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**PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF  
PROPHYLACTIC TAMSULOSIN FOR POSTOPERATIVE URINARY RETENTION IN PRIMARY TOTAL  
HIP AND KNEE ARTHROPLASTY PATIENTS**

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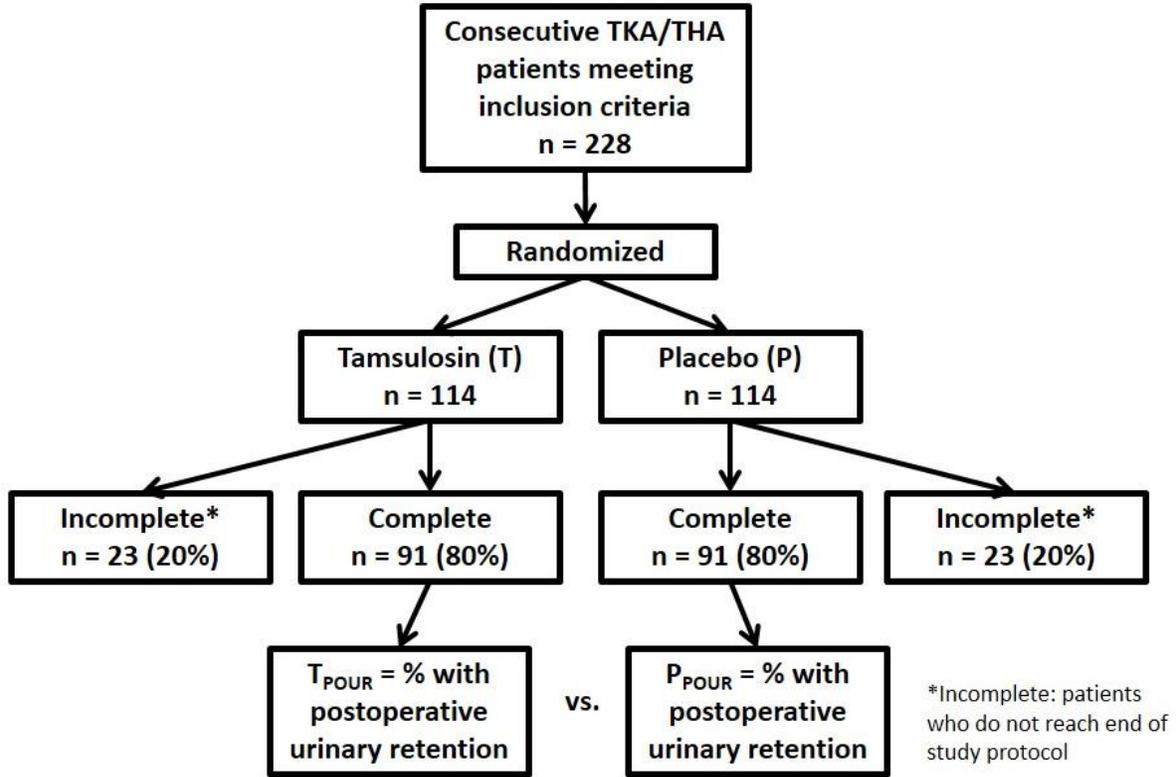
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**LIST OF ABBREVIATIONS**

AE	Adverse Event
ALC	Absolute Lymphocyte Count
AUA	American Urological Association
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
H&P	History & Physical Exam
ISC	Intermittent straight catheterization
MTD	Maximum Tolerated Dose
ORR	Overall Response Rate
p.o.	per os/by mouth/orally
POUR	Postoperative urinary retention
PVR	Estimated post-void residual
SAE	Serious Adverse Event
WBC	White Blood Cells

**STUDY SCHEMA**



**STUDY SUMMARY**

Title	Prospective, randomized, double-blind, placebo-controlled trial of prophylactic tamsulosin for postoperative urinary retention in primary total hip and knee arthroplasty patients
Short Title	Prophylactic tamsulosin for postoperative urinary retention in hip and knee arthroplasty
Phase	Phase 3
Methodology	Prospective, randomized, double-blind, placebo-controlled
Study Duration	1.5 - 3 years until a <i>prior</i> calculated sample size reached (see above)
Study Center(s)	Single-center
Objectives	Determine if prophylactic tamsulosin given beginning five days prior to surgery through post-op day one reduces the incidence of postoperative urinary retention in total hip and knee arthroplasty patients
Number of Subjects	456 screened with a 50% accrual rate (182 total subjects needed with 20% dropout for a total of 228 patients enrolled)

Control Group	91 patients undergoing primary total hip or knee arthroplasty who are on an $\alpha$ 1-adrenoceptor blocker at the time of surgery
Diagnosis and Main Inclusion Criteria	Postoperative urinary retention in primary total knee and hip arthroplasty patients
Study Product(s), Dose, Route, Regimen	Tamsulosin 0.4 mg p.o. daily
Duration of administration	Five days prior to operation until post-op day one (seven days total)
Reference therapy	Placebo
Statistical Methodology	Two-tailed t-test for primary outcome, (80% power, $\alpha = 0.05$ )

## 1. BACKGROUND AND RATIONALE

### 1.1 Disease Background

Postoperative urinary retention (POUR) following total hip and knee arthroplasty is a common complication with a reported mean incidence of 24-32% and a range of 0-75% (1). POUR is usually treated with intermittent or indwelling urinary catheterization which have been associated with postoperative urinary tract infections, can add to the cost of postoperative care, and make the postoperative experience uncomfortable. Tamsulosin has been used off-label to treat POUR and has been shown to reduce POUR following radical prostatectomy (2, 3), prostate brachytherapy (4), and inguinal herniorrhaphy (5). Tamsulosin is a selective alpha-1 adrenergic receptor blocker that works by relaxing the smooth muscles within the bladder neck and prostate. In addition, there is a clinical trial being performed at the Mayo Clinic investigating the prophylactic use of tamsulosin for POUR incidence reduction following spine surgery (clinicaltrials.gov).

### 1.2 Study Agent(s)/Devices Background and Associated Known Toxicities

Tamsulosin has been shown to reduce POUR following radical prostatectomy (2, 3), prostate brachytherapy (4), and inguinal herniorrhaphy (5) and can increase ureteral calculi expulsion rate and speed (6, 7).

The safety of tamsulosin is well known given its selectivity for the genitourinary tract, versus blood vessels (8). Reported adverse reactions include drug allergy (contains sulfa) and floppy iris syndrome (9). Common side effects include orthostatic hypotension, dizziness, fainting, vertigo, headache, nasal congestion and palpitations.

### 1.3 Rationale

This study aims to evaluate the efficacy of prophylactic tamsulosin in reducing the incidence of POUR in primary total knee and hip arthroplasty patients. By reducing the incidence of POUR, it may be possible to reduce catheter-associated urinary tract infections, postoperative discomfort, and thus patient satisfaction, as well as the cost of care for arthroplasty patients.

## 2. STUDY OBJECTIVES

### 2.1 Primary Objectives

- 2.1.1 To compare prophylactic administration of tamsulosin to that of placebo in reducing the incidence of POUR in total hip and knee arthroplasty patients. POUR will be defined as any of the following: 1) Estimated post-void residual (PVR) volume of urine greater than or equal to 200 mL; 2) Estimated retention urine volume of greater than or equal to 200 mL in patients unable to void for 6 hours; 3) Patients experiencing discomfort or distension and unable to void with residual urine volume less than 200 ml.

All patients will fill out the American Urological Association (AUA) Symptom Index (form is attached), preoperatively, and at two-weeks, postoperatively. The scores will be used to compare the results of tamsulosin administration between the two groups by assessing if postoperative scores have returned to preoperative (baseline) scores. Patients will also be asked to document their usage of opioid pain medications, using a medication log, from their time of discharge until their two week follow up appointment.

### 2.2 Secondary Objectives

- 2.2.1 To determine if prophylactic administration of tamsulosin reduces hospital stay or likelihood of discharge to a skilled nursing facility
- 2.2.2 To determine if prophylactic administration of tamsulosin reduces surgical site infection over two weeks, postoperatively
- 2.2.3 To determine if prophylactic administration of tamsulosin reduces acute postoperative pain medication requirements
- 2.2.4 To determine if prophylactic administration of tamsulosin reduces postoperative complications (deep venous thrombosis, pulmonary embolism, cardiovascular event, pneumonia, fevers, urinary tract infection)

### 2.3 Endpoints/Measurements

Primary endpoint of the study is the development of POUR. POUR is defined as any of the following: 1) any estimated post-void residual (PVR) volume of urine greater than or equal to 200 mL per bladder scan; 2) estimated urine volume retention of greater than or equal to 200 mL in patients unable to void within six hours after indwelling urinary catheter removal; 3) patients experiencing bladder discomfort or distention and unable to void with residual urine volume less than 200 mL; 4) requirement of intermittent straight catheterization (ISC) during hospitalization; 5) administration of tamsulosin outside of the study medication during the postoperative hospitalization. The development of POUR will be determined based on recorded values in the electronic medical record of bladder scans, the need for ISC, initiation of tamsulosin in the medication administration record, and mention of urinary retention in daily progress notes or in the discharge summary. If a patient is asymptomatic with regards to urinary symptoms and does not require intermittent urinary catheterization, but does not have any PVR volumes recorded in the medical record, then the patient is clinically deemed to not have developed POUR.

In keeping with our standard of care for arthroplasty patients who develop POUR, as defined in section 2.1.1, after the Foley catheter is discontinued, will be given a trial of intermittent straight catheterization (ISC) for 24 hours. If, after 24 hours of ISC, the patient has not resumed spontaneous voids with a residual volume of less than 200 mL,

management will be continued based on routine protocol for urinary retention after surgery (post-void bladder scan, straight urinary catheterization, possible Foley catheter placement, and possible urology consult).

Secondary measures are: length of hospital stay, incidence of discharge to a skilled nursing facility, surgical site infection, acute postoperative pain medication requirements, and other postoperative complications (deep venous thrombosis, pulmonary embolism, cardiovascular event, pneumonia, fevers, or urinary tract infection).

### 3. PATIENT ELIGIBILITY

Subjects must meet all of the inclusion and exclusion criteria requirements to be registered to the study. Study treatment may not begin until a subject is registered.

#### 3.1 Inclusion Criteria

1. Men age  $\geq$  35 years
2. Primary total hip and knee arthroplasty patients (general, spinal, or epidural anesthesia)
3. No current use (>one month) of alpha blockers
4. Community ambulator
5. Adequate organ and marrow function as defined below:
  - leukocytes  $\geq$  3,000/ $\mu$ L
  - absolute neutrophil count  $\geq$  1,500/ $\mu$ L
  - platelets  $\geq$  100,000/ $\mu$ L
  - creatinine within normal institutional limits
6. Ability to understand, and the willingness to sign, a written informed consent
7. Use of intraoperative foley.

#### 3.2 Exclusion Criteria

1. History of radical prostatectomy
2. Receiving any other investigational agents
3. Revision hip and knee arthroplasty patients
4. Severe liver or kidney disease
5. Taking strong inhibitors of CYP3A4 (ketoconazole, itraconazole, clarithromycin, ritonavir, indinavir/ritonavir, lopinavir/ritonavir, or conivaptan)
6. Being on alpha-blockers (alfuzosin, doxazosin, prazosin, terazosin, tamsulosin, phenoxybenzamine, or silodosin)
7. Being on 5-alpha reductase inhibitors (finasteride, dutasteride)
8. History of allergy or sensitivity to tamsulosin or other alpha-blockers (alfuzosin, doxazosin, prazosin, terazosin, or phenoxybenzamine)

9. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements
10. Taking Sildenafil, [Tadalafil](#), or [Vardenafil](#)

#### 4. TREATMENT PLAN

##### 4.1 Treatment Dosage and Administration

- 4.1.1 Patients will be randomized to receive either a placebo or tamsulosin 0.4 mg daily for five days prior to surgery, the morning of surgery, and the first day post-op to be continued until all capsules are taken. Medication will be provided to patients at either their pre-operative appointment or mailed to them via UPS before their surgery date.
- 4.1.2 Patients will receive tamsulosin/placebo preoperatively on an outpatient basis.
- 4.1.3 All patients will have an indwelling Foley catheter placed intraoperatively, to be discontinued the morning of postoperative day one in keeping with existing protocol for all patients undergoing total hip or knee arthroplasty.

REGIMEN DESCRIPTION					
Agent	Premedications; Precautions	Dose	Route	Schedule	Cycle Length
Tamsulosin	None	0.4 mg daily	Oral	5 days preop through postop day 1	N/A
Placebo	None	1 capsule daily	Oral	5 days preop through postop day 1	
$\alpha$ 1-adrenoceptor blocker	None	Prescribed dose	Oral	Continue current therapy throughout the perioperative period	N/A

##### 4.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluated for toxicity per the Toxicity Assessment Survey (attached). Each patient will be assessed for the development of toxicity per the Time and Events Table, and overall study cohort safety will be statistically compared at defined intervals (See Section 5.4).

#### 4.3 Concomitant Medications/Treatments

Medication contraindications include CYP3A4 inhibitors (ketoconazole, itraconazole, clarithromycin, ritonavir, indinavir/ritonavir, lopinavir/ritonavir, and conivaptan) and other medications that may have an interaction (amiodarone, dronedarone, boceprevir, chloramphenicol, clarithromycin, cobicistat, conivaptan, cyclosporine, delavirdine, doxazosin, fluvoxamine, fosamprenavir, imatinib, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, prazosin, rifampin/isoniazid, rifampin/isoniazid/pyrazinamide, ritonavir, telaprevir, telithromycin, terazosin, tipranavir, voriconazole), Sildenafil, Tadalafil, and Vardenafil .

#### 4.4 Duration of Therapy

End of protocol therapy occurs when 1) patient completes the seven-capsule regimen, 2) adverse reaction to tamsulosin occurs, 3) postoperative complication occurs; deemed prohibitive of further continuation of therapy, 4) patient decides to withdraw, 5) an indwelling catheter is placed for monitoring the fluid and electrolyte intake and output for medical purpose, 6) patient perishes.

#### 4.5 Duration of Follow-Up

Patients will be followed per usual protocol for primary hip and knee arthroplasty patients, including inpatient stay (1-4 days on average) and a two-week clinic follow-up appointment. After patient completes the AUA Symptom Index and the Toxicity Assessment Survey and submits their opioid pain medication log at the two-week follow-up appointment, **active** participation in the study will conclude, however we will monitor their medical records for 30 post operatively

During the inpatient stay, patients will continue to take tamsulosin or placebo until the 7-capsule regimen is complete or until one of the end-of-protocol-therapy criteria listed in section 5.5 is met. If the patient goes on to treatment failure, he may be discharged on tamsulosin at the discretion of his physician. It will be noted if a patient is discharged on tamsulosin and appropriate follow-up will be arranged with either the patient's primary care physician or urologist.

#### 4.6 Removal of Patients from Protocol Therapy

Patients will be removed from therapy when any of the criteria listed in Section 5.5 apply. The Principal Investigator will be notified, and the reason for therapy removal and the date the patient was removed will be documented on the Case Report Form. The patient should be followed-up per protocol.

#### 4.7 Patient Replacement

Patients will not be required to be replaced as the study will continue until the minimal sample size, as determined by a prior sample size calculation, is reached.

### 5. PROCEDURES

#### 5.1 Screening/Baseline Procedures

Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the assessments were done before informed consent was obtained. All screening procedures must be performed within 30 days prior to registration unless otherwise stated. The screening procedures include:

- 5.1.1 *Informed consent*
- 5.1.2 *Medical history*  
Complete medical and surgical history, history of urinary retention, benign prostatic hypertrophy, urogenital procedures
- 5.1.3 *Demographics*  
Age, gender, race, ethnicity
- 5.1.4 *Review of subject eligibility criteria*
- 5.1.5 *Review of previous and concomitant medications*
- 5.1.6 *Physical exam including vital signs, height and weight (Standard of Care)*  
Vital signs (temperature, pulse, respirations, blood pressure), height, weight
- 5.1.7 *Adverse event and efficacy assessment*  
Baseline adverse events will be assessed. Efficacy will be assessed periodically as well. Adverse events and efficacy will be considered in continuation of the study at enrollment intervals (See Section 5.4). See Section 7 for adverse event monitoring and reporting.
- 5.1.8 *Hematology-(Standard of Care)*  
CBC with differential
- 5.1.9 *Serum chemistries (Standard of Care)*  
Basic metabolic panel (BMP) to include: BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), and glucose

## **5.2 Procedures During Treatment**

### **5.2.1 Preoperative**

- Physical exam, vital signs (Standard of Care)
- Hematology (Standard of Care)
- Serum chemistries (Standard of Care)
- Completion of the AUA Symptom Index by the patient
- Completion of the Toxicity Assessment Survey by the patient
- Patient to be given seven capsules of 0.4 mg tamsulosin, with one to be taken daily for the five days before surgery, one on the morning of surgery, and one on the day after surgery. Pills should be administered approximately one half hour following the same meal each day.

### **5.2.2 Postoperative**

- Tamsulosin/placebo taken on postoperative day one
- Completion of the Toxicity Assessment Survey by the patient on post-op day one

**5.2.3 Post-discharge**

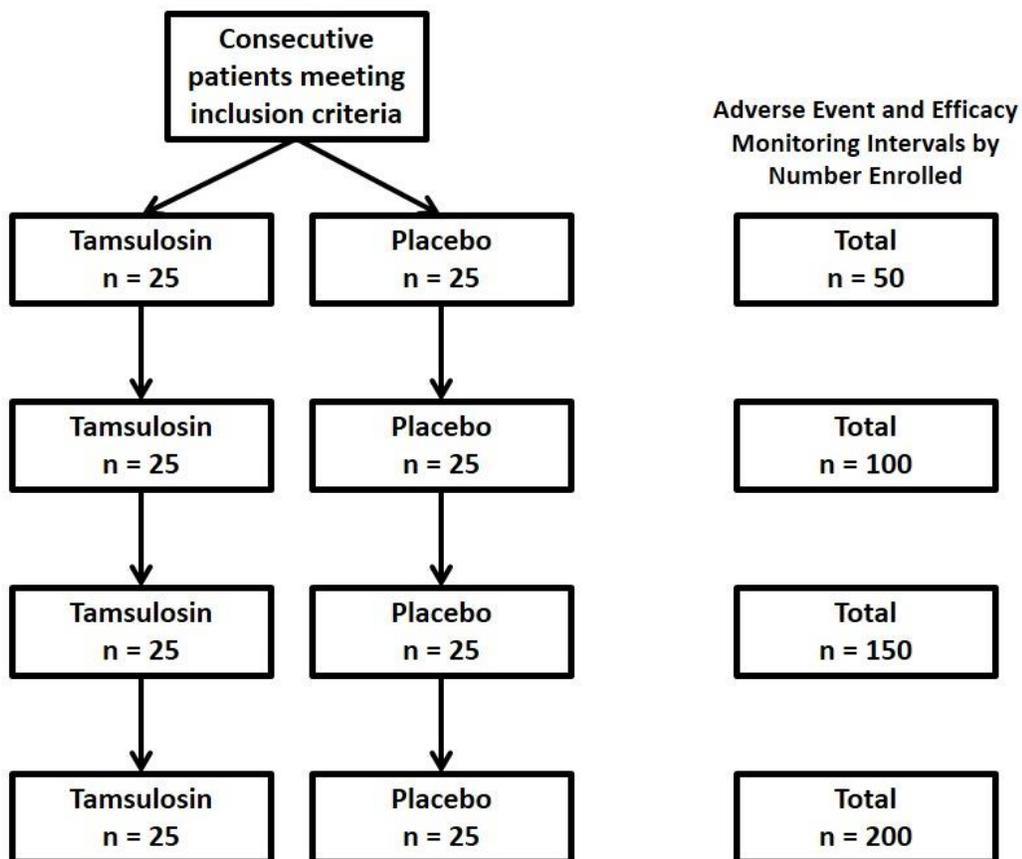
Patients that go on to treatment failure will be discharged with a plan of care dictated by urology (if consulted), or the primary treatment team, which may include Foley catheter placement, tamsulosin, intermittent straight catheterization, outpatient follow-up with urologist or primary care physician, or some combination of the previously mentioned treatment options.

**5.3 Follow-up Procedures**

Completion of AUA Symptom Index, Toxicity Assessment Survey, and opioid pain medication log by the patient.

**5.4 Time and Events Table**

<b>Event</b>	<b>Pre-operative</b>	<b>Inpatient Stay</b>	<b>2-wk Follow-up</b>
Informed Consent	X		
History and PE	X		X
Performance Status	X		
Toxicity Evaluation	X	X	X
AUA retention score	X		X
Opioid Pain Medication log			X



## 5.5 Removal of Subjects from Study/Study Treatment

- 5.5.1 Patient voluntarily withdraws from treatment (follow-up permitted)
- 5.5.2 Patient withdraws consent (termination of treatment and follow-up)
- 5.5.3 Patient is unable to comply with protocol requirements
- 5.5.4 Patient experiences toxicity that makes continuation in the protocol unsafe
- 5.5.5 Treating physician judges continuation in the study would not be in the patient's best interest

## 6.0 Response Criteria

### 6.1 Safety/Tolerability

Analyses will be performed for all patients having received at least one dose of study drug.

## 7.0 ADVERSE EVENTS

### 7.1 Experimental Therapy

- 7.1.1 *Contraindications*  
History of allergy, sulfa allergy potential for cross sensitivity, poor cyp2d6 metabolizers

7.1.2 *Special Warnings and Precautions for Use*

Floppy iris syndrome in patients undergoing cataract surgery while on Flomax

7.1.3 *Interaction with other medications (per Epocrates):*

Amiodarone, dronedarone, boceprevir, chloramphenicol, clarithromycin, cobicistat, conivaptan, cyclosporine, delavirdine, doxazosin, fluvoxamine, fosamprenavir, imatinib, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, prazosin, rifampin/isoniazid, rifampin/isoniazid/pyrazinamide, ritonavir, telaprevir, telithromycin, terazosin, tipranavir, voriconazole

7.1.4 *Adverse Reactions*

	All	Drug related
Any	390 (76)	132 (26)
$\alpha_1$ -adrenoceptor blocker-associated		
Dizziness	44 (8.5)	30 (5.8)
Abnormal ejaculation	25 (4.9)	22 (4.3)
Headache	24 (4.7)	7 (1.4)
Asthenia	20 (3.9)	10 (1.9)
Rhinitis	18 (3.5)	3 (0.6)
Postural hypotension	15 (2.9)	14 (2.7)

Palpitation	14 (2.7)	7 (1.4)
Dry mouth	8 (1.6)	6 (1.2)
Syncope	5 (1.0)	0
Somnolence	4 (0.8)	2 (0.4)
Other		
Impotence	28 (5.4)	15 (2.9)
Decreased libido	6 (1.2)	4 (0.8)
Urinary retention	23 (4.5)	1 (0.2)
Discontinued treatment	86 (217)	26(5)

Others: allergic reaction, angioedema, Steven Johnson syndrome, arrhythmia, priapism (10)

## 7.2 Adverse Event Monitoring

A study coordinator will monitor for AEs with the use of the patient surveys, at the 2-week follow-up appointment, and with a chart review following the 30-day end-of-study-treatment timepoint. Adverse events will be reported in compliance with the IRB standard reporting guidelines. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care. See steps 7.4 and 7.5 for requirements for expedited reporting.

All patients experiencing an adverse event, regardless of its relationship to study drug/device, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline,
- any abnormal laboratory values have returned to baseline,
- there is a satisfactory explanation other than the study drug for the changes observed, or
- death.

### 7.3 Definitions

#### 7.3.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

#### 7.3.2 Severity of Adverse Events

The severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

Moderate (grade 2): the event causes discomfort that affects normal daily activities.

Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.

Life-threatening (grade 4): the patient was at risk of death at the time of the event.

Fatal (grade 5): the event caused death.

#### 7.3.3 Serious Adverse Events

A serious adverse event is defined in regulatory terminology as any untoward medical occurrence that:

##### 7.3.3.1 *results in death,*

If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

##### 7.3.3.2 *is life-threatening,*

The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

##### 7.3.3.3 *requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours,*

##### 7.3.3.4 *results in persistent or significant disability or incapacity,*

7.3.3.5 *is a congenital anomaly/birth defect, or*

7.3.3.6 *is an important medical event.*

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “serious adverse event”.

For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home, convulsions that may not result in hospitalization, or development of drug abuse or drug dependency.

#### 7.4 Steps to Determine if an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event.

Step 2: Grade the adverse event.

Step 3: Determine whether the adverse event is related to the protocol therapy.

Attribution categories are as follows:

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

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol,
- the drug package insert, or
- the current Investigator’s Brochure

#### 7.5 Reporting Requirements for Adverse Events

All AEs will be reported in adherence to IRB standard reporting guidelines.

7.5.1 Follow expedited reporting procedures when the AE meets any of the following criteria:

1. Any serious event (injuries, side effects, deaths or other problems), which, in the opinion of the Principal Investigator, was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject

4. Any new information (e.g., publication, safety monitoring report), interim result, or other finding that indicates an unexpected change to the risk/benefit ratio for the research
5. Any breach in confidentiality that may involve risk to the subject or others
6. Any complaint of a subject that indicates an unanticipated risk, or that cannot be resolved by the Principal Investigator

#### 7.6 Unblinding Procedures

Unblinding will occur when the safety of a patient requires this and will be up to the judgment of the treating physician. The investigators will be notified of such unblinding.

#### Stopping Rules

The study will be stopped when the adverse event rate exceeds that of the expected rate listed above or greater than two serious adverse events occur and are judged to be the direct result of the investigatory agent.

### 8. DRUG/DEVICE INFORMATION

#### 8.1 Tamsulosin

- Other names for the drug: Flomax™
- Classification: alpha-1 selective alpha blocker
- Mode of action: selective  $\alpha_1$  receptor blocker that has preferential selectivity for the  $\alpha_{1A}$  receptor in the prostate versus the  $\alpha_{1B}$  receptor in the blood vessels
- Storage and stability: stable at room temperature
- Preparation: 0.4 mg capsule
- Route of administration for this study: oral
- Incompatibilities (per Epocrates): amiodarone, dronedarone, boceprevir, chloramphenicol, clarithromycin, cobicistat, conivaptan, cyclosporine, delavirdine, doxazosin, fluvoxamine, fosamprenavir, imatinib, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, prazosin, rifampin/isoniazid, rifampin/isoniazid/pyrazinamide, ritonavir, telaprevir, telithromycin, terazosin, tipranavir, voriconazole
- Availability: commercially available as a generic
- Side effects: Of the more common drug-related side effects, dizziness, abnormal ejaculation, headache, asthenia, postural hypotension, palpitation, dry mouth and impotence per **(10)**. Please refer to the package insert for a comprehensive list of adverse events.
- Nursing implications: no additional duties will be required of Nursing that are not otherwise performed per postoperative protocol for total arthroplasty patients.

**8.2 Return and Retention of Study Drug/Device**

If the patient does not take all of the prescribed capsules, the remaining capsules will be destroyed per University policy.

**9. CORRELATIVES/SPECIAL STUDIES**

No special correlative studies are planned.

**10. STATISTICAL CONSIDERATIONS****10.1 Study Design/Study Endpoints**

Prospective, double blinded, randomized single-center study comparing the efficacy of tamsulosin in reducing POUR incidence in primary total hip and knee arthroplasty patients.

Adverse events will be monitored at intervals of 50 (25 in each group). If AEs in the trial group exceed those in the placebo group, and this difference is statistically significant and related to the active drug (tamsulosin), then the study will be terminated. Minor adverse events will be examined via statistical tests (chi-square) at each interval. If there are severe adverse events noted in the intervention group, the study may be halted until further review.

**10.2 Sample Size and Accrual**

POUR occurs in approximately 40% of patients following primary total hip or knee arthroplasty. Risk factors for POUR include male sex, total hip arthroplasty, intrathecal morphine and epidural anesthesia. A sample size of 91 in each arm (tamsulosin versus placebo) is needed with continuity correction if a reduction of 50% (or a POUR incidence of 20%) is to be detected with a power of 80% at a significance level of  $\alpha < 0.05$ . 114 patients are need in each arm assuming an accrual rate of 80% for a total of 228 patients.

**10.3 Data Analyses Plans**

Chi-square test will be used to compare the primary outcome of the incidence of POUR between those taking and those not taking tamsulosin at the time of surgery, as well as the secondary measure of the incidence of discharge to a skilled nursing facility between the two groups. T-test will be used to compare the secondary measures of length of hospital stay and postoperative pain medication requirements (average daily dose) between the two groups. Regression analysis will be performed of other postoperative complications including surgical site infection, deep venous thrombosis, pulmonary embolism, urinary tract infection, pneumonia, cardiovascular event, fevers, and the duration of anesthesia between the two groups. Significance will be set at  $\alpha = 0.05$ .

**11. STUDY MANAGEMENT****11.1 Conflict of Interest**

The investigators of this study have no financial, board or publishing conflicts of interest.

**11.2 Institutional Review Board (IRB) Approval and Consent**

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment into this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA, and regional, state, and local regulations. Once this essential information has been provided to the patient, and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient, and by the person who conducted the informed consent discussion.

### **11.3 Registration Procedures**

All patients must be registered before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the study coordinator.

### **11.4 Data Management and Monitoring/Auditing**

Study coordinator will continually update an anonymized database of patients, their endpoints, secondary measures, adverse events.

### **11.5 Adherence to the Protocol**

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

#### **11.5.1 Emergency Modifications**

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

#### **11.5.2 Other Protocol Deviations/Violations**

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- is generally noted or recognized after it occurs,
- has no substantive effect on the risks to research participants,
- has no substantive effect on the scientific integrity of the research plan or the value of the data collected, or
- did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- has harmed or increased the risk of harm to one or more research participants,
- has damaged the scientific integrity of the data collected for the study,
- results from willful or knowing misconduct on the part of the investigator(s), or
- demonstrates serious or continuing noncompliance with federal regulations, state laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

**Protocol Deviations:** Personnel will report to any data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

**Protocol Violations:** Study personnel should report violations within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report unanticipated problems.

#### **11.6 Amendments to the Protocol**

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and, if required, the amended consent form, must be sent to the IRB for approval prior to implementation.

#### **11.7 Record Retention**

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. Study documents should be kept on file until three years after the completion and final study report of this investigational study.

#### **11.8 Obligations of Investigators**

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all Case Report Forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

## **12. REFERENCES**

1. Balderi T, Carli F. Urinary retention after total hip and knee arthroplasty. *Minerva anestesologica*. 2010;76(2):120-30. PubMed PMID: 20150853.

2. Jeong IG, You D, Yoon JH, Hong S, Lim JH, Hong JH, et al. Impact of tamsulosin on urinary retention following early catheter removal after robot-assisted laparoscopic radical prostatectomy: a prospective randomized controlled trial. *International journal of urology : official journal of the Japanese Urological Association*. 2014;21(2):164-8. doi: 10.1111/iju.12225. PubMed PMID: 23906190.
3. Patel R, Fiske J, Lepor H. Tamsulosin reduces the incidence of acute urinary retention following early removal of the urinary catheter after radical retropubic prostatectomy. *Urology*. 2003;62(2):287-91. PubMed PMID: 12893337.
4. Merrick GS, Butler WM, Wallner KE, Lief JH, Galbreath RW. Prophylactic versus therapeutic alpha-blockers after permanent prostate brachytherapy. *Urology*. 2002;60(4):650-5. PubMed PMID: 12385927.
5. Mohammadi-Fallah M, Hamedanchi S, Tayyebi-Azar A. Preventive effect of tamsulosin on postoperative urinary retention. *Korean journal of urology*. 2012;53(6):419-23. doi: 10.4111/kju.2012.53.6.419. PubMed PMID: 22741052; PubMed Central PMCID: PMC3382693.
6. Arrabal-Martin M, Valle-Diaz de la Guardia F, Arrabal-Polo MA, Palao-Yago F, Mijan-Ortiz JL, Zuluaga-Gomez A. Treatment of ureteral lithiasis with tamsulosin: literature review and meta-analysis. *Urologia internationalis*. 2010;84(3):254-9. doi: 10.1159/000288224. PubMed PMID: 20389151.
7. Lee SW, Woo SH, Yoo DS, Park J. Effect of tamsulosin on stone expulsion in proximal ureteral calculi: an open-label randomized controlled trial. *International journal of clinical practice*. 2014;68(2):216-21. doi: 10.1111/ijcp.12271. PubMed PMID: 24372674.
8. Yuan J, Liu Y, Yang Z, Qin X, Yang K, Mao C. The efficacy and safety of alpha-1 blockers for benign prostatic hyperplasia: an overview of 15 systematic reviews. *Current medical research and opinion*. 2013;29(3):279-87. doi: 10.1185/03007995.2013.766594. PubMed PMID: 23323875.
9. Chang DF, Campbell JR. Intraoperative floppy iris syndrome associated with tamsulosin. *Journal of cataract and refractive surgery*. 2005;31(4):664-73. doi: 10.1016/j.jcrs.2005.02.027. PubMed PMID: 15899440.
10. Narayan P., Rao Tunuguntla HSG. Long-Term Efficacy and Safety of Tamsulosin for Benign Prostatic Hyperplasia. *Reviews in Urology Vol. 7 SUPPL. 4* 2005:S42-S48

	<p style="margin: 0;"><b>Appendix 1: AUA Symptom Index</b></p> <p style="margin: 0;"><b>American Urological Association (AUA) Symptom Score</b></p>
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Patient ID: \_\_\_\_\_ Date: \_\_\_\_\_

**Have you noticed any of the following when you have gone to the bathroom to urinate over the past two weeks?**

Circle the correct answer for you and write your score in the right-hand column.

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your score
<b>Incomplete emptying</b> – It does not feel like I empty my bladder all the way.	0	1	2	3	4	5	
<b>Frequency</b> – I have to go again less than two hours after I finish urinating.	0	1	2	3	4	5	
<b>Intermittency</b> – I stop and start again several times when I urinate.	0	1	2	3	4	5	
<b>Weak stream</b> – I have a weak urinary stream.	0	1	2	3	4	5	
<b>Straining</b> – I have to push or strain to begin urination.	0	1	2	3	4	5	
	None	1 time	2 times	3 times	4 times	5 times or more	Your score
<b>Nocturia</b> – I get up to urinate after I go to bed until the time I get up in the morning.	0	1	2	3	4	5	

**Total AUA Symptom Score**

 <p>University of Michigan Health System</p>	<p>Appendix 2:  Toxicity Assessment Survey</p>
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Patient ID: \_\_\_\_\_ Date: \_\_\_\_\_  
\_\_\_\_\_

**Are you experiencing any of the following symptoms?**

1. Dizziness: yes / no
2. Headache: yes / no
3. Palpitations (a rapid, fluttering, or pounding heart): yes / no
4. Fainting: yes / no
5. Drowsiness: yes / no



**Patient Prescription Pain Medication Log**

Once you are discharged, you will be instructed to take a **prescription** pain medication according to your surgeon's orders and pain levels. We would like to know how you are controlling your pain post-surgery from the day of your discharge up until your first follow up appointment. If you would please note how many pills of the **prescription medication** you take and how many times per day, it would be greatly appreciated. Then please bring this chart with you to your appointment and the research coordinator can get it from you. Thank you for your time and willingness to participate in our research. It is greatly appreciated.

Wishes for a speedy recovery,  
The University of Michigan Orthopaedic Surgery Research Team

Patient ID Number \_\_\_\_\_

Prescription Medication Name: \_\_\_\_\_

\_\_\_\_\_ Dosage: \_\_\_\_\_ (mg)

	<b>Pills taken</b>					
<b>EXAMPLE</b>	<b>1</b>	<b>0</b>	<b>2</b>	<b>0</b>	<b>1</b>	<b>1</b>
Day 1						
Day 2						
Day 3						
Day 4						
Day 5						
Day 6						
Day 7						
Day 8						
Day 9						
Day 10						
Day 11						
Day 12						
Day 13						
Day 14						
Day 15						
Day 16						
Day 17						
Day 18						

Principal Investigator (PI) Oversight Meeting Log

PI:  
Study:  
Sponsor:

Instructions: This log documents meetings held with the PI to review study status, enrollments, AEs, MAIs, lab results and issues/deviations.

Date of Discussion	Patient# (if applicable)	Topics Discussed	Names of Attendees	P D