TITLE: A prospective trial comparing office-based MR-guided prostate biopsy approaches: transrectal biopsy compared with a transperineal approach

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Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM.

List of Abbreviations

AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
CTSC	Clinical Translational Science Center
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
DRE	Digital Rectal Examination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HUD	Humanitarian Use Device
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
MR	Magnetic Resonance
PHI	Protected Health Information
PI	Principal Investigator
PSA	Prostate Specific Antigen
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
TP-Bx	Transperineal biopsy
TR-Bx	Transrectal biopsy
UAP	Unanticipated Problem
WCM	Weill Cornell Medicine

Protocol Summary

Full Title:	*A prospective trial comparing office-based MR-guided prostate biopsy approaches: transrectal biopsy compared with a transperineal approach*
Principal Investigator:	*Jim C. Hu*
Sample Size:	*N*= 1,500 men
Study Population:	*Men >18 years of age with suspicion for prostate cancer based upon an elevated PSA or abnormal digital rectal examination. Men who have had prior prostate biopsies and men on active surveillance are eligible for inclusion.*
Study Design:	*The purpose of the study is to compare the safety and efficacy of transperineal biopsy versus transrectal biopsy performed in the outpatient setting.*
Study Duration:	*6 months*
Primary Objective:	*To compare infection rates, uro-sepsis hospitalizations, and patient-reported pain of in-office transperineal versus transrectal biopsy.*
Secondary Objectives:	*To gather outcomes including adverse events such as bleeding and urinary retention. To compare detection of clinically significant and insignificant prostate cancer.*

1. Study Objectives

1.1 Primary Objectives

The primary objective of this study is to compare infection rates, uro-sepsis hospitalizations, and patient-reported pain of in-office transperineal versus transrectal biopsy. We will be using the data from the biopsy pathology report (standard of care)--no additional biopsy specimen will be collected.

1.2 Secondary Objectives

Secondary outcomes include other adverse events such as bleeding and urinary retention, which will be categorized and compared with Common Terminology Criteria for Adverse Events (CTCAE). Additionally, we will compare detection of clinically significant and insignificant prostate cancer.

2. Background

2.1 Study Design

The feasibility of outpatient transperineal biopsy (TP-Bx) has been well demonstrated.(Bianco & Martínez-Salamanca, 2016; Merrick et al., 2016; Smith et al., 2014) New technology now allows for fusion of MRI images with TP devices, allowing for targeting of cancerous-appearing lesions on MRI. Such technology that fuses MRI-imaging with transrectal biopsy (TR-Bx) has become routine in U.S. clinical practice, with improved cancer detection rates as compared with standard TRUS.(Ahmed et al., 2017; Robertson, Emberton, & Moore, 2013) Our randomized trial will compare the safety and efficacy of TP-Bx versus TR-Bx performed in the outpatient setting.

The primary objective of this study is to compare infection rates, uro-sepsis hospitalizations, and patient-reported pain of in-office transperineal versus transrectal biopsy. Secondary outcomes include other adverse events such as bleeding and urinary retention, which will be categorized and compared with Common Terminology Criteria for Adverse Events (CTCAE). Additionally, we will compare detection of clinically significant and insignificant prostate cancer.

ARM 1:

Men will be randomized to receiving either TP or TR targeted biopsy. We will use block randomization by date, assigned by using www.random.org (Odd will be TP, even will be TR). Lesions with PI-RADS >=3 will be targeted with 1 biopsy for every 3 mm in size, and then a standard template will be performed. All men will receive a urine culture within 2 weeks of biopsy and will be started on antibiotic prophylaxis prior to biopsy in accordance with AUA antimicrobial prophylaxis guidelines. (AUA 2016) Men with a positive urine culture will be treated with culture-specific antibiotics and must have a documented negative urine culture prior to biopsy.

ARM 2:

Men will receive a TP targeted biopsy, followed by a TR targeted biopsy on a single procedure date. All men will receive a urine culture within 2 weeks of biopsy and will be started on antibiotic prophylaxis prior to biopsy in accordance with AUA antimicrobial prophylaxis guidelines. (AUA 2016) Men with a positive urine culture will be treated with culture-specific antibiotics and must have a documented negative urine culture prior to biopsy.

Our hypothesis is that TP-Bx is less painful, has lower infection rates, and results in fewer adverse events than TR-Bx, with similar cancer detection rates.

2.2 Rationale and Justification

Interest in transperineal prostate biopsy (TP-Bx), as compared to transrectal biopsy (TR-Bx), has increased in recent years.

TR-Bx, either performed with fusion of MRI-imaging or as a standard template, is the current standard of care for prostate cancer detection in the United States. The infectious risks associated with TR-Bx have increased over the past decade, likely due to increased microbial resistance and widely varying prophylactic regiments (Borghesi et al., 2017)

TP-Bx, performed through the perineum and avoiding the rectal mucosa, minimizes transmission of the rectal flora to the prostate and may result in lower infectious complications than TR-Bx. These infectious complications, which include bacteremia and sepsis, can result in lengthy and costly hospitalizations. (Anastasiadis, van der Meulen, & Emberton, 2015)

Furthermore, given anatomic considerations when performing TR-Bx, the anterior and apical regions of the prostate are often under sampled unless specifically targeted. (Numao et al., 2012; Volkin et al., 2014) TP-Bx offers an additional advantage of easier access to these regions within the prostate and may improve cancer detection in these areas.

2.3 Risk/Benefit Assessment

The risks associated with this study are no greater than the current standard of care TRUS biopsy performed for the diagnosis of prostate cancer. To our knowledge, there are comparable risks of discomfort associated with TR and TP biopsy. Both procedures may miss clinically-significant prostate cancer, though this is a known limitation of prostate sampling.

Patients with elevated PSA, abnormal digital rectal examination and concerning findings on MRI will receive a targeted prostate biopsy, which may improve the detection of clinically significant cancer as compared with standard template TR. TP biopsy may be associated with lower risk of infection though this remains to be demonstrated.

3. Subject Selection

3.1 Study Population

Men diagnosed with prostate cancer who meet the inclusion and exclusion criteria listed below will be eligible for participation in this study.

3.2 Inclusion Criteria

1. Men aged >18 years with suspicion for prostate cancer based upon an elevated PSA or abnormal DRE; or
2. Men who have had prior prostate biopsies; or
3. Men on active surveillance

3.3 Exclusion Criteria

1. Men with active urinary tract infection; or
2. Metastatic prostate cancer; or

3. History of colorectal surgery limiting insertion of transrectal probe; or
4. Evidence of acute or chronic prostatitis; or
5. Concern for perineal cellulitis or fistula

4. Registration Procedures

4.1 Patient Registration

Patients will be centrally registered with the Office of Billing Compliance. To register a patient, submit the following documents via the JIRA Registration Process:

- Legible copy of the HRBAF
- First and last page of signed informed consent form

Registration must be completed within 24 hours of the signing of informed consent.

5. Study Procedures

Men will be randomized to receiving either TPM or TRUS targeted biopsy. Lesions with PI-RADS ≥3 will be targeted with 1 biopsy for every 3 mm in size, and then a standard template will be performed. All men will receive a urine culture within 2 weeks of biopsy and will be started on antibiotic prophylaxis prior to biopsy in accordance with AUA antimicrobial prophylaxis guidelines. (AUA 2016) Men with a positive urine culture will be treated with culture-specific antibiotics and must have a documented negative urine culture prior to biopsy.

5.1 Duration of Therapy and Criteria for Removal from Study

Subjects will be followed through their prostate cancer treatment.

5.2 Duration of Follow Up

Subject follow-up period is approximately 6 months.

6. Statistical Considerations

The study will be designed as an equivalence trial with an alpha of 0.05, power of 80%, SD of 1.6, and equivalence limit of 1 point. This suggests a sample size of 440 per arm, for which we would add 10% for dropout, thus 500 patients per arm.

6.1 Study Design/Endpoints; Sample Size/Accrual Rate

Given the prospective nature, there will be a continuously accruing series to end on 01/10/2020; we hope to accrue 1,500 patients through that time.

6.2 Analysis of Endpoints

We will perform statistical analyses using SPSS and Stata software. Specifically, we will create frequency tables to evaluate the distributions of dichotomous and categorical outcomes with predictor variables. We will compare dichotomous outcomes using chi-square tests or Fisher exact tests. For continuous variables, means, medians, and standard deviations will be computed and compared utilizing t-tests for normally distributed variables and Wilcoxon signed rank sum tests for not normally distributed variables.

7. Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The

investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by patients or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

7.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

7.1.1 Investigational Agent or Device Risks

Focal therapy risks include bleeding, infection, injury to urethra/bowel/bladder, pan, and less commonly, fistula or osteomyelitis.

7.1.2 Adverse Event Characteristics and Related Attributions

We will utilize the CTCAE classification system to categorize AEs.

Attribution of the AE:

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

7.1.3 Recording of Adverse Events

All adverse events will be recorded on a patient specific AE log. The AE log will be maintained by the research staff and kept in the patient's research chart.

7.1.4 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

7.2 Definition of SAE

SAE's include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition. *(Modify as necessary)*

7.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

7.2.2 Reporting of SAE to FDA

If an SAE occurs on this study, the event will be filed on a MedWatch form with the FDA. The investigator must notify the FDA of any SAE's as soon as possible but no later than 7 calendar days after the initial receipt of the information.

Food and Drug Administration
Center for Devices and Radiological Health
MDR Policy Branch
10903 New Hampshire Avenue
WO Bldg. 66, Room 3217
Silver Spring, MD 20993-0002

7.3 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the patient discontinues participation from the study.

8. Data and Safety Monitoring Plan (DSMP)

The attending physician will monitor the subject in real time during the procedure. All men will receive a urine culture within 2 weeks of biopsy and will be started on antibiotic prophylaxis prior to biopsy in accordance with AUA antimicrobial prophylaxis guidelines. (AUA 2016) Men with a positive urine culture will be treated with culture-specific antibiotics and must have a documented negative urine culture prior to biopsy.

The risks associated with this study are no greater than the current standard of care TR biopsy performed for the diagnosis of prostate cancer. Subject safety will be assessed in real-time by physician. Any AEs or SAEs that occur will be reported to the WCM IRB.