Document Coversheet

Study Title:

Does Prophylactic Antibiotic Decrease the Rate of Urinary Tract Infection after Robot Assisted Radical Cystectomy

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PROTOCOL TITLE:

Does Prophylactic Antibiotic Decrease the Rate of Urinary Tract Infection after Robot Assisted Radical Cystectomy?

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1 OBJECTIVES

To investigate, through an evidence-based randomized controlled trial, the effect of prophylactic antibiotic administration (PAA) during the postoperative period on urinary tract infection (UTI) rates after robot-assisted radical cystectomy.

1.1 Primary Objective

- To determine if the utilization of a prophylactic antibiotic during the postoperative period will decrease the rate of UTI post robot-assisted radical cystectomy

1.2 Secondary Objective

- To identify pre- and post-operative factors that may be associated with the development of a 90-day UTI following radical cystectomy.

2 BACKGROUND

Bladder cancer has the sixth highest incidence rate and ninth highest death rate among cancers in the United States. In 2017, it was responsible for an estimated 5% of new cases and 3% of deaths (1).

Radical cystectomy and pelvic lymph node dissection have been the mainstays of treatment options for muscle-invasive bladder cancer patients and refractory non muscle invasive disease (2). Robot-assisted radical cystectomy (RARC) has a high morbidity rate. According to Novara and colleagues, there is a 90-day complication rate of 58%, with 15% being high-grade (3). While RARC provides comparable oncological and functional outcomes to the traditional approach, it is superior in terms of perioperative outcomes including lower risk of blood loss and transfusion (4-9). A review of the International Robotic Cystectomy Consortium (IRCC) identified the most common complications within 90 days of RARC including, by organ system, gastrointestinal (27%), infection (23%), and genitourinary (17%). Under infections, a recurring complication is the development of urinary tract infections (UTI) (3, 10, 11). UTI rates may be explained by the use of the intestinal segment as a urine reservoir in place of the bladder. Reducing UTI numbers may result in a reduction in readmissions, which may lessen the burden on the healthcare system.

Preventing post-operative infections demands serious thought in the field of urologic surgery. Prophylactic antibiotic administration (PAA) has been utilized extensively around the world to manage complications and infections. Previous studies have revealed low surgical site infection rates after a cystectomy with the steady administration of prophylactic antibiotics (12, 13). Additionally, PAA is used to reduce the UTI in children with vesicouretereal reflux (14). For the management of urinary tract infections after RARC, debate remains on what is the most effective strategy. Current standard of care is administration of a single intravenous dose of ertapenem one hour before surgical incision, with no postoperative antibiotics given. Generally, *Escherichia coli, Enterococcus faecalis*, and *Pseudomonas aeruginosa* are the most commonly encountered bacteria that need to be managed (15). Therefore, a prophylactic antibiotic course should keep those bacteria in mind. Unpublished data from our database revealed that approximately 50% of patients developed a urinary tract infection (following RARC), with the mean number of UTI per patient at 3.4. *Enterococcus* and *E. coli* were among the most common organisms identified (16). Given the commonness of UTI in the cystectomy cohort, it becomes imperative to understand the best way to manage this complication.

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3 INCLUSION AND EXCLUSION CRITERIA

Adults unable to consent, individuals who are not yet adults (infants, children, and teenagers), pregnant women, and prisoners will not be included in this study. Participants will be screened for eligibility based on their pre-operative visit report.

3.1 Inclusion Criteria

1. Age ≥ 18 years of age.
2. Any patient that electively chooses to have a cystectomy is eligible to participate in the study. Indications for a person who may undergo a cystectomy include having a diagnosis of muscle-invasive bladder cancer (MIBC) or refractory non-muscle invasive bladder cancer (NMIBC).
3. Any patient that will electively choose to have a robot-assisted radical cystectomy and is able to provide consent.
4. Participant or legal representative must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.

Refer to **Appendix** for the Investigator Study Eligibility Verification Form: Inclusion Criteria.

3.2 Exclusion Criteria

1. Patients with a history of myasthenia gravis.
2. Patients with a history of QT prolongation or taking other drugs that prolong QTc should be excluded.
3. Patients with renal dysfunction, creatinine clearance (mL/min) < 30.
4. Pregnant or nursing female participants.
5. Females who receive a fertile sex sparing RARC.
6. Unwilling or unable to follow protocol requirements.
7. Patients who receive a prophylactic antibiotic or antibiotic for any other reason prior to discharge.
8. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug.

Refer to **Appendix** for the Investigator Study Eligibility Verification Form: Exclusion Criteria.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this study.

4 LOCAL AND STUDY-WIDE NUMBER OF SUBJECTS

A maximum of 100 evaluable participants at Roswell Park will be enrolled: 50 patients in the intervention arm and 50 in the standard of care arm.

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5 LOCAL AND STUDY-WIDE RECRUITMENT METHODS

Patients will be recruited from the Urology Clinic at Roswell Park Comprehensive Cancer Center and will only include cystectomy patients. Patients who will be coming in for their pre-operative appointments will be identified through the bi-weekly cystectomy pathway meeting that reviews all current, future and previous patients that have received a cystectomy at Roswell Park.

Patients will be approached at their pre-operative appointment and will be counseled about the study and if interested will be free to participate. Randomization will minimize any selection bias as the groups will be pre-determined by a statistician using a random number generator.

6 MULTI-SITE RESEARCH

Not applicable. This is a single site study.

7 STUDY TIMELINES

Patients will be enrolled in the study following cystectomy up to 120 days of post-operative follow-up. We anticipate the study to take 4.5 years to complete given the current volume of cystectomies at Roswell Park.

8 STUDY ENDPOINTS

8.1 Primary Endpoint

- To determine if utilizing a prophylactic antibiotic course vs. standard of care will lead to a decrease in the number of UTI infections post cystectomy.
    - The primary end-point is the 90-day UTI status, which is treated as dichotomous data and will be summarized by group using frequencies and relative frequencies.

8.2 Secondary Endpoint

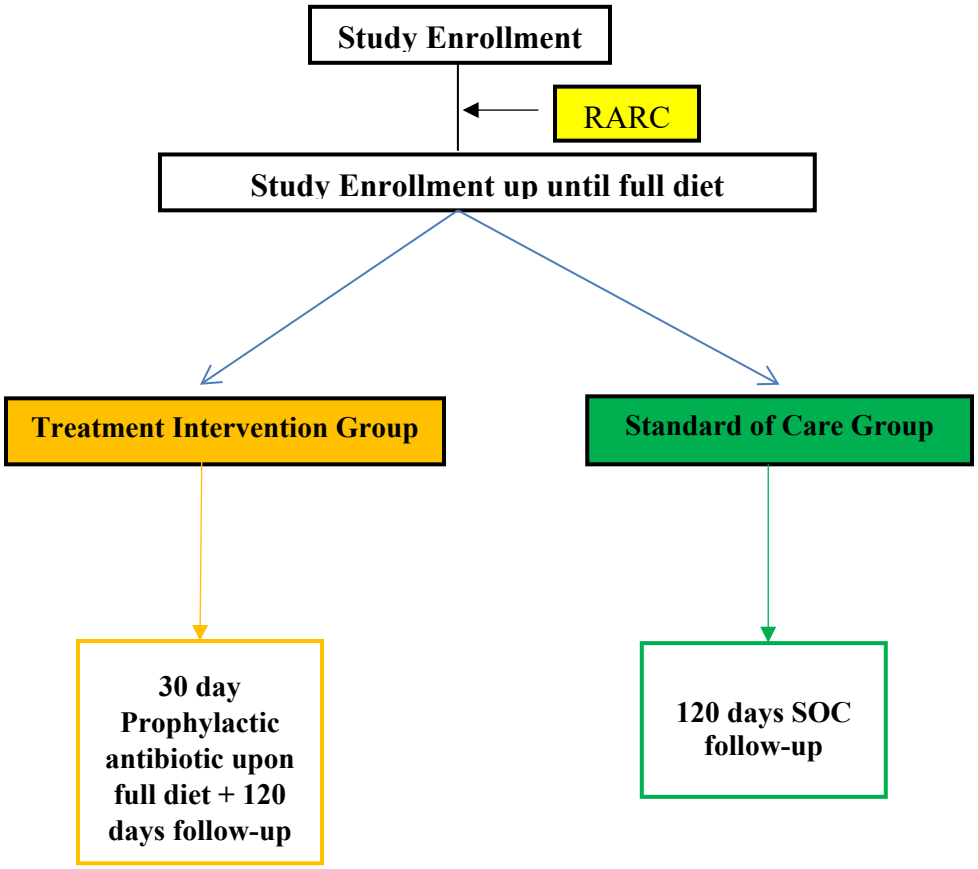
- To identify predictors of UTI from pre-operative and post-operative data.
    - Univariate associations between pre/post-operative factors and UTI status will be evaluated using stratified logistic regression models (stratified by antibiotic use).
- The development of Clostridium difficile (C Diff) in those who had prophylactic antibiotics.
- To identify which antibiotic is better suited as a prophylactic.

9 DESIGN

This is a single center, randomized clinical trial comparing the effectiveness of a prophylactic antibiotic course on the rates of urinary tract infections post-cystectomy. There will be two arms: a standard of care group that will receive the usual standard of care post-operatively and a treatment intervention group that will receive the standard of care and one of two prophylactic antibiotic courses (Trimethoprim-Sulfamethoxazole or Nitrofurantoin) upon full diet clearance by physician. The study schema is depicted in **Figure 1**.

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Figure 1 Study Schema



The standard of care procedure for all patients undergoing RARC is one dose of prophylactic Ertapenem 1 gm at induction (Levofloxacin 500 mg or Clindamycin 900 mg in allergic patients).

Study participants will be randomized and will follow treatment based on the group they are assigned. Once they have completed their inpatient stay, they will be followed-up for 120 days post-operatively at their regularly scheduled surgical follow-up appointments to monitor the development of a UTI. Patients follow up at 2 weeks, 6 weeks, and 3 months post discharge. A plethora of clinical characteristics, perioperative outcomes, and demographics are collected prospectively for all cystectomy patients in the Urology Department at Roswell Park Comprehensive Cancer Center.

10 TREATMENT

Patients in the intervention group will be prescribed a prophylactic antibiotic once a full diet is initiated by their physician.

At the time of full diet, patients in the intervention group will be prescribed a prophylactic antibiotic daily for one month (30 days).

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Prophylactic Antibiotics

Werntz et al, found that primarily using Trimethoprim-sulfamethoxazole (TMP-SMX) 160 mg/800 mg daily if there is no allergy or contradiction, or nitrofurantoin 100 mg daily if TMP-SMX was unavailable, or ciprofloxacin 250 mg daily reduced UTI's in the first 30 days post radical cystectomy by 60% (12). For the study, only TMP-SMX and nitrofurantoin will be used. Previous research in our laboratory found the commonest overall causative organisms for UTI were Enterococcus Faecalis followed by Escherichia Coli then Klebsiella. Enterococcus was found to be highly resistant to macrolides and fluoroquinolones (16). Therefore, ciprofloxacin, a fluoroquinolone, will be omitted due to resistance concerns.

- The primary prophylactic antibiotic option will be Trimethoprim-sulfamethoxazole (TMP-SMX). The participant will not take TMP-SMX if they are allergic to Sulfa based drugs, or if they have a glucose-6-phosphate-dehydrogenase deficiency
- The second prophylactic antibiotic option is nitrofurantoin monohydrate/macrocrystals

Patient antibiotic compliance will be assessed at follow-up appointments using a drug diary. Patients will be instructed to bring the drug diary with them to each follow up and must complete half the doses (15 days) to be considered evaluable.

11 PROCEDURES INVOLVED

This is a randomized clinical trial looking at the effectiveness of post-operative prophylactic oral antibiotics and the effect on postoperative infectious complications in cystectomy patients.

11.1 Participant Randomization and Registration

Eligibility of each participant will be established prior to randomization.

Informed consent ***MUST*** be completed prior to receiving any study related procedures/ treatments.

Randomization will be done by the biostatistician at time of participant enrollment.

Eligible, consenting patients will be randomized into two groups (intervention or placebo control):

- Patients in the control group will receive the standard of care.
- Patients in the intervention group will receive the usual standard of care along with a one month prescription for an oral antibiotic to be taken once a day upon full diet clearance.

Patients in both arms will be followed-up for 120 days to determine if there will be any differences in the development of a UTI

12 WITHDRAWAL OF SUBJECTS

All patients including those who were non-compliant with their antibiotic regiment, meaning they did not complete the full antibiotic course (missing more than 15 doses), will be followed for the protocol defined safety/toxicity period (of 30 days) during their follow-up visits, if they are in the experimental arm. Once they are beyond this safety window, those who were non-compliant will be replaced. If a patient misses their follow ups, they will be replaced. Patients who took 15-29 of the doses will be partially analyzed. The patients may withdraw from the study at any moment and only their partial data will be analyzed. Patients with partial data may be replaced with patients with full data in order to meet the 50-patient limit.

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13 RISKS TO SUBJECTS

13.1 Trimethoprim-sulfamethoxazole (TMP-SMX Bactrim™)

The most common adverse reactions include nausea, vomiting, anorexia and allergic skin reactions. Fatalities associated with the administration of sulfonamides, although rare, have occurred due to severe reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias. Sulfonamides, including sulfonamide-containing products such as sulfamethoxazole/trimethoprim, should be discontinued at the first appearance of skin rash or any sign of adverse reaction. These are rare.

Any clinical sign of a skin rash or any sign of an adverse reaction, the participant will stop this treatment. TMP-SMX is contraindicated in patients with a history of drug-induced immune thrombocytopenia with use of trimethoprim and/or sulfonamides, in patients with documented megaloblastic anemia due to folate deficiency, patients with marked hepatic damage, and with severe renal insufficiency.

13.2 Nitrofurantoin monohydrate/macrocrystals

The most common adverse reactions include nausea, flatulence, vomiting, anorexia, stomach pain, diarrhea, weakness, headaches and drowsiness. Acute, subacute, or chronic pulmonary reactions have been observed in patients treated with nitrofurantoin monohydrate/macrocrystals. If these reactions occur, nitrofurantoin monohydrate/macrocrystals should be discontinued and appropriate measures taken. Reports have cited pulmonary reactions as a contributing cause of death. Acute pulmonary reactions are commonly manifested by fever, chills, cough, chest pain, dyspnea, pulmonary infiltration with consolidation or pleural effusion on x-ray, and eosinophilia. Neuropathies in the hand and feet which may become severe or irreversible have occurred. Relevant contraindications include anuria, oliguria, or significant impairment of renal function.

14 POTENTIAL BENEFITS TO SUBJECTS

Patient benefits may include lower urinary tract infection rates, thus less readmissions and hospital visits, thus less of a healthcare and economic burden.

15 DATA AND SPECIMEN BANKING

Not applicable.

16 MEASUREMENT OF EFFECT

A plethora of clinical characteristics, perioperative outcomes, and demographics are collected prospectively for all cystectomy patients in the Urology department at Roswell Park Comprehensive Cancer Center. UTI assessment will be based on symptoms observed at each clinical visit up to 120 days. All cystectomy patients at Roswell Park Comprehensive Cancer Center follow up at 2 weeks, 6 weeks, and 3 months post discharge. Symptoms include dysuria (a burning sensation while urinating), urinary frequency and urgency, pain and inflammation around the stoma, suprapubic/perineal pain, hematuria (blood in urine), fever, chills, marked fatigue and more. As per the AUA guidelines, UTI is defined as a positive urine culture plus the symptoms (17). Specifically, we will define UTI as the presence of positive urine culture ($\geq 10^5$ cfu/mL with no more than 2 organisms) and documented urinary symptom. Asymptomatic patients with

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positive urine cultures are not considered as UTI. Multiple markers of UTI including frequency, duration, and occurrence from cystectomy date will be assessed. As per standard protocol, a urine culture is administered upon symptoms. Positive samples will be compared regarding the causing bacteria.

17 SAFETY EVALUATION

17.1 Adverse Events

An adverse event or adverse experience (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite').

An AE is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan in other study-related documents.

17.2 Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be clinically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

17.3 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF.

However, clinically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

17.4 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

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If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7 mEq/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

17.5 Preexisting Medical Conditions (Baseline Conditions)

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

17.6 Grading and Reporting Adverse Events

17.6.1 Grading and Relationship to Drug

The descriptions and grading scales found in the CTEP Version 5.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. CTEP Version 5.0 of the CTCAE is identified and located at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm .

AEs not covered by specific terminology listed should be reported with common medical terminology and documented according to the grading scales provided in the CTCAE Version 5.0.

The relationship of event to study drug will be documented by the Investigator as follows:

Unrelated: The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs administered to the participant.

Unlikely: The event is doubtfully related to investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.

Possible: The event follows a reasonable temporal sequence from the time of drug administration but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs.

Probable: The event follows a reasonable temporal sequence from the time of drug administration and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions or concomitant drugs.

Definite: The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

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17.6.2 Reporting Adverse Events

Routine AEs occurring between the start date of intervention until 30 days after the last intervention, or until the event has resolved, the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible, will be reported. New information will be reported after it is received.

Guidelines for Routine Adverse Event Reporting for Phase 1 Studies (Regardless of Expectedness)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated	X	X	X	X
Unlikely	X	X	X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

Guidelines for Routine Adverse Event Reporting for Pilot, Phase 2, and Phase 3 Studies (Regardless of Expectedness)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated			X	X
Unlikely			X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

17.7 Serious Adverse Events

A serious adverse event (SAE) is any adverse event (experience) that in the opinion of either the investigator or sponsor results in **ANY** of the following:

- Death.
- A life-threatening adverse event (experience). Any AE that places a participant or participants, in the view of the Investigator or sponsor, at immediate risk of death from the reaction as it occurred. It does NOT include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.
- Important Medical Event (IME) that, based upon medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

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17.7.1 Reporting Serious Adverse Events

All new SAEs occurring from the date the participant signs the study consent until 30 days after the last intervention or a new treatment is started, whichever comes first, will be reported. The Roswell Park SAE Source Form is to be completed with all available information, including a brief narrative describing the SAE and any other relevant information.

SAEs occurring after the 30 day follow-up period that the investigator determines to be possibly, probably or definitely related to the study intervention should be reported.

SAEs identified as an Unanticipated Problem by the Investigator must be reported. Please refer to Section 17.9 for details on reporting Unanticipated Problems.

17.8 Follow-Up for Serious Adverse Events

All related SAEs should be followed to their resolution, until the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible. New information will be reported when it is received.

17.9 Unanticipated Problems

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:
    - The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of participant privacy or confidentiality of data.
    - The characteristics of the participant population being studied.
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized and if in relation to an AE is also deemed Serious per Section 17.7.

17.9.1 Reporting Unanticipated Problems

The Reportable New Information (RNI) Form will be submitted to the CRS Quality Assurance (QA) Office within 1 business day of becoming aware of the Unanticipated Problem. After review, CRS QA Office will submit the RNI to the IRB.

When becoming aware of new information about an Unanticipated Problem, submit the updated information to CRS QA Office with an updated Reportable New Information Form. The site Investigator or designated research personnel will report all unanticipated problems to the IRB in accordance with their local institutional guidelines.

18 DATA MANAGEMENT AND CONFIDENTIALITY

Data will be stored on a secured, password protected Roswell Park server in the Urology department that is maintained by the information technology department. Access will be limited to the PI and study team. Participants will be free to determine whether to respond to requests for

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participation. All participants, even after providing consent, are free not to answer any questions, or may choose to end their participation and thus can privately maintain control over the level of information provided to us.

Study-related patient data will be collected digitally, on an excel file which is stored in a safe encrypted drive. Information to be collected includes patient name, date of birth, medical record number, the treatment received, information about the patient's health, including past medical history, treatment, diagnosis, test results and clinical symptoms of UTI. All paper files, consents, will be stored in locked data cabinets in our secure laboratory in the Grace Cancer Drug Center. Individual privacy will be maintained in all published and written data resulting from the study. After all data is collected, it will be de-identified. This de-identified data will be kept indefinitely, in paper and electronic form and on computers accessible to the investigators and their research assistants. Any paper or electronic files containing identifiers will not be taken off Roswell Park premises.

19 STATISTICAL PLAN

19.1 Demographics

Patient demographic and clinical characteristics will be reported by group (antibiotic versus control) using the appropriate descriptive statistics. Comparisons will be made using two-sided Mann-Whitney U and Fisher's exact tests for continuous and categorical variables, respectively.

19.2 Randomization

Subjects will be randomized in a 1:1 fashion to the antibiotic and control groups using a permutation block design (block sizes of 4). Randomization will not be stratified by any demographic /clinical factor. The randomization list will be generated by the Roswell Park Department of Biostatistics and Bioinformatics.

19.3 Sample Size Determination

The sample size calculations are based on the primary analysis, which compares the 120-day UTI rate between groups using a one-sided Fisher's exact test. Based on a retrospective review of institutional data, the historic 90-day UTI rate for this patient population is 0.50. With a sample size of n=43 per group, our research can reach 80% power (at a significance level of 0.05) to detect a decrease in the 90-day UTI rate to 0.215 for the antibiotic group (equivalent to an odds ratio of 0.27).

If a patient is non-compliant with their antibiotic regiment, meaning they did not take the antibiotic for more than 15 of the 30 days, they will be followed for the protocol defined safety/toxicity period during their follow-up visits, if they are in the experimental arm. Once they are beyond this safety window, they will be kept on the study to analyze partial data for the remainder of the 120 day follow up period. Considering the possibility of drop-out, we are going to recruit 50 patients in each study arm.

19.4 Primary Analysis

The primary objective is to evaluate the effect of prophylactic antibiotic during the postoperative period on UTI rates post robot-assisted radical cystectomy. The primary end-point is the 90 day UTI status, which is treated as dichotomous data and will be summarized by group using

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frequencies and relative frequencies. The following hypotheses will be evaluated using a one-sided Fisher's exact test:

H_0:$\pi_C < \pi_A$ versus H_A:$\pi_C > \pi_A$,

where π_C and π_A are the 90-day UTI rates for the control and antibiotic groups, respectively. πC, which is estimated by our current data, is 0.5; πA is based on literatures of antibiotic use after cystectomy and is estimated as 0.215. 95% confidence intervals about the 90-day UTI rates will be obtained for each group using Jeffrey's prior method.

19.5 Secondary Analysis

The secondary objective is to identify pre- and post-operative factors that may be associated with the development of a 90-day UTI. Univariate associations between pre/post-operative factors and UTI status will be evaluated using stratified logistic regression models (stratified by antibiotic use). Odds ratios and corresponding 95% confidence intervals will be obtained from model estimates.

19.6 Interim Analysis

No formal interim analyses are planned.

20 PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS

The Roswell Park Data Safety Monitoring Committee will assess the progress of the study, the safety data, and critical efficacy endpoints (Phase I studies will be reviewed quarterly; Phase II, III and pilot investigator-initiated studies will be reviewed semi-annually). The DSMC will review the study and will make recommendations that include but not limited to; (a) continuation of the study, (b) modifications to the design (c) suspension of or, (d) termination of the study.

21 VULNERABLE POPULATIONS

Not applicable.

22 COMMUNITY-BASED PARTICIPATORY RESEARCH

Not applicable.

23 SHARING OF RESULTS WITH SUBJECTS

Clinically relevant individual response data is shared with the participant either in a clinical follow-up or over the phone.

24 SETTING

Recruitment will occur at Roswell Park Comprehensive Cancer Care Center. The actual treatment will occur post-operatively.

25 PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF SUBJECTS

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain

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confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

26 RESOURCES AVAILABLE

Our research team is comprised of surgeons, clinical and research fellows, research assistants and coordinators, medical illustrators, and engineers highly experiences in conducting clinical research. Our diverse team has worked on similar projects and has extensive experience in undergoing clinical trials.

Dr. Khurshid Guru's laboratory, the Advanced Technologies Laboratory for Advanced Surgery (ATLAS) is located at Grace Cancer Drug Center is approximately 1400 sq. feet. A major portion of the lab is dedicated for industrial and human factor engineering researches and sciences. The laboratory is fully equipped to safely carry out and develop the proposed work. The innovative multidisciplinary team utilizes the lab space for equipment storage and data analysis. Space and network access are readily available throughout the study period. The PI, Dr. Khurshid Guru, and the research team members have their dedicated equipped work space with secretarial support.

All participating research members will receive an in-service that adequately explains the research protocol, procedures and individual duties. Dr. Khurshid Guru performs approximately 45-50 RARC's a year. Dr. Qiang Li performs RARC as well. Every RARC cystectomy patient who meets the inclusion/exclusion criteria will be approached for the study. We estimate the study will enroll 100 participants over 4.5 years.

27 PRIOR APPROVALS

Not applicable.

28 COMPENSATION FOR RESEARCH-RELATED INJURY

If the subject believes they have been injured as a direct result of their participation in this research study, they will be advised to notify the Roswell Park Patient Advocate at (716) 845-1365 or the Study Doctor at (716) 845-4107.

Medical diagnosis and treatment for the injury will be offered, and a determination will be made regarding appropriate billing for the diagnosis and treatment of the injury. A financial counselor (716-845-3161) will be able to provide an explanation of coverage and to answer questions the subject may have regarding study related billing.

The subject is not prevented from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

29 ECONOMIC BURDEN TO SUBJECTS

Patients randomized to the treatment arm will have their prescriptions paid for by the Urology Department Chair Fund at Roswell Park Comprehensive Cancer Center.

30 CONSENT PROCESS

This study will not be initiated until the protocol and informed consent document(s) have been reviewed and approved by a properly constituted Institutional Review Board (IRB) or Independent

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Ethics Committee (IEC). Each participant (or legal guardian) shall read, understand, and sign an instrument of informed consent prior to performance of any study-specific procedure. It is the responsibility of the investigator to ensure that the participant is made aware of the investigational nature of the treatment and that informed consent is given.

The Investigator is responsible for the retention of the participant log and participant records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and will not be made publicly available. The investigator is also responsible for obtaining participant authorization to access medical records and other applicable study specific information according to Health Insurance Portability and Accountability Act regulations (where applicable).

This study will be conducted in compliance with all applicable laws and regulations of the state and/or country and institution where the participant is treated. The clinical trial should be conducted in accordance with the ethical principles embodied in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, consistent with good clinical practice and the applicable regulatory requirements and according to the guidelines in this protocol, including attached appendices.

The RPCI SOP: Informed Consent Process for Research (HRP-090) will be followed.

31 PROCESS TO DOCUMENT CONSENT IN WRITING

The Investigator (or IRB specified designee) is responsible for obtaining written consent from each participant or the participant's legally authorized representative in accordance with GCP guidelines using the approved informed consent form, before any study specific procedures (including screening procedures) are performed. The informed consent form acknowledges all information that must be given to the participant according to applicable GCP guidelines, including the purpose and nature of the study, the expected efficacy and possible side effects of the treatment(s), and specifying that refusal to participate will not influence further options for therapy. Any additional information that is applicable to the study must also be included. Additional national or institutionally mandated requirements for informed consent must also be adhered to. The participant should also be made aware that by signing the consent form, processing of sensitive clinical trial data and transfer to other countries for further processing is allowed.

The Investigator or designee shall provide a copy of the signed consent form to the participant and the signed original shall be maintained in the Investigator File. A copy of the signed consent form must be filed in the participant file. At any stage, the participant may withdraw from the study and such a decision will not affect any further treatment options.

The Roswell Park “SOP: Written Documentation of Consent (HRP-091)” will be followed.

Patients will be consented before or after surgery (up until full diet clearance). Patients will only be consented when they are fully conscious and have voluntary control over their actions and not taking any medications that may affect their judgement.

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32 DRUGS OR DEVICES

32.1 Trimethoprim/ Sulfamethoxazole DS (Bactrim™)

32.1.1 Active Substance and Source

Each double strength (DS) tablet contains 160 mg trimethoprim and 800 mg sulfamethoxazole.

Inactive ingredients:

Docusate sodium 85%, sodium benzoate 15%, sodium starch glycolate, magnesium stearate and pregelatinized starch

32.1.2 Drug Shipment

Drug will be supplied by the study.

32.2 Nitrofurantoin monohydrate/macrocrystals (Macrobid®)

32.2.1 Active Substance and Source

Each hard gelatin capsule shell of contains the equivalent of 100 mg of nitrofurantoin in the form of 25 mg of nitrofurantoin macrocrystals and 75 mg of nitrofurantoin monohydrate.

Inactive ingredients: Each capsule contains carbomer 934P, corn starch, compressible sugar, D&C Yellow No. 10, edible gray ink, FD&C Blue No. 1, FD&C Red No. 40, gelatin, lactose, magnesium stearate, providone, talc, and titanium dioxide.

32.2.2 Drug Shipment

Drug will be supplied by the study.

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34 APPENDICES

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Appendix A INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM INCLUSION CRITERIA

Participant Name: _____

Medical Record No.: _____

Title: Does Prophylactic Antibiotic Decrease the Rate of Urinary Tract Infection after Robot Assisted Radical Cystectomy?

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Age ≥ 18 years of age.	
☐	☐	☐	2. Any patient that electively chooses to have a cystectomy till their discharge date is eligible to participate in the study. Indications for a person who may undergo a cystectomy include having a diagnosis of muscle-invasive bladder cancer (MIBC) or refractory non-muscle invasive bladder cancer (NMIBC).	
☐	☐	☐	3. Any patient that will electively choose to have a robot-assisted radical cystectomy and is able to provide consent.	
☐	☐	☐	4. Participant or legal representative must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.	

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

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Appendix B INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM EXCLUSION CRITERIA

Participant Name: _____

Medical Record No.: _____

Title: Does Prophylactic Antibiotic Decrease the Rate of Urinary Tract Infection after Robot Assisted Radical Cystectomy?

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Patients with a history of myasthenia gravis.	
☐	☐	☐	2. Patients with a history of QT prolongation or taking other drugs that prolong QTc should be excluded.	
☐	☐	☐	3. Patients with renal dysfunction, creatinine clearance (mL/min) < 30.	
☐	☐	☐	4. Pregnant or nursing female participants.	
☐	☐	☐	5. Females who receive a fertile sex sparing Robot Assisted Radical Cystectomy.	
☐	☐	☐	6. Unwilling or unable to follow protocol requirements.	
☐	☐	☐	7. Patients who receive a prophylactic antibiotic or antibiotic for any other reason prior to discharge.	
☐	☐	☐	8. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug.	

Participant meets all entry criteria: ☐ **Yes** ☐ **No**

If "NO", do not enroll participant in study.

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

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Appendix C Drug Diary

Study No.: _____ Patient Name: _____

Drug Name: _____Medical Record No.: _____

Study Medication Calendar for Antibiotic

You should swallow your medication, unchewed, with a large glass of water (at least 8 ounces) at approximately the same time every day, once a day. If you miss a dose and it is within 8 hours of the missed dose-take the missed dose as soon as possible with food. If it is longer than 8 hours since the missed dose-do not take any of the drug that day, but wait until the next day to take your regularly scheduled dose.

Please complete this calendar on a daily basis immediately after you take your tablets. Fill in the date for each day, write the drug dose that you take each day, and write the total number of tablets you take each day.

Start Date: _____

Take _____ tablets once a day

Cycle Day	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date							
Dose							
Number of tablets taken	AM	AM	AM	AM	AM	AM	AM

Cycle Day	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Date							
Dose							
Number of tablets taken	AM	AM	AM	AM	AM	AM	AM

Cycle Day	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Date							
Dose							
Number of tablets taken	AM	AM	AM	AM	AM	AM	AM

Cycle Day	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Date							
Dose							
Number of tablets taken	AM	AM	AM	AM	AM	AM	AM

Cycle Day	Day 29	Day 30
Date		
Dose		
Number of tablets taken	AM	AM

Please remember to bring this calendar and your study medication bottle (including any unused tablets) with you to your next clinic appointment.

Coordinator's Use Only

$$\%\ Compliance = \left(\frac{Number\ of\ Pills\ Dispensed - Number\ of\ Pills\ Returned}{Number\ of\ Pills\ Scheduled}\right) \times 100$$

$$___\%\ Compliance = \left(\frac{\ \ -\ \ }{\ \ \ \

Study team signature: _____ Date: _____

de medicamentos

Apéndice C Diario

Nombre del paciente:_____

Nombre del fármaco:_____No de expediente médico:_____

Calendario de medicación de estudio para antibióticos

Debe tragar su medicamento, sin masticar, con un vaso grande de agua (al menos de 8 onzas) aproximadamente a la misma hora todos los días, una vez al día. Si olvida una dosis y es menos de 8 horas a la dosis olvidada, tome la dosis olvidada lo antes posible con alimentos. Si han pasado más de 8 horas desde la dosis olvidada, no tome ninguno de los medicamentos ese día, pero espere hasta el día siguiente para tomar la dosis programada regularmente.

Por favor complete este calendario diariamente inmediatamente después de tomar sus tabletas. Complete la fecha de cada día, escriba la dosis del medicamento que toma cada día y escriba la cantidad total de tabletas que toma cada día.

Fecha de inicio:_____

Tome las tabletas una vez al día

Día del ciclo	Día 1	Día 2	Día 3	Día 4	Día 5	Día 6	Día 7
Fecha							
Dosis							
No.de tabletas tomadas	AM	AM	AM	AM	AM	AM	AM

Día del ciclo	Día 8	Día 9	Día 10	Día 11	Día 12	Día 13	Día 14
Fecha							
Dosis							
No. de tabletas tomadas	AM	AM	AM	AM	AM	AM	AM

Día del ciclo	Día 15	Día 16	Día 17	Día 18	Día 19	Día 20	Día 21
Fecha							
Dosis							
No. de tabletas tomadas	AM	AM	AM	AM	AM	AM	AM

Día del ciclo	Día 22	Día 23	Día 24	Día 25	Día 26	Día 27	Día 28
Fecha							
Dosis							
No. de tabletas tomadas	AM	AM	AM	AM	AM	AM	AM

Día del ciclo	Día 29	Día 30
Fecha		
Dosis		
No. de tabletas tomadas	AM	AM

Por favor recuerde llevar este calendario y el frasco del medicamento del estudio (incluidas las tabletas que no haya utilizado) a su próxima cita clínica.

Solo para uso del coordinador

