R&B Form No. 1A

St. Luke's Medical Center RESEARCH AND BIOTECHNOLOGY

CLINICAL RESEARCH PROPOSAL

Research Title: Post Procedural Infections in Antibiotic Prophylaxis-Free Transperineal Prostate Biopsy : A Double Blinded Randomized Controlled Clinical Trial, A 2 Center Experience in the Philippines

Investigators:		**Name and Signature**		**Unit/Position**
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		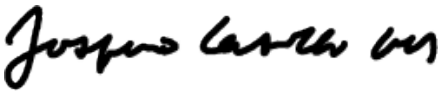 Josefino C. Castillo, MD		Co-Investigator
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		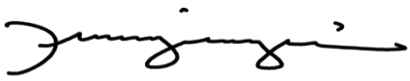 Francis John C. Pile, MD		Co- Investigator
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Inst./Dept./Center/Group:		Institute of Urology		

Brief Description / Summary

Prostate Cancer is one of the leading cancers in men. Its diagnosis is confirmed through a biopsy of the prostate. It is historically done through the transrectal route, however, due to numerous infectious complications such as urinary tract infection and sepsis, the transperineal route has been gaining popularity in recent years. It is said to be a clean alternative to transrectal biopsy since the needle does not pass through the rectum. Traditionally, antibiotic prophylaxis is recommended when performing prostate biopsy through the transrectal route. Currently there is no recommendation whether to give prophylaxis through the transperineal route. This study aims to determine whether prophylaxis may be omitted during transperineal prostate biopsy and ultimately to reduce antimicrobial exposure and decrease burden of antimicrobial resistance. This study is a randomized controlled trial to be conducted at St. Luke's Medical Center Quezon City and Global City on patients undergoing transperineal biopsy of the prostate from the year 2024-2025. The results of this study aims to help create guidelines for international societies regarding the standard protocols of prostate biopsy.

Introduction

Prostate Cancer is the most common cancer among men. It is the 4th most common cancer worldwide. In 2020, 1.41 million people were diagnosed with prostate cancer [1]. Increased incidence is attributed to awareness and availability of resources to diagnose this disease. Prostate Specific Antigen (PSA) is the initial screening tool to diagnose prostate cancer, however, definitive diagnosis is achieved through tissue diagnosis through a biopsy[2]. Historically, the transrectal approach has been the most common way to obtain prostatic tissue samples. Antibiotic prophylaxis is routinely given during the procedure, but despite this, 5-7% of patients develop post infectious complications. Infections requiring hospitalization are seen in 1-3% of patients[3]. Complications of prostate biopsy include bacteriuria, bacteremia, and sepsis[4]. Most infections are caused by bacterial transfer from the rectum to the prostate[5]. In recent years, Transperineal biopsies are being favored over transrectal biopsies for a number of reasons such as improved cancer detection rates, improved sampling of the anterior apex, and an overall reduced risk of false negative results. It is also considered as a sterile alternative to the standard Transrectal biopsy as it involves passing the needle through the perineal skin without having to pass through the rectum to reach the prostate [6,7]. Available literature showed a 2% rate of post infectious complications through this route[6]. A meta-analysis of eight observational studies suggests that the low infection rate after transperineal prostate biopsy is maintained without peri- procedural antibiotics. Presently, there has been no level 1 evidence to support this idea [5].

According to the European Association of Urology guidelines on prostate biopsy, there is a growing evidence that antibiotics may be omitted in transperineal biopsies, however more clinical trials are required before making a final recommendation regarding this matter. This study aims to provide further evidence on surgical prophylaxis for transperineal prostate biopsies, and contribute to the growing concern of antimicrobial resistance[8]. This year alone, there has been no reported post procedure infectious complication following a transperineal biopsy. The question of whether antibiotics are indicated as prophylaxis remains unanswered.

Significance of the Project and Rationale:

The Center of Disease Control and Prevention considers Antimicrobial Resistance as a global threat with millions affected worldwide. This occurs when microorganisms develop the ability to evade antimicrobials and can affect individuals at any stage of life. Antimicrobial-resistant infections requiring second-and third-line treatment alternatives can cause serious side effects such as organ failure, prolonged care and recovery, and even no treatment options for some cases. Surgical antibiotic prophylaxis is a high volume of antimicrobial use worldwide, and is a common area of antibiotic misuse[9]. Therefore, to reduce further emergence of antimicrobial resistance, and to preserve antimicrobial effectiveness in the future, surgical prophylaxis is an aspect of patient care in which antibiotic use should be optimized[9]. Guidelines recommend that Fluoroquinolones are the first line agent used as prophylaxis for transrectal biopsies, however, there has been an increased resistance of normal gut flora to Fluoroquinolones which may be the reason for increased incidence of post transrectal biopsy related infections despite antimicrobial prophylaxis[8]. Local resistance patterns in our institution shows an increasing resistance pattern to Cephalosphorins, which is the standard prophylactic regimen for transperineal prostate biopsies done at our hospital. Our Antimicrobial Stewardshop Program recommends Cefoxitin as the antibiotic of choice for prophylaxis for transrectal prostate biopsies. No recommendations has been set for transperineal prostate biopsies. For urologists, guidelines set by the Americal Urological Association on pre procedural antibiotics for transrectal prostate biopsies, which recommend a fluoroquinolone, or a 3rd generation Cephalosphorin is being followed. This is due to lack of standardized guidelines for transperineal prostate biopsies. Currently, all urologists give antibiotic prophylaxis in the form of a 2nd generation Cephalosphorin. No post procedural antibiotics are being given. The fear of sepsis previously experienced in transrectal biopsies still haunts urologists. Approximately 300 transperineal prostate biopsies are performed at our institution yearly, therefore, if the results of this study is positive, that would greatly reduce number of patients exposed to antibiotics. The effectiveness of Cephalosphorins are also decreasing, based on the hospital's antibiogram with increased emergence of esbl+ E. Coli strains obtained from genitourinary specimen cultures. Urologists deal with diseases of the urinary tract, and at times, these diseases are complicated by infections. Diseases such as in urolithiasis, Benign Prostatic Hyperplasia, Neurogenic bladders, and Catheter Associated Urinary Tract Infections all require the use of antimicrobials, and if the effectiveness of our current antibiotics are decreased due to resistant strains, then it becomes a health care burden for all. Results of this study can be useful in clinical practice, not only in Urology, but in other subspecialties as well. Given the limited health resources available in our country, actions of medical professionals should always be supported with high level evidence, such as this study. Addressing these knowledge gaps is crucial for improving antibiotic prophylaxis guidelines, enhancing patient outcomes, and reducing antibiotic resistance. This study would also promote judicious use of antibiotics, which may lessen

the burden of antimicrobial resistance. The conclusions derived from this study, as well as from the other reviews and investigations, can be used to develop and/or revise, if necessary, regulatory action and policymaking best practices. Lastly, given that this study will be conducted in a developing nation like the Philippines, it can serve as a reference for subsequent research on related topics.

Background Information and Brief Literature Review

Transperineal MRI fusion biopsy is an advanced technique for diagnosing and characterizing prostate cancer. This procedure combines pre-biopsy MRI images with real-time ultrasound guidance to precisely locate suspicious areas in the prostate gland.[10-12] Transperineal MRI fusion biopsy improves the accuracy of prostate tissue sampling by identifying lesions that are clinically significant. It is done by combining high-resolution anatomical information from an MRI with live ultrasound visualization.[12-14] Studies have shown that this approach improves cancer detection rates and reduces the chances of missing significant tumors compared to the transrectal ultrasound-guided biopsy.[7,10-16] Also, transperineal approach offers significant benefits in terms of sampling quality, mainly for the anterior zone of the prostate, and lowers the risk of UTI by avoiding inserting the needle through the rectal wall, despite an apparent longer process duration and a steep learning curve for the operator[17].

Antibiotic prophylaxis plays an important role in preventing post biopsy complications such as urinary tract infections and sepsis. According to guidelines, antibiotic prophylaxis is indicated for all patient's undergoing transrectal biopsy. Fluoroquinolones were the first line agent used as prophylaxis, however, its overuse have resulted in an increase of post biopsy infections worldwide. The major risk factors is the presence of fluoroquinolone resistant bacteria in the rectal flora, which is introduced to the prostate through the transrectal route[18].

A systematic review involving 1596 patients by Pradere et al. showed that infectious rates were significantly lower following the transperineal route[19]. Another systematic review done by Berry et al. involving 73,630 patients showed that the trans perineal route was associated with significantly lower rates of sepsis[20].

The first comparative study on administering prophylaxis for transperineal biopsies was published in 2021 by Pirola et al. and they concluded that transperineal biopsies without prophylaxis was safe, and did not have a relevant impact on the incidence of post procedural infections, and that omission of pre operative antibiotics would critically reduce the unnecessary administration of antibiotics worldwide[6].

Jacewisz et al. (2022) conducted a randomized controlled trial of patients who were suspected of having prostate cancer and were due to undergo transperineal prostate biopsies[21]. The patients were randomized into receiving prophylaxis or not. The non-inferiority threshold of 4% was not exceeded indicating that the rate of infections in patients who did not receive antibiotic prophylaxis prior to transperineal prostate biopsy was not higher than in those who did receive it. They concluded that it may be justifiable to exclude antibiotic prophylaxis in this particular population[21].

A meta analysis and systematic review on infection rates after transperineal biopsy with and without prophylactic antibiotics was published in 2022 by Castellini, et al. included 8 studies involving 3,662 patients. A total of 2368 were given prophylaxis and 1294 patients were not. The review found that there were no significant differences in infection rate, fever, sepsis, or readmissions between patients with or without prophylaxis[22].

In 2022, another systematic review was published of which included 106 studies, of which 37, 805 men received prophylaxis and 4772 men had none. Results showed that out of the group which received antibiotics, 19 developed sepsis. In the group without prophylaxis, only 4 developed sepsis. For overall infections, which includes non-septic infections, 403 out of 29,880 and 58 out of 4772 developed events. The results also showed no significant differences in the rates of infectious complications[23].

To date, there is still no definite guideline to whether antibiotic prophylaxis should be given or may be safely omitted for transperineal prostate biopsies despite growing body of evidence. More Randomized Clinical Trials are needed to reach this conclusion.

The following criteria should be met to define UTI: 1. Symptoms of dysuria, urgency, frequency, or hematuria, fever, flank pain, nausea/vomiting; AND 2. Pyuria and/or bacteriuria[26]. The following criteria should be met to define sepsis: 1.Temperature >38°C or <36°C Heart rate >90/min Respiratory rate >20/min, PaCO2 <32 mm Hg (4.3 kPa), White blood cell count >12 000/mm3 or <4000/mm3 or >10% immature bands, or evidence of organ failure; AND 2. urinary pathogen growth in urine or blood cultures[27]. The EAU classifies UTI as Localised or Systemic. Localised UTI is defined as signs and symptoms of frequency, urgency, Incontinence, urethral purulence, and suprapubic pain, which applies to both sexes, and with no signs of systemic infection. Systemic UTI is defined as signs and symptoms of systemic infection such as fever or hypothermia, chills, Delirium, Hypotension, Tachycardia, and Costovertebral angle pain and tenderness. Pyelonephritis and prostatitis are included in this classification.

The prevalence of Prostatitis is 8.2%. Prostatitis is classified into four clinical entities including acute bacterial prostatitis, chronic bacterial prostatitis, chronic pelvic pain syndrome and asymptomatic prostatitis. Diagnostic evaluation includes history and physical examination, urinalysis, urine gram stain and culture, pre- and post-prostatic massage, and Prostate specific Antigen. Complete Blood Count, Blood culture is not routinely done, but may be necessary in a patient who appears ill[28].

Acute Bacterial prostatitis is defined as bacterial infection of the prostate which may lead to overwhelming sepsis or development of prostatic abscess. An organism must be isolated on culture. Most commonly isolated organism is E. Coli. Diagnosis is based on symptoms alone which include irritative and/or obstructive symtpoms. Pain and systemic symptoms may be present as well. On physical examination, prostate appears boggy, tender, and enlarged. Diagnosis is made through a urinalysis and urine culture. Presence of more than 10 WBCs per hpf suggests a positive diagnosis. It is usually treated with antibiotcis[28].

Chronic Bacterial Prostatitis is a bacterial infection of the prostate lasting more than 3 months. Urine cultures are persistently positive for the same organism. E. coli is still the most common organism isolated. Patients present with recurrent or relapsing urinary tract infections, urethritis, or epididymitis with the same bacterial strain. Diagnosis is made through history or physical examination, Voiding test such as pre and post prostatic massage and a positive urine culture[28].

Asymptomatic prostatitis is diagnosed when inflammatory cells are identified incidentally on prostate biopsy on an asymptomatic patient. Treatment is catered based on the primary reason for urologic consultation. Further urologic evaluation is indicated if the reason for consult is an increased PSA[28].

Preoperative antibiotic prophylaxis is the administration of antibiotics before surgery to reduce the risk of post operative infection. Although the timing of antibiotic administration varies, the goal of preoperative systemic antibiotic prophylaxis is to maintain the highest tissue concentrations at baseline and during surgery. The literature recommends at least 30 minutes and no more than 60 minutes before skin incision to achieve the optimal time for preoperative administration of the most commonly used antibiotics[29].

Post biopsy infection is the Occurrence of Lower Urinary tract Infection symptoms such as frequency, dysuria, and urgency, or Severe Urinary Tract Infection such as loin pain, rigour and fever[3]. Microbiologic tests include a positive urinalysis, and urine culture. Occurrence of urosepsis, meeting a SOFA score of > 2 in the presence of a urinary tract pathogen, all of which occurring within 2 weeks post biopsy.

Objectives

General Objective

To compare incidence infectious complications in patients given antibiotic prophylaxis versus no prophylaxis among patients at St. Luke's Medical Center Global City and Quezon City from March 2024- January 2024

Specific Objective

1. To compare the incidence of urinary tract infection and sepsis between patients without and with antibiotic prophylaxis undergoing prostate biopsy.

2. To compare Hospital admissions, Emergency room visits, and non-infectious complications between the no prophylaxis versus prophylaxis groups.

Methods

Study design and setting

This will be a randomized controlled trial to be conducted at St. Luke's Medical Center Global City and Quezon City from June 2024 to June 2025**.**

Study population

The study population will include patients indicated to undergo prostate biopsy as part of Prostate Cancer Diagnosis.

Criteria for Subject Selection Inclusion Criteria

1. Age 40-75 years.
2. American Society of Anesthesiologists score of I or II
3. Those undergoing Transperineal Prostate Biopsy
4. Urinalysis Negative Patients
5. Non Tender Prostate on DRE
6. Asymptomatic Patients
7. Charlson Score <5

Exclusion Criteria

1. Acute prostatitis within the last 6 months.
2. History of documented Urinary Tract Infection (UTI), or symptoms of UTI (painful micturition, Frequency, Urgence, suprapubic or flank pain, cloudy and foul-smelling urine) for the past 6 months.
3. Tender and boggy prostate on initial DRE
4. With ongoing antibiotics treatment for the past month
5. History of antibiotic allergy
6. Prior definitive therapy for prostate cancer, such as radiation therapy or partial gland ablation.
7. Those with uncontrolled diabetes mellitus, immunocompromised or immunosuppressed status.
8. Those with other pre-existing urinary tract conditions such as Benign Prostatic Hyperplasia in retention, Urinary retention from neurogenic causes, and those with indwelling stents or urethral catheters
9. Those with Prosthetic Heart Valves
10. Patients with ongoing infection elsewhere
11. Patients with Bleeding Disorders
12. Patients with Asymptomatic Bacteriuria

Description of Study Procedure

Method of subject selection and recruitment

Patients with suspicion of prostate cancer who were advised to undergo biopsy will be recruited. This is done on an outpatient setting wherein the procedure will be explained and will be invited to join the study. Consultants who agreed to participate will inform the patient regarding the study and if patient is interested**,** the number of the patient will be given to the primary investigator with the patient's consent. The patient will be contacted and the study will be explained. Once the patient agrees to join, he will be sent an electronic copy of the consent form via email, and he will be given time to read and research regarding the procedures to be performed. He will be provided with a hard copy of the consent if he wishes. Questions regarding the study, risks, and benefits, will all be explained by the primary investigator. Participating consultants will be advised of the requirements of the study, inclusion and exclusion criteria, and the required laboratory tests to be performed before enrolling a patient and prior to scheduling the biopsy. The only laboratory test required for our research is a negative urinalysis. If patient consents, and signs the consent form, he will be screened for eligibility using the inclusion and exclusion criteria. Clinical and demographic data will be taken from patient records**.** Demographic data will include Age, BMI, Prostate volume, PSA, Number of cores taken, and history of previous biopsy, ASA and Charlson Scores. All clinical and demographic data, and laboratory tests performed will be double checked by the primary investigator to finalize recruitment. Data of each participant will be saved in a password protected excel file. Should they have more inquiries regarding the study, they may

contact the primary investigator whose number will be found at the informed consent form, and will be given to them personally. Other consultants will be invited personally and the study will be presented during the weekly conference to recruit more patients.

Informed Consent

All participants will be asked to sign an informed consent prior to joining the study. The primary investigator will explain the objectives of the study, nature of participation, voluntariness or right to refuse without consequence to their treatment, and right to withdraw. The participants will be

given the opportunity to ask questions about the study and the contact number of the primary investigator will be included in the consent forms.

Method of subject assignment to study groups

The primary investigator will be the one to approach the potential participants for their informed consent. Among those who consented, They will be screened for eligibility, then randomized using a pre generated sequential list using an online application https://www.random.org/ either to group A (no antibiotic prophylaxis) and to group B (with antibiotic prophylaxis using 1g IV Cefoxitin).

Description of procedure/s for all study groups

Group A – Experimental Group

In the experimental group, patients will be given normal saline solution in a syringe, which is identical to syringes used to give antibiotics 1 hour prior to the procedure. Both solutions will be clear, which means neither patient or doctor will be aware of what was given as to avoid bias. Only the staff of the stone center will be aware of this. They will be instructed by the researcher or the consultant or research assistant to perform this one hour prior to the procedure just like giving prophylactic antibiotics.

Group B With Antibiotic Prophylaxis using Cefoxitin 2g IV

Patients will be given 2g IV of Cefoxitin 1 hour prior to the procedure.

After being given NSS or Cefoxitin, both groups will undergo transperineal prostate biopsy. Standard skin preparation will be done for both groups. Excessive hair is shaved off the perineum. The perineum is prepared using Betadine (10% povidone-iodine). The perineum is then prepped with betadine solution starting from the center of the perineum with 1 passage from inside to outside for 5 times Biopsy will then be performed. Biopsy procedure to be done is the standardized technique recommended by the American urologic Association, which involves a targeted (lesion centered) biopsy, followed by a systematic biopsy to get a representation of all parts of the prostate gland. After the procedure, the post biopsy site will be cleaned thoroughly using cutasept solution**.** The patient will then be awaken once the procedure is done, and will be sent to the recovery room for observation. Patients should void prior being discharged home. A temporary urinary catheter is placed if patients develop acute urinary retention. Patients will then be taught on the symptoms of UTI or sepsis and advised to seek medical attention if these occur.

Randomization and Blinding procedures

Once the patient has given his signed consent, and patient is eligible to join the study, he will then be randomized into the experimental or control group using the online app https://www.random.org. The app generates a sequential list which prevents the investigator from learning allocation before a patient is registered into the study and from altering allocation afterwards, thus full concealment. Randomization will be performed by a research assistant not involved in the administration of treatments or data collection. The sequential list will be saved in a password protected file only accessible to the research assistant.. After a patient has been allocated, the group assignment will be permanent and unmodifiable. The randomization codes will be kept by the research assistant as well. Antibiotic or placebo will be administered by the stone center staff before the patient is put to sleep. The primary investigator will not be part of the biopsy procedure for blinding purposes.

Risks

One of the common side effects of prostate biopsy is infection. According to studies, 2% patients may experience mild disease not requiring hospitalization, and 1% may experience severe infections requiring hospitalization despite antibiotics. Based on literature, there will be no added risk of infection whether a patient is given antibiotics or not.

The most common side effect of antibiotic administration (Cefoxitin) is Diarrhea. Other rare side effects seen in less than 1% of patients given this drug includes Anemia, or decrease in hemoglobin, Increase in eosinophils in the blood, elevated liver enzymes, Decrease in platelets, and decrease in white blood cells. Patients who have allergies to antibiotics may also experience hypersensitivity reactions to this drug. There is also risk of alteration of the normal bacterial flora, which promotes antimicrobial resistance. This will decrease susceptibility of bacteria to antimicrobials making infections harder to treat.

Benefits

You will not receive direct benefits by participating in this study, however you may be spared from potential side effects of antibiotics. Furthermore, future prostate biopsy patients will benefit from enhanced guidelines on the need for prophylactic antibiotics to balance the risk of infection versus occurrence for antibiotic resistance.

Criteria for withdrawing subjects from the study and stopping the study as a whole

Patients experiencing an adverse event such as symptoms of urinary tract infection like hematuria, dysuria, frequency, and urgency and systemic symptoms such as fever, generalized weakness, malaise will be evaluated right away initially with a complete blood count, urinalysis, and urine culture. Patients who will satisfy the criteria of Urinary Tract Infection, will be considered as having post biopsy infectious complications, and will be evaluated for possible sepsis. According to literature, 2% of patients undergoing prostate biopsy may experience mild post biopsy infection. 1% of patients may develop severe infections or urosepsis requiring hospitalization[22]. Computed sample size for the study is a total of 120 patients, with 60 patients in each arm. Hence, if more than 2 patients develop mild biopsy infection, and more than 1 patient develop severe infections from the experimental group, the study will be terminated and conclusion will be recommendation of administration of antibiotic prophylaxis. Patients who were not able to complete the procedure due to any circumstance, those who cannot tolerate anesthesia, those with adverse effects from anesthesia or antibiotics, and patients not compliant to follow up tests will be withdrawn from the study.

Data to be gathered

Patients who will pass the inclusion criteria will have their demographic data recorded such as age, sex, Height, Weight, BMI, Charlson Scores, Prostate volume, PSA, and History of Previous Biopsies. Post operatively, UTI will be assessed using a symptom checklist, which includes dysuria, urgency, frequency, or hematuria, fever, flank pain, nausea/vomiting. Signs of Systemic Inflammatory Response Syndrome (SIRS) will be gathered in patients who develop signs of urinary tract infection, namely, Temperature, Heart Rate, Respiratory Rate, White Blood Cell Count, and Blood Pressure. Incidence of sepsis and UTI In both groups will be recorded. Patients with Fever, or 2 or more signs of SIRS will be advised admission immediately. Histopathology results, 30 day readmissions, 30 day emergency room visit, and non infectious complications based on the Clavien Dindo classification will also be gathered.

Laboratory/assessment procedures to be performed

A thorough history and physical examination will be performed. Physical Examination will include a Digital Rectal Examination. Preoperatively, a negative urinalysis will be required. Urinary Tract Infections will be assessed through clinical assessment with a thorough history and physical examination, and laboratory assessment through a urinalysis and urine culture done at 7 days. Patients assessed with UTI will have additional clinical evaluation, based on the assessment of the primary investigator along with the attending consultant.

Follow-up procedures

All patients will be followed for 30 days for and assessed for post procedure infection. Initial assessment will be at 7 days post operatively with a history and physical exam. Symptoms of Urinary tract infection will be recorded. Urinalysis and urine culture will also be taken this time. Patients who are asymptomatic will be followed for 30 days, and will be asked to report symptoms of infection. All events within 30 days such as hospital admissions, emergency room visits, and non-infectious complications such as acute urinary retention will be reported. Mild and self limiting lower urinary tract symptoms, and hematuria will not be recorded as urinary tract infection as these are commonly seen after prostate biopsy. Patients who remain asymptomatic after the 30th post operative day will be treated as not having a post procedural infection. Persistent and severe lower urinary tract symptoms with associated fever will be assessed as having developed a post procedural infection, and patients will be treated accordingly. For patients who report symptoms on initial assessment, or within the 30 day time period, patients will be asked to contact primary investigator immediately for assessment, and will be asked to do a baseline Complete Blood Count, Urinalysis, and Urine Culture. Patients with mild to moderate illness (symptoms of fever and lower urinary tract symptoms such as those mentioned above, without urosepsis, circulatory failure and/or organ dysfunction may be treated as outpatient. Patients will be started on Ciprofloxacin 500mg 2x a day for 4 weeks, in line with recommendations of the European Association of Urology on treating Acute Prostatitis. Patients with marked debility and signs of sepsis as mentioned above, patients in whom there is uncertainty in diagnosis, and patients in whom there is concern about adherence to treatment, or patients unable to maintain oral hydration, or take oral medications, are patients in whom hospitalization will be advised. Baseline Complete Blood Count, Creatinine, Urinalysis, Urine Culture and Sensitivity and additional Blood culture and sensitivity will be done. Patients will be admitted in the private room of the hospital, and will be started on Broad Spectrum Antibiotics. Other additional medical management may vary depending on signs, symptoms and culture results. Hospital stay may vary as well, depending on signs and symptoms.

Patients with adverse effects will be followed until resolution or stabilization. A cut-off of 30 days was chosen because the vast majority of post-biopsy infections will occur within this time period. A standard data collection form will be used and information will be recorded in a password protected Excel spreadsheet. Any time post biopsy, patients may call the primary investigator to have them properly assessed and advised, in coordination with consultants on board the study, and possible a referral to infectious disease service for treatment planning. Treatment costs will be shouldered by the study as part of indemnification. A budget proposal will be submitted to cover for treatment costs. For patients with mild symptoms which may be treated as outpatient, a budget of 10,000 pesos per patient will be given.

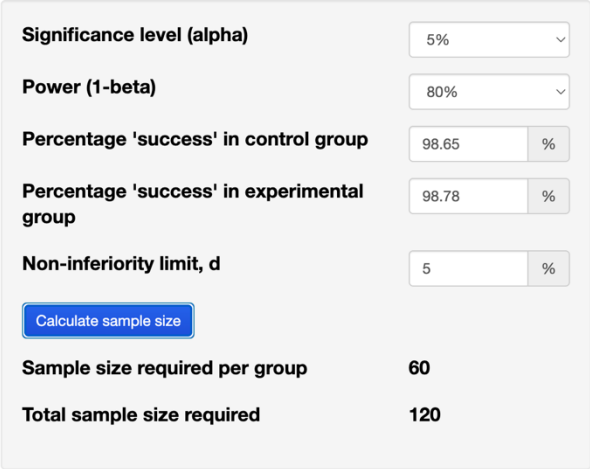
Description of Outcome Measures

Primary outcome is the incidence of Urinary tract infection and Sepsis. Urinary tract infection is based on the European Association of Urology guidelines on infection. Localized UTI is defined as having symptoms of Dysuria, Urgency, Frequency, Incontinence, and Pressure or cramping in the lower abdomen. Systemic UTI is defined by the presence of localized symptoms plus one of the following: Fever or hypothermia, Rigors, shaking or chills, Delirium, Hypotension, Tachycardia, and Costovertebral angle pain and tenderness. Mild, and Self-limiting lower urinary tract symptoms such as hematuria and dysuria which spontaneously resolves will not be assessed as urinary tract infection, as these are commonly seen after prostate biopsy and rarely require treatment.

Secondary outcome includes the following: 30 day hospital admissions, 30 day emergency room visits, and non-infectious complications such as acute urinary retention will be recorded.

Sample Size and Sampling Technique

A minimum sample of 60 patients per group is needed for a non-inferiority study with binary outcomes. Basourakos, et al reported that rates of post-biopsy genitourinary infections were 1.35% in the AP group and 1.22% in the NAP group[24]. The target set was at least 80% power and 90% confidence interval. This was computed using Sealed Envelope Ltd. 2012. Power calculator for binary outcome non-inferiority trial. There are paucity of data regarding post prostate biopsy infections in patients without antibiotic prophylaxis. Similarly, data on post biopsy infections in Filipinos are lacking. A study reported by Yaddao, et al., published in the Philippine Journal of Urology, reported an infection rate of 5% occurring after biopsy, hence, we chose 5% as our non-inferiority limit.



Data Analysis

To assess the primary and secondary outcomes, we analyzed the 90% confidence interval (CI) of the difference in proportions, following Altman's recommendation. Non-inferiority was established if the upper bound of the 90% CI was less than 5%. Descriptive statistics, including median, percentages, 90% CI, or interquartile range (IQR), were reported as appropriate. For comparisons between groups, an independent t-test was used for continuous variables, while the chi-square or Fisher's exact test was applied for categorical variables. All statistical calculations were performed using MedCalc Statistical Software version 23.2.6

Ethical Considerations

The study will be subjected for approval from the Ethics Review Board before the start of recruitment. The study will be monitored and audited by the Ethics Review Board of the Hospital. They will have access to all documents and data. The study shall abide by the Principles of the Declaration of Helsinki (2013) and will be conducted along the Guidelines of the International Conference on Harmonization-Good Clinical Practice (ICH-GCP), E6 (R2) and other ICH-GCP 6 (as amended); National Ethical Guidelines For Health and Health-Related Research (NEG HHRR), 2017. The Clinical Protocol and all relevant documents shall be reviewed and approved by the SLMC Institutional Ethics Review Committee. Patient confidentiality shall be respected by ensuring anonymity of patient records. Each patient document is CODED and will not contain any identifying information in order to ensure confidentiality. All study data shall be recorded and investigators are responsible for the integrity of the data i.e accuracy, completeness, legibility, originality, timeliness and consistency. The manner of disseminating and communicating the study results shall guarantee the protection of the confidentiality of patient's data. All study-related documents such as all versions of the protocol, ethical clearance, data collection forms, hard copies of source documents, signed informed consent forms shall be kept and stored by the Principal Investigator in strict confidentiality for at 1 year; after which they will be shredded.

Maintaining the confidentiality of the patients joining the study is primarily considered and it will be maintained by using alphanumeric codes. Confidentiality of the Patients will be maintained all throughout the study in accordance with the Republic Act 10173 of Data Privacy Act of 2012 and only the summary results and findings will be included in this paper without revealing patient identity. Information that will be gathered for this study regarding the general data and health status of the patients will not be disclosed and published.

The data collection forms will be placed inside opaque and unmarked white envelopes. These forms will be placed inside the locked cabinet within the Institute of Urology when not in use. The data will be encoded into a Microsoft Excel spreadsheet and all the files will be password protected and will be stored in a secured hard drive bought especially for data storage. The hard drive will have its own password so as not to be accessed by other people. Only the principal investigator will have access to the said password protected files, key for cabinet lock, and hard drive. All files will be deleted and destroyed after 1 year following the conclusion of the study.

There is no foreseen added risk in either patient groups since previous studies have shown no significant difference in the occurrence of infection or sepsis among those given and not given prophylactic antibiotics for transperineal MRI fusion biopsy of the prostate. Also the procedure itself is safe and is part of the standard diagnostics for patient indicated for prostate biopsy. There is no additional benefit for the patients who will participate in the study. However, future prostate biopsy patients will benefit from enhanced guidelines on the need for prophylactic antibiotics to balance the risk of infection versus occurrence for antibiotic resistance. The participants will not receive any form of compensation.

Adverse events will be closely monitored and coordinated through records review of patient charts and follow-up check-up within 24 hours and 48 hours post intervention through tele consult. Patients will be asked to follow up within 14 days. Patients will also be advised to contact anyone

from the study team for any symptoms and will be advised accordingly. Patients who undergo transperineal MRI fusion biopsy very seldom experience minor, self-limiting side effects from the procedure. These can include perineal pain or discomfort, bleeding, bruising, haematuria (14.5%) and haematospermia (37.5%)[16] Patients may also expect to experience infectious complications from the biopsy such as urinary tract infection. The most dreaded adverse event from prostate biopsy is sepsis.

GANTT chart

Tasks	2024												2025	
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb
Drafting of proposal														
Submission of proposal for checking of research advisers/consultant s	■													
Submission of proposal for ethical clearance		■	■	■										
Data collection					■	■	■	■	■	■	■	■	■	
Drafting of results, discussion, and conclusion												■	■	■
Finalization of research paper for submission														■

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Appendix

INFORMED CONSENT

Informed Consent Form for Songco, Joseph Vincent M., Castillo, Josefino C., Serrano, Dennis P., Pile, Francis John C., Sunga, Paul Anthony L., Alaban, Cesar Alfred C.
St. Luke's Medical Center

Post Procedural Infections in Antibiotic Prophylaxis-Free Transperineal Prostate Biopsy : A Double Blinded Randomized Controlled Clinical Trial, A Two Center Experience in the Philippines

PART I: INFORMATION SHEET

INTRODUCTION

I am Dr. Joseph Vincent M. Songco, fourth year Urology resident of St. Luke's Medical Center. We are currently doing a study on the role of Antibiotic Prophylaxis in Transperineal Biopsy of the prostate. I am inviting you to be part of this research. This research has been approved by the Ethics Review Board of St. Luke's Medical Center.

PURPOSE OF THE RESEARCH

The Center of Disease Control and Prevention considers Antimicrobial Resistance as a global threat with millions affected worldwide. This occurs when microorganisms develop the ability to evade antimicrobials and can affect individuals at any stage of life. Antimicrobial-resistant infections requiring second-and third-line treatment alternatives can cause serious side effects such as organ failure, prolonged care and recovery, and even no treatment options for some cases.

Prostate Cancer is the most common cancer among men and is the 4th most common cancer worldwide. Definitive diagnosis is achieved through biopsy. The transrectal approach has been the most common way to obtain prostatic tissue samples, but despite routine antibiotic prophylaxis, 5-7% of patients still develop post-infectious complications including bacteriuria, bacteremia, and sepsis.

In recent years, Transperineal biopsies are being favored as a sterile alternative, which involves passing the needle through the perineal skin without having to pass through the rectum to reach the prostate with a reduced incidence of post infectious complications. There is growing evidence that antibiotics may be omitted in transperineal biopsies, however, more clinical trials are required before making a final recommendation.

This year alone, there has been no reported post procedure infectious complication following a transperineal biopsy. The question of whether antibiotic prophylaxis are indicated remains unanswered. This clinical study aims to assess whether antibiotic prophylaxis may be omitted when performing transperineal prostate biopsies and to contribute to the growing concern of

antimicrobial resistance. If antibiotics and antifungals lose their effectiveness, then we lose the ability to treat infections.

Previous studies have shown no significant difference in the occurrence of infection or sepsis among those given and not given prophylactic antibiotics for transperineal MRI fusion biopsy of the prostate. This study will tell us if we have the same findings with foreign literature.

TYPE OF RESEARCH INTERVENTION

This will be a randomized controlled trial to be conducted at St. Luke's Medical Center Global City and Quezon City from February 2024 to January 2025. If you agree to join this study, you will be randomly allocated to one of two groups before you undergo transperineal MRI fusion biopsy, group A with no antibiotic prophylaxis (Plain NSS Group) , and to group B with antibiotic prophylaxis (Cefoxitin 2g Intravenously). Cefoxitin is an antibiotic with a broad spectrum. It is part of the cephalosphorin family of antibiotics and is effective for multiple microorganisms, which makes it an appropriate prophylactic antibiotic. It is given intravenously, meaning it will be administered through an intravenous line via a syringe. Your participation will be for a total of 30 days following biopsy to evaluate for incidence of infection.

PARTICIPANT SELECTION

You are invited to take part in this study because you are a patient who is indicated to undergo prostate biopsy as part of Prostate Cancer diagnosis, is aged ≥40 years and with no active infection.

Your contact information was given to us by your attending physician because you are interested to join the study. This informed consent form will explain everything you need to know regarding the study.

Patients with the following condition will not be included in the study

1. Acute prostatitis within the last 6 months.
2. History of documented Urinary Tract Infection (UTI), or symptoms of UTI (painful urination, Frequency, Urgency, suprapubic or flank pain, cloudy and foul-smelling urine) for the past 6 months.
3. Tender and boggy prostate on initial DRE
4. Any intake of antibiotics for the past month
5. History of antibiotic allergy
6. Prior definitive therapy for prostate cancer, such as radiation therapy or partial gland ablation.
7. Those with uncontrolled diabetes mellitus, immunocompromised or immunosuppressed status
8. Those with other pre-existing urinary tract conditions such as Benign Prostatic Hyperplasia in retention, Urinary retention from neurogenic causes, and those with indwelling stents or urethral catheters
9. Those with Prosthetic Heart Valves
10. Patients with ongoing infection elsewhere

11. Patients with Bleeding Disorders
12. Patients with Asymptomatic Bacteriuria

VOLUNTARY PARTICIPATION

Your participation in this research study is strictly voluntary. You may be asked to cooperate to have any laboratory tests and physical examinations the study team considers necessary. After submitting this consent form, you are still free to withdraw at any time without question. Non-participation or withdrawal from the study will not have any repercussions. Rest assured that treatment will remain the same, regardless of your decision. Your study doctor may also withdraw you from the study at any time should he feel it is in your best interest.

PROCEDURES AND PROTOCOL

Definition of terms

1. **Randomized Clinical Controlled Trial:** A scientific study where participants are randomly assigned to different groups, with one group receiving the treatment being tested and another serving as a control group. The aim is to minimize bias and assess the effectiveness of the treatment.

2. **Antibiotic Prophylaxis Free:** Refers to a situation where no preventive antibiotics are administered. This could relate to medical procedures (such as Transperineal Prostate Biopsy) or situations where antibiotics are typically used to prevent infections.

3. **Antimicrobial-Resistance:** The ability of microorganisms to resist the effects of medications designed to kill or control them, leading to difficulties in treating infections. It is often seen in urine culture results showing resistance to mupltiple antimicrobials

4. **Organ Failure:** The inability of an organ to perform its normal functions, often due to disease or injury. Measured clinically from clinical signs and symptoms. Measured using The SOFA score, which composes of Six distinct scores, one for each of the respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems (central nervous system)make up the final result. Each organ system received a score ranging from 0 to 4, with a minimum SOFA score of 0 and a maximum SOFA score of 24**.**

5. **Transrectal Approach:** A medical approach or procedure conducted through the rectum.

6. **Post-Procedural Complications:** Complications that arise after a procedure. Classified using Clavien Dindo Classification.

7. **Bacteriuria:** The presence of bacteria in the urine seen through a microscope.

8. **Bacteremia:** The presence of bacteria in the bloodstream, often indicating an infection. Confirmed through blood cultures.

9. **Sepsis:** A severe, life-threatening response to an infection that can lead to organ failure. Defined using sirs Criteria. 1.Temperature >38°C or <36°C Heart rate >90/min Respiratory rate >20/min, PaCO2 <32 mm Hg (4.3 kPa), White blood cell count >12 000/mm3 or <4000/mm3 or >10% immature bands, or evidence of organ failure; AND urinary pathogen growth in urine or blood cultures.

10. **Adverse Events:** Undesirable and unintended events or side effects that occur during or after medical treatment.

11. **Urinary Tract Infection:** Symptoms of dysuria, urgency, frequency, or hematuria, fever, flank pain, nausea/vomiting; AND Pyuria and/or bacteriuria.

12. **Urosepsis:** 1.Temperature >38°C or <36°C Heart rate >90/min Respiratory rate >20/min, PaCO2 <32 mm Hg (4.3 kPa), White blood cell count >12 000/mm3 or <4000/mm3 or >10% immature bands, or evidence of organ failure; AND urinary pathogen growth in urine or blood cultures

13. **Prostatitis:** Classified into four clinical entities including acute bacterial prostatitis, chronic bacterial prostatitis, chronic pelvic pain syndrome and asymptomatic prostatitis. Diagnostic evaluation include history and physical examination, urinalysis, urine gram stain and culture, pre- and post-prostatic massage, and Prostate specific Antigen. Complete Blood Count, Blood culture is not routinely done, but may be necessary in a patient who appears ill.

14. **Acute Bacterial Prostatitis:** Defined as bacterial infection of the prostate which may lead to overwhelming sepsis or development of prostatic abscess. An organism must be isolatedd on culture. Most commonly isolated organism is E. Coli. Diagnosis is based on symptoms alone which include irritative and/or obstructive symtpoms. Pain and systemis symptoms may be present as well. On physical examination, prostate appears boggy, tender, and enlarged. Diagnosis is made through a urinalysis and urine culture. Presence of more than 10 WBCs per hpf suggests a positive diagnosis. It is usually treated with antibiotcis.

15. **Chronic Bacterial Prostatitis:** A bacterial infection of the prostate lasting more than 3 months. Urine cultures are persistently positive for the same organism. E. coli is still the most common organism isolated. Patients present with recurrent or relapsing urinary tract infections, urethritis, or epididymitis with the same bacterial strain. Diagnosis is made through history or physical examination, Voiding test such as pre and post prostatic massage and a positive urine culture.

16. Asymptomatic prostatitis: Diagnosed when inflammatory cells are identified incidentally on prostate biopsy on an asymptomatic patient. Treatment is catered based on the primary reason for urologic consultation. Further urologic evaluation is indicated if the reason for consult is an increased PSA.

B. Description of the Process

If you decide to participate in the study, the informed consent form should be signed prior to enrollment. Once the consent form is signed, you will be enrolled in the study, and your participation starts.

You will then be randomized to either group A (Plain NSS group), and to group B (with antibiotic prophylaxis using 2g intravenous Cefoxitin.) using an online application, Your names will be entered, and it will randomly assign you to either group A or B. The investigators will not be aware of your group assignment. The application prevents the investigators from knowing the allocation and from altering the allocation, thus full concealment of assignment. Both you and the investigator will not be aware of the group assignments. The assignment of groups will be randomized and will be done by a research assistant not involved with the administration of medication and the biopsy.

In the experimental group, patients will be given normal saline solution in a syringe 1 hour before the procedure, which is identical to syringes used to give antibiotics. Both solutions will be clear, which means neither patient or doctor will be aware of what was given as to avoid bias. For the control group, antibiotic prophylaxis will be administered within 1 hour before the start of the procedure. Once under anesthesia, you will be positioned, and the perineal skin will be prepped according to the standards set by the hospital ensuring that the biopsy site is sterile. Once prepared, biopsy of the prostate will be done. After the biopsy, post operative site will be cleansed with cutasept antiseptic solution and will be dressed with sterile gauze.

You will then be awoken once the procedure is done, and will be sent to the recovery room for observation. Pain medication will be given as well. You must be able to urinate prior to discharge home, otherwise, a temporary urinary catheter is placed if you develop acute urinary retention. You will then be taught on the symptoms of UTI or sepsis and advised to seek medical attention if these occur.

You will be contacted after 7 days following biopsy to evaluate for incidence of infection. Your urine will be collected for analysis, and urine culture. These samples will be discarded after analysis.

If you develop symptoms mild to moderate illness namely:

Fever, pain while urinating, frequent urination, feeling the need to urinate despite having an empty bladder, bloody urine, and pressure or craping in the groin or lower abdomen.

You should contact the primary investigator and you will be treated accordingly.

If you develop symptoms mentioned above, with the following:
1. Temperature >38°C or <36°C
2. Heart rate >90/min
3. Respiratory rate >20/min
4. White blood cell count >12 000/mm3 or <4000/mm3 or >10% immature bands,

5. evidence of organ failure such as decreased blood pressure, difficulty of breathing, severe abdominal pain, and neurologic symptoms such as confusion

You will need to go to the emergency room, because you will have to be admitted and be admitted in the hospital, and you will be treated accordingly.

A standard data collection form will be used and information will be recorded in a password protected Excel spreadsheet. You will be followed until resolution of symptoms.

If you do not develop any symptoms, then you will be followed after 14 days, and your participation will end.

DATA TO BE GATHERED

The investigators plan to find out the incidence of infection in patients undergoing transperineal prostate biopsy. This will be measured by signs and symptoms felt by that patient such as fever, dysuria (Painful discharge of urine), **(**urgency and hesitancy with findings of pyuria (white blood cells**)**, and/or bacteriuria (microorganisms seen on microscopic analysis of urine) on urinalysis, and growth of microorganisms on urine culture.

DURATION

The research takes place over 30 days following biopsy to evaluate for incidence of infection. A urinalysis and urine culture will be collected on the 7th day post biopsy.

RISKS

One of the common side effects of prostate biopsy is infection. According to studies, 2% patients may experience mild disease not requiring hospitalization, and 1% may experience severe infections requiring hospitalization despite antibiotics.

Urinary Tract Infection (UTI) is a common infection that happens when bacteria, often from the skin or rectum, enter the urethra and infect the urinary tract. The infections can affect several parts of the urinary tract but the most common type is a bladder infection and kidney infection. Sepsis is a serious condition that happens when the body’s immune system has an extreme response to an infection. The body’s reaction causes damage to its own tissues and organs.

Sepsis can affect anyone but people who are older, very young, pregnant or have other health problems are at higher risk. Common signs of sepsis include fever, fast heart rate, rapid breathing, confusion and body pain. It can lead to septic shock, multiple organ failure and death.

The most common side effect of antibiotic administration (Cefoxitin) is Diarrhea. Other rare side effects seen in less than 1% of patients given this drug includes Anemia, or decrease in hemoglobin, Increase in eosinophils (a type of white blood cell) in the blood which may signify inflammation or allergic reaction, elevated liver enzymes which may indicate liver damage,

Decrease in platelets, and decrease in white blood cells. Patients who have allergies to antibiotics may also experience hypersensitivity reactions to this drug.

There is a risk of alteration of the normal bacterial flora, which promotes antimicrobial resistance. This will decrease susceptibility of bacteria to antimicrobials making future infections harder to treat.

OTHER RISKS

There may also be discomfort when taking urine samples as some patients may be asked to drink water if the patient has no urge to urinate during the time of collection. There will be discomfort of putting the urine in the small collection bottle which is done during urination and the collection bottle must be maintained to be clean and must be a sterile bottle to protect the urine sample from bacteria.

BENEFITS

There is no additional benefit for the patients who will participate in the study, however you may be spared from potential side effects of antibiotics. Furthermore, future prostate biopsy patients will benefit from enhanced guidelines on the need for prophylactic antibiotics to balance the risk of infection versus occurrence for antibiotic resistance. Results of this study, if positive, will reduce exposure of many patients to antibiotics, which can help with the burden of antimicrobial resistance.

REIMBURSEMENTS

Urinalysis and urine culture 7 days post biopsy will be covered by the study. Treatment costs of adverse events will be covered by the study. There will be no transportation allowance given.

CONFIDENTIALITY

Maintaining your confidentiality is primarily considered and it will be maintained by using alphanumeric codes. This will be maintained all throughout the study in accordance with the Republic Act 10173 of Data Privacy Act of 2012 and only the summary results and findings will be included in this paper without revealing your identity. Information that will be gathered for this study regarding your general data and health status will not be disclosed and published.

The data collection forms will be placed inside opaque and unmarked white envelopes. These forms will be placed inside the locked cabinet within the Department of Urology when not in use. The data will be encoded into a Microsoft Excel spreadsheet and all the files will be password protected and will be stored in a secured hard drive bought especially for data storage. The hard drive will have its own password so as not to be accessed by other people. Only the principal investigator, Co authors, and the IRB will have access to the said password protected files, key for cabinet lock, and hard drive. All files will be deleted and destroyed after 1 year following the conclusion of the study.

SHARING THE RESULTS

Results of this study will be submitted for publication to international societies to further enhance guidelines.

RIGHT TO REFUSE OR WITHDRAW

You have the right to cancel this consent at any time by giving written notice to Dr. Joseph Vincent M. Songco. If you cancel this consent, then St. Luke's Medical Center and Dr. Joseph Vincent M. Songco will no longer use or disclose your medical information, unless it is necessary to do so to preserve the scientific integrity of the study. However, canceling this consent will not affect previous uses and disclosures and your medical information would not be removed from the study records.

If you fail to give your consent by signing this document, or if you cancel your consent later, then you will be not be eligible to participate in this study and will not receive any treatment provided as part of the study. Unless and until you do cancel the consent, it will remain valid and effective.

PARTICIPATION IN THE STUDY

If you do not wish to take part in the research, you will be provided with the established standard procedure available at the institution.

WHO TO CONTACT

You may contact Dr. Joseph Vincent M. Songco at 09178122923 for any inquiries regarding the research and to report any adverse event. You may also contact Dr. Gelza Zabat, the IERC Chair, to know more of your rights as a participant to this study.

PART II: CERTIFICATE OF CONSENT

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about the study and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant: _____

Signature of Participant: _____

Date:

If Illiterate

A literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumb-print as well.

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____AND **Thumb print of participant: Signature of witness _____**

Date: [MM/DD/YYYY]

STATEMENT BY THE RESEARCHER OR PERSON TAKING CONSENT

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1. Skin preparation
2. Randomization to the antibiotic group, or the placebo group
3. Prostate Biopsy
4. Post operative Monitoring

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this Informed Consent Form has been provided to the participant.

Print Name of Researcher or person taking the consent _____

Signature of Researcher or person taking the consent _____

Date:

Dummy Tables

Table 1. Demographic and clinical characteristics of patients included

	Overall	With prophylaxis (n=, %)	Without prophylaxis (n=, %)	p-value	95% Confidence Interval
Age in years, mean					
BMI					
Prostate volume (cm^3), mean					
PSA (ng/ml), mean					
Number of cores, mean					
History of previous biopsy					
PI-RADS Prostate Imaging: Reporting and Data System **2 3 4 5**					

Table 2. Comparison of incidence of urinary tract infections and sepsis between patients with and without antibiotic prophylaxis

	Overall	With prophylaxis (n=, %)	Without prophylaxis (n=, %)	Risk Ratio (95% CI)	p-value
UTI					
Sepsis					

Figure 1. Study Diagram