpMRI
4. No evidence of suspicious lesions on mpMRI
5. Irreversible coagulopathy
6. Contraindication to sedation

4.1 Study participation

Subject participation includes one standard care biopsy session during which both transperineal and transrectal biopsies will be obtained using ultrasound/MRI fusion guidance to sample suspicious lesions identified on MRI. Two biopsy cores per lesion with MRI suspicion score > 2/5 will be obtained using each approach per standard practice. A follow-up visit after one week will be in accordance with current post-biopsy management practices, and further clinical management will proceed as per standard of care following the biopsy results.

Before enrollment, patients will undergo routine 3 Tesla mpMRI with T2 3D, DCE and DWI imaging following the NYULMC standard prostate imaging protocol. Each study will require approximately 45 minutes to acquire imaging. Prospective candidates for the study will undergo this imaging prior to enrollment into the study and biopsy. The results of the mpMRI will be provided according to the standardized NYULMC template. Lesions identified on mpMRI with high suspicion score (3, 4 or 5 out of 5) will be considered for targeting on biopsy. Men without evidence of lesion on mpMRI or with low suspicion lesions are not eligible for the study.

Study participants will then undergo standard of care pre-biopsy procedure including initiation of peri-procedure antibiotics and pre-procedure Fleets enema. Biopsy will be performed in the Smilow Prostate Cancer Center. All biopsies will be performed using general anesthesia per standard of care protocol. Biopsies will then be performed according to the standard procedure detailed below.

4.2 Intervention

Computerized targeting of mpMRI lesions will be performed using Artemis™ software system per standard practice. This software requires an initial transrectal ultrasound measurement of the prostate in order to obtain a 3D image of the prostate on ultrasound. The computerized co-registration will then be performed by software within the Artemis™ system and will fuse the MR imaging with real-time ultrasound imaging (this will require approximately 10 minutes). Upon completion of co-registration, the Artemis™ system will be used to target suspicious lesions identified by mpMRI and these biopsies and locations will be mapped within the Artemis software. A total of two computerized targeted biopsies per mpMRI lesion will be made using the Artemis™ system using each biopsy approach. A maximum of three mpMRI lesions will be targeted. The operator of the Artemis™ system biopsies will not be blinded to the mpMRI results. After completion of the targeted transrectal prostate biopsy, the patient will be repositioned to lithotomy position to expose the perineum. The physician will replace the transrectal ultrasound probe and obtain biopsies through transperineal needle placement into the same targets planned on the Artemis fusion software. Biopsy specimens will be collected in labeled jars for transport to the pathology lab in accordance with biopsies that are already performed as part of a patient's regular treatment at NYU Smilow Cancer Center. No additional cores will be collected for this study than what is normally taken for a standard of care whole biopsy (non-targeted and targeted biopsy). The targeted biopsies will require between 5-10 minutes of time per approach to acquire. After pathology analysis, leftover tissue remaining after analysis will be not be kept for further research analysis and will not be discarded. All biopsies will be archived as required by law.

This is an outpatient procedure. Patents will undergo a voiding trial prior to discharge. If they fail same day voiding trial, a Foley catheter will be placed with a second trial performed approximately one week after treatment per standard care.

The targeted biopsies will require 4 cores per lesion for each patient. A maximum of three mpMRI lesions will be allowed to be targeted. It is very rare (<5% of positive mpMRI) for there to be more than three lesions identified on mpMRI. The 4 cores taken per targeted lesion is the current standard at the Smilow Prostate Cancer Center. Typically, a biopsy will be done through one approach (transrectal or transperineal). For the purposes of this study, both approaches will be used per targeted lesion. However, only two cores will be taken for each approach which will not result in any extra cores taken for research purposes. As both approaches are considered routine, performance of both approaches during a biopsy sitting should not result in an increased likelihood of comorbidity and will not extend a subject's time under anesthesia by any significance.

Risks of performing the two targeted biopsy approaches in one setting are the same risks inherent to traditional systematic standard care prostate biopsy, including bleeding, infection, urinary retention, and voiding dysfunction.

4.3 Endpoints

i. Predictor variables:
   a. Biopsy approach
      i. *Variable type:* Dichotomous (categorical)
      ii. *Potential outcomes:* Transperineal vs Transrectal
   b. Location of target lesion within the prostate is a prominent consideration for targeting accuracy, as lesions in the anterior prostate are known to be difficult to access using a posterior approach (transrectal biopsy).
      i. *Variable type*: Categorical
      ii. *Potential outcomes*: (Left vs right) + (Anterior vs posterior) + (apex vs midgland vs base)

ii. Outcome variables:
   a. Length of core-cancer involvement - A larger amount of cancer within each core as a result of improved lesion targeting provides better disease characterization. Data regarding core cancer length measurements in transperineal targeted biopsy is limited. Previous studies have shown median CCL in MRI-targeted transperineal biopsy to be 2mm (range 1-5mm).[11] However, MRI-guided biopsies were performed under cognitive US-MRI fusion and thus did not benefit from automated image coregistration, which was shown to significantly increase mean CCL.[12] To our knowledge there is no precedent for estimation of CCL in targeted transperineal biopsies using automated US/MRI fusion.
      i. *Variable type*: Continuous
      ii. *Scale*: millimeters
      iii. *Validity*: Greater tumor length per core provides better diagnostic information and has been shown to correlate with Gleason score and pathologic stage at radical prostatectomy.[9]
      iv. *Source*: Histological analysis (pathologist's report)

   b. Number of cancers detected using each approach- The relative cancer detection rates (CDRs) between approaches correlate to the sensitivity of detecting cancer in high risk foci, and should be directly compared between the two modalities as a marker of targeting accuracy.
      i. *Variable type:* Continuous
      ii. *Potential outcomes:* 0-100%
      iii. *Validity:* Since each lesion serves as its own control, a higher percentage of cancer-positive results using a given approach directly corresponds to accuracy of targeting using that technique
      iv. *Source:* Histological analysis (pathologist's report)

   c. Concordance of Gleason score between biopsy and prostatectomy- This measurement correlates to the accuracy of the biopsy technique compared to pathological analysis of the excised prostate gland (gold standard) and is the ultimate metric for **characterization of disease**. However, this is likely to include only a small number of study subjects and therefore may not demonstrate a definitive difference between the two techniques.
      i. *Variable type*: Categorical

ii. *Potential outcomes*: True concordance, upstage at final pathology, downstage at final pathology
iii. *Source:* Histological analysis (pathologist's report)

4.4 Follow-up

The first clinical follow-up visit will be scheduled 1 week after biopsy. At that time the patient's clinical condition will be assessed according to standard of care post-biopsy evaluation. All study participants will be evaluated for additional complications to ensure that the targeted biopsies do not confer additional risk for complications. However, given that the maximum number of biopsies will be within the standard of care range, we do not anticipate an increase in complication rates. Biopsy results will be revealed to the patient at that time.

The primary endpoint of the trial will be assessed upon accrual and biopsy of the planned number of study participants. The primary objective will be assessed by quantifying the core cancer lengths of positive biopsy results (diagnosis of CaP, Gleason 3 or higher, in any given core) for each technique of targeted biopsy. Secondary endpoints will be evaluated via rate of positive biopsy using transperineal versus transrectal targeted techniques for prostate sampling. Furthermore, cancer characteristics including Gleason score and disease volume will be evaluated across techniques. All adverse event data will also be recorded.

Patients diagnosed with CaP will be offered standard of care treatment options as based upon the stage and grade characteristics of the identified disease. Targeted biopsy results that reveal CaP will be considered in the same fashion as CaP diagnosed with standard of care biopsy. All recommendations regarding the appropriate management of any CaP diagnosed will then be based upon biopsy features and patient decision.

4.5 Biostatistics

Sample size justification
Evaluation of cancer-core length will be the primary endpoint, as reported above. The necessary sample size will be powered to observe a significant difference in CCL between techniques. The limited available data regarding CCL obtained from transperineal targeted biopsy may not serve as an accurate estimate within our population due to potential differences in targeting techniques as well as patient demographics and selection criteria for biopsy.

Our data from a recent study of patients receiving both targeted and systematic transrectal biopsies demonstrated that the mean CCL per positive core per patient is 4.7 ± 3.3mm in MRI-targeted transrectal biopsies compared to 2.8 ± 2.4mm in systematic biopsies.[12] The mean difference of 1.9mm was significant ($p = 0.03$) in a cohort of 67 biopsy-naive men out of 125 recruited at our institution over 9 months, and likely reflected improved sampling of cancer foci. Similarly, retrospective analysis of 601 MRI-targeted transrectal biopsies at our institution demonstrates that the mean difference between the largest CCL

and second largest CCL found on targeted biopsy of the same lesion is 2.1 ± 2.4mm. This difference in CCL may also be considered as reflective of a discrepancy in lesion targeting accuracy between two cores. The average of these two estimates of difference in CCL (1.9mm and 2.1mm) is 2.0mm.

For the present study, a conservative estimate of the mean difference in CCL obtained by transperineal vs transrectal targeted biopsy is 1.0mm, or half of the aforementioned difference of 2.0mm. Assuming a tolerance for α error of 5%, 80% power, and a mean difference of 1.0 ± 2.4mm, a sample size of 46 cancer-positive lesions would be needed to demonstrate a difference in targeting ability between the two biopsy techniques.

Positive results will be compared on a per-lesion basis, where the largest CCL of the two cores taken from each approach will be compared. Preliminary data from MRI-targeted biopsy since 2012 at the NYU SPCC has demonstrated approximately 55% and 95% cancer detection rate among patients with MRI suspicion scores of 4 and 5, respectively. Additionally, the average number of cancer-positive lesions among men with prostate cancer detected on targeted biopsy is 1.2. Given the approximate time-course for the study, accrual rate,cancer detection rate in our previous trial, and potential screen failures, we anticipate that recruitment of 80 patients will be feasible and provide sufficient power to demonstrate a difference of 1.0 mm in cancer-core length between the two techniques.This sample size also accounts for potential screen failure for patients consented who have not yet had their standard of care MRI of the prostate.

Statistical analysis for primary objective

Measurements of cancer-core length from transrectal and transperineal biopsies may be compared using a two-tailed, paired samples T test or Wilcoxon Signed Rank Test in order to accept or reject the hypothesis that transperineal biopsy provides higher CCL per positive core than transrectal biopsy.

Statistical analysis for secondary objectives

Cancer detection rate (CDR) and concordance may also be compared between techniques using McNemar's test. Multivariate analysis to determine predictors of improved diagnosis with either technique will be performed using binomial logistic regression.

5. DIAGNOSTIC AGENTS

5.1 Pre-Enrollment Procedures

A. MRI: Multi-parametric MRI of the Prostate
Eligible candidates for this study will have undergone a pre-biopsy mpMRI of the prostate as part of their standard care. Men identified as having highly suspicious regions on this MRI will be offered enrollment into the study to target these areas. All mpMRI procedures will have been performed according to standard of care for

this radiology procedure. All mpMRI of the prostate will be performed using a 3 Tesla magnet following the NYULMC standard prostate imaging protocol. Imaging will be conducted by pelvic phased array coils. No endorectal coil will be utilized. Suspicion of cancer will be graded according to the standard NYULMC Department of Radiology scale.

5.2 Diagnostic Intervention

B. Artemis Biopsy: Artemis, Eigen's 3-D prostate imaging device, is a FDA approved Class II medical device for planning and guiding a transrectal prostate biopsy.

In MRI/TRUS fusion planning, the previously available imaging study (MRI) is used by a trained radiologist to mark out regions of interest for targeting. This information is transferred to Artemis when a fusion plan is initiated. The MRI image and the 3D TRUS image are co-registered, and regions of interest marked on the MRI are mapped on to the 3D TRUS image. The urologist then plans biopsy targets in these regions of interest that are overlaid on the 3D TRUS image.

After planning, traditional needle guidance to the planned location as per normal biopsy technique is performed. At all times, the physician uses the live ultrasound image and Artemis guidance to biopsy tissue from the planned location. Transrectal Artemis biopsy is not investigational. This is currently the standard of care biopsy in our practice at NYU. It is FDA approved for this application, has several publications regarding technique from many institutions, and NYU urologic oncologists have performed roughly 1200 such biopsies at NYU since 2009, as part of our standard clinical protocol.

A new attachment will be added to the Artemis device to facilitate transperineal targeted biopsy. Transperineal biopsy itself is not investigational. This is a well-described biopsy technique that is used often in contemporary clinical practice, frequently to improve sampling when patients have a history of negative transrectal biopsies. The attachment to the Artemis device does have 510K regulatory clearance and we do not anticipate additional risks to standard of care transperineal biopsy.

After obtaining 2 cores of the suspicious lesion via transrectal Artemis biopsy, the patient is repositioned to allow for transperineal needle access. The Artemis fusion system allows for visualization of the previously accessed target and 2 additional cores are obtained via transperineal placement of the biopsy needle. For sequential patients, we will switch the order (transperineal before transrectal) for every other patient in order to mitigate any bias from starting with the same approach for each case.

6. STUDY WORK FLOW

6.1 Recruitment

Subjects will initially be identified from the population of men undergoing outpatient management for suspected or known prostate cancer at NYU Smilow Prostate Cancer Center. Potential participants will be those under the care of the investigators. A member of the research teamwill screen the patients for eligibility for the study through chart review, and all information will be obtained either directly from the patient and/or their medical record. Screening criteria include PSA history, digital rectal exam, and mpMRI to determine initial eligibility, which will be followed by evaluation of exclusion criteria for enrollment into the study. Any information collected for this study in a patient who is determined to be ineligible will be destroyed.

A member of the research team will inform patients of their eligibility for the trial and potential risks and benefits. Decision as to whether or not to take part in this study is completely voluntary and formal consent will be obtained prior to pre-treatment evaluation.

6.2 Study Timeline

i. Visit 1 (week 0)
    a. Baseline visit to determine patient eligibility based on careful review of patient medical history and risk for prostate cancer. If available, patient mpMRI will be reviewed as well. This visit will occur as part of their standard clinical care with the investigator for suspected or known prostate cancer. The research team will review the consent form with the potential subject and answer all questions. Once eligibility is confirmed and the patient agrees to participate in the study, informed consent is signed, and the patient will be scheduled for prostate biopsy at their next visit (2-4 weeks).
    b. If no mpMRI is available, the patient will be scheduled for this imaging study as per our institution's standard of care before finally determining eligibility. This will be done regardless of participation in the study.

ii. Visit 2 (week 2-4)
    a. Approximately 2-4 weeks after the initial visit, each subject will return for prostate biopsy. All biopsies will be done in one operative session and will be performed as outpatient procedures.

iii. Visit 3 (week 4-5)
    a. All study participants will have a follow up visit approximately one week following biopsy for clinical evaluation of recovery from biopsy and to review biopsy results. At this point, all patients will be managed according to standard of care based upon biopsy results.

6.3 Evaluation During and After Intervention

Subjects will be monitored by a qualified anesthesiologist during and after the procedure. Following the biopsy, patients will be relocated to the recovery bay adjacent to the procedure room for observation. All patients will be evaluated clinically one week after

biopsy to assess for biopsy complications including risk of infection, persistent hematuria or rectal bleeding. Any identified complications will be recorded and treated according to severity.

7. TOXICITY / SIDE EFFECTS (Adverse Event Reporting)

7.0 Definitions:

7.0.1 Adverse Event: Any unfavorable and unintended sign, symptom or disease temporally associated with the use of a medical treatment, regardless of whether it is related to the medical treatment.

7.0.2 A serious adverse event (SAE) is defined as any adverse event that results in death, a life-threatening experience, inpatient hospitalization, prolongation of existing hospitalization, persistent disability, or congenital anomaly or birth defect.

7.0.3 Study therapy is the required treatment or procedure defined on the protocol.

7.0.4 Non-protocol therapy is defined as any treatment or procedure not described in the protocol

7.1 Adverse event assessment:

7.11 The type of event using NCI Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 will be identified and graded for severity.

7.12 The relationship of the adverse event to the therapy or procedure will be determined as follows: Unrelated; Unlikely; Possible; Probable; Definite

7.13 For reporting purposes, an adverse event is considered unexpected when either the type of event or severity of the event is not listed in the study consent

7.2 Serious Adverse Events (SAEs):

7.11.A All study-related, unexpected Grade 3 or 4 SAEs will be immediately reported to the IRB. These toxicities will be reviewed by the principal investigator and appropriate measures taken in terms of delaying, modifying or stopping therapy.

7.11.B The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized for adverse event reporting *(http://ctep.cancer.gov/reporting/ctc.html)*.

7.11.C SAEs must be followed until resolution or deemed irreversible.

7.2 Routine reporting:

7.21.A Institutional Review Board rules.

A reportable events log will kept over the course of the study for all adverse events as well as all protocol deviations and exceptions. This log will be submitted to the IRB for review during each annual continuation submission.

7.3 Potential Adverse Events

This is a minimal risk study where loss of confidentiality is a potential risk. The PI will adhere to a data monitoring plan to ensure there is no breach in confidentiality.

-There is also risk associated with prostate biopsy (transrectal or transperineal). This includes bleeding, infection, urinary retention, and erectile dysfunction. Because it is not standard to have both approaches done in one sitting for a biopsy, the PI will also monitor the study for an unexpected increase in risk for these potential adverse events.

7.5 Potential Benefits of Study

- This study provides an additional opportunity to sample areas of suspicion for prostate cancer, and may help better characterize disease to provide more information to guide subjects' treatment. It is hoped the knowledge gained will be of benefit to others in the future

7.6 Informed Consent Process

Study subjects will meet with a member of the research team, who will obtain informed consent in person by paper, during an office visit. The consent form will be signed and dated by the participant. In the event the participant is illiterate, an impartial witness will also sign and date the consent form to indicate that the consent form was presented orally to the participant. The member of the research team obtaining consent will also sign and date the form. Afterwards, a copy of the consent form will be provided to the participant for their personal records. A log will be kept documenting informed consent and each participant will be added to the log after signing the consent form. The original signed consent form will be added to the participant's study file.

7.7 Privacy and Confidentiality

Study/subject documents will be de-identified and labeled according to trial entry number. Only the PIs and Study coordinator will have access to this data. Data will be kept in a secure, password-protected database kept on the PI's computer in the Urology office. No identifying information will be kept in this database.

7.9 Cost/Reimbursement

Eigen (Grass Valley, CA) will provide the transperineal biopsy attachment to our institution. Participants will be receiving medical care as a part of this research study, which is done as a part of regular care. The patients or the insurance company will be charged or held responsible for the costs of that care. Subjects will not receive compensation for participating in this study.

8. DATA SAFETY MONITORING PLAN

-Dr. Samir Taneja will be responsible for overseeing the data safety monitoring plan

-All consent forms, once signed, will be coded numerically. Each consented patient will have that matching number assigned to him as the source of identification for participants. This information will be kept in a limited database with identifiers such as name and medical record and will be used to identify subjects in a separate informational database containing no identifiers and only information relevant for analysis to the study. Each database will be kept on separate computers and can only be accessed by the PI and Study Coordinator. They will be kept in a secure password protected folder on the NYU network for server redundancy as implemented by NYU Medical Center to ensure data protection. Signed consent forms along with the participant's study file will be locked away in a secure room that can accessed only by the Study Coordinator.

-An initial review of adverse events from the prostate biopsy will be done after 5 patients have undergone prostate biopsy (transrectal and transperineal). If after initial review, the risks associated through performing both approaches in one sitting are minimal as expected, review for adverse events will be done quarterly. Any serious adverse events will be reported to the IRB within 48 hours.

-Dr. Samir Taneja will ensure adherence to the data safety plan and confidentiality through observation and making quarterly checks. Any serious breaches in confidentiality will be reported to the IRB within 48 hours.

-There are no formal stopping rules for the study. A summary report will be submitted to the IRB during each annual continuation detailing any adverse event associated with prostate biopsy as well as any failures to adhere to the study design and data monitoring plan.

9. CRITERIA FOR REMOVAL FROM STUDY

The patient may withdraw consent for the study at any time.

If at any time the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (i.e., a change in diagnosis), the patient will be removed from the study.

10. INVESTIGATOR RESOURCES

10.1 Qualifications

Dr. Samir Taneja is the Principal Investigator of the Study. He is the Director of the Division of Urologic Oncology in the Department of Urology at the NYU Langone

Medical Center. He is also the Program Leader of the Genitourinary Oncology Program of the NYU Cancer Institute.

Sub-Investigators of this study will be Drs. James Wysock, William Huang, and Marc Bjurlin.

Dr. James Wysock is an Assistant Professor in the Department of Urology at NYU Langone Medical Center.

Dr. William Huang is a Associate Professor in the Department of Urology. He is also Co-Director of the Robotics Program as well as Chief of Urology Service at Tisch Hospital.

Dr. Marc Bjurlin is a Clinical Assistant Professor in the Department of Urology.

All Investigators will be performing all procedures, including biopsies, on participants currently under their respective care.

Dr. Andrew Rosenkrantz is an Assistant Professor from the NYU Department of Radiology. His responsibilities will include performing and interpreting the imaging portions of the trial.

Richard Huang will be responsible for data entry and management and is familiar with IRB regulations and HIPAA compliance.

10.2 Use of NYU Facilities

Several NYU facilities will be used for this trial. The Smilow Prostate Cancer Center is a treatment facility which contains an OR, RR and will also be used for patient follow-up visitations. NYU Pathology lab will be used for histologic examination. Radiology testing will be done at an FPO here at NYU and laboratory studies will also be done at the NYU lab.

10.3 Conflict of Interest

There are no potential conflicts of interest for this trial.

11.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

12.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION

12.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

Records to be Kept

12.2 Investigator Study Files: The Principal Investigator is responsible for maintaining study files for a period of 2 years after the investigation is discontinued. The following documents should be kept in the study files:

12.2.1 Curricula vitae of all sub investigators and the current Human Subjects Protection certifications

12.2.2 The original protocol and all amendments

12.2.3 Final IRB approval, annual renewals and all IRB correspondence

12.2.4 Blank Case Report Forms

12.2.5 Copy of all IRB approved Informed Consent forms with applicable version date

12.2.6 Copy of all patients' signed informed consent forms

12.2.7 The final completed case report forms for all patients is the responsibility of the investigator. They will be available for review by the investigator of the trial, health care personnel involved in this study, the IRB, DHHS, and the FDA.

13.0 REFERENCES

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