Preoperative tamsulosin for the prevention of postoperative urinary retention: a randomized, double-blind, placebo-controlled trial

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1.0 PROTOCOL SUMMARY

Postoperative urinary retention (POUR) complicates up to 30% of general abdominal operations. It results in patient discomfort, embarrassment, interference with therapies, and significant nursing burden. More importantly, urinary retention necessitates use of intermittent catheterization or placement of an indwelling urinary catheter, which exposes the patient to an increased risk of urinary tract infection (UTI), urethral injury, and potentially increased hospital length of stay and cost. For these reasons, a safe and effective intervention for preventing POUR would be highly valuable. Despite such a need, no contemporary studies exist evaluating medications that can be used to prevent POUR in broad general surgery populations. To address this gap, we are designing a prospective, randomized, double-blind, placebo-controlled trial to test the hypothesis that preoperative loading with tamsulosin will prevent POUR in patients undergoing elective, inpatient complex intra-abdominal surgery and thereby lead to improved short-term outcomes.

Tamsulosin is a safe and widely-used selective $alpha_{1A}$ adrenergic blocker commonly used for the treatment of lower urinary tract symptoms in men with benign prostatic hypertrophy. It has also been shown to have some benefit in reducing POUR and need for catheterization in men undergoing inguinal hernia repair and other outpatient urologic procedures. To test our hypothesis, we will conduct a randomized, double-blind, placebo-controlled trial in which we administer tamsulosin or placebo for 7 days pre-operatively to patients scheduled for inpatient complex intra-abdominal surgery, and then compare the rates of POUR in each group (Aim 1). We also propose a retrospective analysis of our data to identify risk factors for POUR and subgroups of patients that would derive the greatest benefit from preoperative tamsulosin (Aim 2). Furthermore, we propose to determine if preoperative tamsulosin therapy leads to improved short-term outcomes, including reduced rate of UTI and shorter hospital length of stay (Aim 3).

2.0 INTRODUCTION

Postoperative urinary retention refers to the inability to void spontaneously or completely following surgery. It complicates up to 69% of operations, depending on the type of surgery, and can have significant consequences for the patient.[1] The etiology of postoperative urinary retention is likely multifactorial, with contributing factors including sympathetic stimulation secondary to pain and surgery, local edema, intraoperative bladder distention, patient anxiety, immobilization, damage to parasympathetic nerves of the S2 to S4 dermatome, and medication effects.[2] It is typically self-limited, and is managed with intermittent or indwelling urinary catheterization until resolution. Multiple risk factors for postoperative urinary retention have been identified. These include opioid use, neuraxial anesthesia, type of operation such as anorectal procedures and lower limb joint arthroplasties, older age, male gender, and pre-existing lower urinary tract symptoms.[2]

Although an often underemphasized problem following surgery, postoperative urinary retention occurs frequently and can have significant consequences for the patient. Direct effects of urinary retention include patient discomfort, embarrassment, and the consequences of bladder distention such as hemodynamic effects (rarely), prolonged detrusor dysfunction, and possible kidney disease.[2] Indirect effects of urinary retention are a result of the need for catheterization to empty the bladder. Perhaps the most significant of these is catheter-associated urinary tract infection (CAUTI). UTI is one of the most common hospital-acquired infections, and 70-80% of these are associated with an indwelling

urinary catheter.[3] The most important predictor of CAUTI is duration of catheterization, with an estimated 4 to 7% risk of developing bacteriuria for each day of indwelling catheter use.[3] Furthermore, indwelling catheters cause gross hematuria and urethral stricture in up to 5% and 7%, respectively, of patients with short-term indwelling urinary catheters.[4] Concentrated efforts to reduce catheter-associated UTI invariably involve early removal of indwelling urinary catheters (IUC). However, in order to facilitate early catheter removal without a large associated risk of catheter reinsertion, targeted efforts must be made to reduce the risk of urinary retention.

Tamsulosin is a selective alpha-1A adrenoreceptor antagonist that has been demonstrated to be effective in treating lower urinary tract symptoms in men with benign prostatic hypertrophy.[5] Furthermore, it is a safe and well-tolerated medication with more minimal cardiovascular effects than other less-selective alpha blockers.[5] It is thought to relieve lower urinary tract symptoms by relaxation of the smooth muscle present in the bladder neck, urethral sphincter, and prostate. Tamsulosin has been studied previously in surgical patients, and was found to reduce the rate of POUR from 21.1% (placebo) to 5.9% in men undergoing varicocelectomy, inguinal hernia repair, and scrotal surgery.[6] It has not previously been studied in broad general surgery populations, and has not been dosed more than approximately 24 hours pre-operatively. Steady-state concentration of tamsulosin is not achieved until the fifth day of once-daily dosing, which the rationale for the longer preoperative treatment duration this this study.

In summary, POUR is a common, and not inconsequential, complication following general surgery procedures. In particular, it results in the need for catheterization, exposing the patient to all of the concomitant risks. Therefore, the ability to prevent urinary retention, thereby mitigating the need for catheterization, would provide significant benefit to surgical patients.

3.0 STUDY AIMS

In this study, we will test the hypothesis that preoperative loading of the alpha-adrenergic receptor inhibitor tamsulosin will decrease the incidence of postoperative urinary retention in patients undergoing elective complex intra-abdominal surgery, thereby also decreasing the rate of UTI and hospital length of stay. To test this hypothesis, we will accomplish the following aims:

3.1 Specific Aim 1: Determine if tamsulosin administered preoperatively and perioperatively is more effective than placebo in preventing postoperative urinary retention in patients undergoing elective, inpatient, complex intra-abdominal surgery.

We hypothesize that patients treated with tamsulosin for 7 days preoperatively and immediately postoperatively will have a lower incidence of postoperative urinary retention and need for catheterization compared to those patients treated with placebo. To test this hypothesis, we will investigate the following sub-aims:

3.1.1 *Aim 1a.* Determine the frequency of postoperative urinary retention in each group, as defined by need for at least a single intermittent catheterization after surgery or following the removal of IUC.

3.1.2 *Aim 1b.* Measure the ability to spontaneously and completely void in patients after the removal of IUC by measuring time until first void, post void residual urine volume, and number of intermittent catheterizations.

3.1.3 *Aim 1c.* Determine the rate of IUC replacement.

3.1.4 *Aim 1d.* Measure frequency of adverse effects of tamsulosin therapy.

3.2 Specific Aim 2: Identify risk factors for postoperative urinary retention based on preoperative characteristics and type of operation, and identify which patient population benefits the most from preoperative tamsulosin therapy.

We hypothesize that there are identifiable patient- and operation-related characteristics that can predict postoperative urinary retention. In testing this hypothesis, the following two sub-aims will be investigated:

3.2.1 *Aim 2a.* Determine what preoperative patient characteristics and operative characteristics predict postoperative urinary retention.

3.2.2 *Aim 2b.* Determine which subgroup of patients derives the greatest benefit from preoperative tamsulosin therapy.

3.3 Specific Aim 3: Determine if preoperative tamsulosin therapy results in improved short-term outcomes.

In this aim, we will test the hypothesis that reducing the rate of postoperative urinary retention leads to decreased rate of UTI and decreased hospital length of stay. We therefore propose the following sub-aims:

3.3.1 *Aim 3a.* Compare and contrast rates of postoperative UTI in patients randomly assigned to tamsulosin therapy compared to those in the placebo arm.

3.3.2 *Aim 3b.* Determine postoperative length of stay in the two groups of patients.

3.4 Endpoints

3.4.1 Primary endpoint

3.4.1.1 Need for any intermittent catheterization after initial IUC removal

3.4.2 Secondary endpoints

3.4.2.1 Need for replacement of IUC
3.4.2.2 Adverse events of tamsulosin and placebo
3.4.2.3 Time from catheter removal, last intermittent catheterization (if performed in the operating room or post-anesthesia care unit), or departure from operating room (if no IUC) until first spontaneous void

3.4.2.4 Total number of intermittent catheterizations required per subject
3.4.2.5 Post void residual urine volume after first spontaneous void, as measured by bladder scanning
3.4.2.6 Need for discharge from the hospital with an IUC
3.4.2.7 Urinary tract infection diagnosed within 30 days of operation
3.4.2.7.1 Defined as a symptomatic, culture-confirmed UTI with $>10^5$ CFU with a single pathogen if diagnosed while inpatient
3.4.2.7.2 Defined as a subject self-reported, clinician-diagnosed UTI (if diagnosed as an outpatient or at another facility)—to be collected over the phone at 30 day follow up contact with subject
3.4.2.8 Hospital length of stay in days

4.0 SELECTION OF PATIENTS

4.1 Study population

Patients will be identified from the general surgery clinics at the University of Wisconsin Hospital and Clinics (UWHC), UW Digestive Health Center (UW DHC), The American Center (TAC), and the UW East Clinic. This includes patients who are being evaluated and worked up for surgery.

4.2 Eligibility Criteria

4.2.1 Inclusion Criteria

Patients must be 18 years of age or older, English-speaking, able to provide informed consent, and scheduled to undergo an elective, complex intra-abdominal operation with a planned postoperative inpatient stay of at least 1 night. Eligible operations will include any of the following operations approached via any operative approach (i.e. open, laparoscopic, hand-assisted laparoscopic, single-incision laparoscopic, or robotic):

4.2.1.1 Partial colectomy
4.2.1.2 Total abdominal colectomy
4.2.1.3 Proctocolectomy
4.2.1.4 Low anterior resection
4.2.1.5 Abdominoperineal resection
4.2.1.6 Restorative proctocolectomy/IPAA
4.2.1.7 Proctopexy (transabdominal) for prolapse
4.2.1.8 Intestinal stricturoplasty
4.2.1.9 Lysis of adhesions
4.2.1.10 End or diverting colostomy reversal
4.2.1.11 Ileostomy reversal
4.2.1.12 Closure of enterocutaneous, enteroenteric, or enterocolic fistula
4.2.1.13 Partial or complete gastrectomy
4.2.1.14 Small bowel resection
4.2.1.15 Small bowel diversion/ostomy

4.2.1.16 Large bowel diversion/ostomy
4.2.1.17 Pancreaticoduodenectomy
4.2.1.18 Pancreatectomy
4.2.1.19 Hepatectomy
4.2.1.20 Gastric bypass
4.2.1.21 Sleeve gastrectomy
4.2.1.22 Nissen/Dor/Toupet fundoplication
4.2.1.23 Transabdominal adrenalectomy
4.2.1.24 Splenectomy
4.2.1.25 Complex abdominal wall hernia repair (i.e. Rives-Stoppa type repair, large laparoscopic ventral hernia repair)
4.2.1.26 Exploratory laparotomy
4.2.1.27 Other comparable complex intra-abdominal operations

4.2.2 Exclusion Criteria

4.2.2.1 Less than age 18
4.2.2.2 Allergy or contraindication to tamsulosin
4.2.2.3 Serious sulfa allergy
4.2.2.4 Current use of alpha blocker (alfuzosin, doxazosin, prazosin, silodosin, terazosin, verapamil, tamsulosin, phenoxybenzamine) or oral alpha agonist (midodrine)
4.2.2.4.1 Initiation of one of these medications during the intervention phase of the study will result in subject withdrawal from the study.
4.2.2.5 Current warfarin use
4.2.2.6 Pre-existing indwelling urinary catheter, suprapubic catheter, or urostomy
4.2.2.7 End stage renal disease or dialysis-dependence
4.2.2.8 Sitting systolic blood pressure in the upper extremity of less than 100mmHg at time of eligibility screening
4.2.2.9 Presence of orthostatic hypotension at the time of eligibility screening
4.2.2.9.1 Orthostatic hypotension is defined as a drop in systolic blood pressure of 20mmHg from sitting to standing, or drop in diastolic BP of 10 mmHg from sitting to standing after 2-3 minutes of standing after being in a sitting position
4.2.2.10 Anticipated inability to take oral medications on post-operative day #0
4.2.2.11 Anticipated requirement for IUC beyond post-operative day #2
4.2.2.12 Non-English speaking
4.2.2.13 Pregnant or breast-feeding
4.2.2.14 Unwillingness to answer all 7 questions on the IPSS survey
4.2.2.15 Lacking capacity to provide informed consent

5.0 RESEARCH DESIGN AND METHODS

5.1 Collaborating sites

There are no collaborating sites. Patients will be identified from the general surgery clinics at UWHC, the UW DHC, The American Center (TAC), and UW East Clinic. All patients enrolled in the study will undergo surgery at, and be admitted to, UWHC.

5.2 Data extraction from medical record

The following information will be extracted from the subject's medical record at the time of preoperative visit, following enrollment in the study: date of birth, age, gender, race, height, weight, information about planned surgery, co-morbidities, past medical history, past surgical history, current medications, allergies, and smoking history. Additional data extracted from the subject's medical record following their operation includes: operation performed, length of operation (minutes), type of anesthesia (general, regional, MAC, local), volume of intravenous fluids administered intra-operatively, estimated blood loss, placement of epidural, type of anesthetic medications used, placement/removal of IUC in the operating room, volume of urine output in the operating room, and whether or not straight catheterization was performed at the conclusion of the case in the operating room.

Data to be extracted from the medical record following discharge from the hospital includes: hospital length of stay (days), whether or not the subject was discharged with an indwelling catheter, diagnosis of urinary tract infection within 30 days of operation, and urine culture data if applicable.

All of the data extracted from a subject's medical record will be entered into the ICTR OnCore Clinical Research Management System.

5.3 Data collection

At the time of the pre-operative visit, following enrollment in the study, subjects will fill out the International Prostate Symptom Score (IPSS) Survey. This survey is a validated, self-administered 7-item questionnaire that assesses obstructive lower urinary tract symptoms. Additionally, subjects will be administered a questionnaire that asks about history of prior problems with urinary retention and prior urinary tract surgeries or procedures, consisting of a total of 3 questions. Subjects may decline to answer the survey questions on the IPSS survey, but this will result in ineligibility for the trial, as IPSS score is a stratification variable for randomization. Subjects may skip the urinary tract surgery/history questions if they feel uncomfortable or embarrassed, and this will not result in exclusion from the study. Case report forms (CRFs) will be utilized to collect data prospectively during the subject's postoperative course while inpatient. This data will be collected by a study team member, and will include time of arrival and departure from the operating room, time of first void, date/time of IUC removal, date/time of first void after catheter removal, first post-void residual volume, date/time of first straight catheterization (if applicable), date/time of all subsequent straight catheterizations (if applicable), date/time of IUC replacement (if applicable), and date/time of the first two adequate voids (if applicable). Finally, subjects will be contacted by telephone 30-

40 days after the date of surgery to ask if they have been treated for a urinary tract infection since discharge from the hospital (in order to capture UTIs that are diagnosed outside of our hospital system). Additionally, data regarding adverse events will be collected using an Adverse Event Log. A study team member will make contact with the subject at two separate time points to inquire about adverse events: 1) on the day of surgery (in person, in the hospital), and 2) postoperatively via telephone call 30-40 days after surgery. Additionally, adverse events will be abstracted from the electronic medical record during the immediate postoperative period. AEs occurring following surgery up until 48 hours after discontinuing study drug will be abstracted from the subject's EMR.

5.4 Confidentiality protections, sharing of data, disposition of data

Subjects enrolled in the study will be sequentially assigned a unique 3-digit study identification number, which will be used to identify the subject throughout the course of the study. The link between the subject's identifiers (i.e. name, MRN, birthdate) and the subject ID will be available in the OnCore system. All data exported from the system will only contain the Subject ID number, and will not contain other subject identifiers.

All paper forms containing subject information or data will be kept locked in the offices of the PI or study coordinator.

5.4.1 ICTR OnCore Clinical Research Management System

This study will utilize the clinical research management software, Online Collaborative Research Environment (OnCore), adopted by the School of Medicine and Public Health (SMPH) and available to all researchers conducting clinical research studies. The instance of OnCore that will be utilized for this study is supported and managed by the UW Institute for Clinical and Translational Research (ICTR). OnCore-CRM has been, and continues to be deployed nationally at multiple academic medical centers, some of which are NIH Clinical and Translational Science Award (CTSA) sites including UW ICTR, and is an extension of technology currently used in more than two dozen Cancer Centers around the country.

ICTR OnCore is a sophisticated, web-based data management system that: a) ensures secure, easy data entry at multiple sites; b) integrates multiple data sources such as individual studies and patient registries; c) provides controlled, secure access to sensitive data using role-based access control; d) provides workflow automation; and e) allows export and reporting of data for Data and Safety Monitoring Boards and biostatisticians.

This software provides protocol management functions (e.g. subject scheduling; screening, data organization), maintains updated forms, addresses budget development, billing, and fiscal management, generates summary reports, and provides essential links with other research administration and electronic medical records systems. ICTR OnCore eases the burden of the individual researcher and unifies protocol management within research programs and including researchers at multiple sites, enhancing protocol integrity and regulatory compliance efforts.

Current Status: Both UW ICTR and SMPH are committed to the use of ICTR OnCore on an enterprise-wide scale. ICTR OnCore completed the initial pilot phase in 2009 and has been fully implemented for all clinical research groups across the infrastructure. Many workflows and processes have been identified and standardized within ICTR OnCore for use across the spectrum.

ICTR OnCore-CRM is hosted by the UW School of Medicine and Public Health (SMPH) Information Technology (IT) Office on its server farm with redundant systems at two, environments are maintained for production, training, and testing. The application-programming model employed in ICTR OnCore-CRM conforms to the Java 2 Platform, Enterprise Edition (J2EE) standard for web-based applications. J2EE is a widely accepted standard for developing multi-tier enterprise applications and is based on standardized, modular components. The J2EE standard includes compliance tests to ensure portability of applications. In addition to portability, J2EE provides a JDBC API for database access and a proven security model that is applicable to Internet applications. J2EE also supports Enterprise JavaBeans components, Java Servlets API, JavaServer Pages, and XML technology. The ICTR OnCore-CRM application uses these, Apache Web services, and an application server (JBoss/TomCat). The backend is an Oracle® relational database management system maintained by SMPH IT. Both the database and application servers are behind a firewall maintained by SMPH IT staff. Several complete environments are maintained for production, training, testing, and validation. This provides for a high level of system security and reliability.

The data collected during the course of the study will be stored in OnCore. However, as is necessary for the completion of remote data analysis and travel to/from conferences where data may be presented, data exported from OnCore may be transferred to a limited number of password-protected and encrypted laptops belonging to study staff as necessary. In this case, data would be stored on a password protected and encrypted USB drive in order to transfer data to the laptop. Laptops and USB drives will only contain data that has been exported from OnCore and containing only Subject ID number without associated subject identifiers. Only study staff will have access to such USB drives and laptops. Laptops and USB drives will not contain the key to the code.

The clinical research pharmacy will maintain the randomization code sheet, and this will not be made accessible to other study team members until completion of the study (or at interim data and safety monitoring analysis). Unblinding at interim data analysis will only occur for subjects whose data collection is complete.

5.5 Sub-studies/correlative studies

The data collected during this study will be used to retrospectively identify risk factors that are associated with urinary retention as described in Specific Aim 2. This analysis will be performed both on the placebo treated group alone and the overall study population. Logistic regression will be used for this analysis. The response variable will be the primary endpoint (need for any

intermittent catheterization). The various preoperative and operative variables collected during the study will be used as predictor variables in this analysis.

5.6 Timeline

5.6.1 Screening for eligibility

Pre-screening of general surgery clinic patients will occur prior to initial contact. If a patient is found to be eligible on pre-screening and upon contact has expressed interest in learning more about the study, then formal screening for eligibility will occur after informed consent is obtained. If the subject is determined to be potentially eligible based on the gross eligibility criteria reviewed during the pre-screening process, the subject will be invited to learn more about the study. If the patient is interested in participating in the study at that time, the enrollment protocol, including obtaining informed consent, will be initiated. If the patient has another scheduled preoperative visit that will occur more than one week prior to their scheduled surgery date, then the informed consent and enrollment procedures may be deferred until the next visit. Likewise, if the patient does not have another preoperative clinic visit appointment scheduled, but would like more time to make a decision about participation in the study, arrangements will be made for future follow up with a study team member as described below.

5.6.2 Consent/Enrollment/Baseline

After the pre-screening procedures determine the subject may be potentially eligible, and the subject has expressed an interest in participating in the study, we will proceed with the informed consent process (either at the initial or subsequent preoperative clinic visit). As part of formal screening for eligibility, all women of childbearing age and potential will be given a pregnancy test. Upon completion of the screening procedures, and determination that the subject is eligible to participate, the individual will be considered enrolled in the study. Due to constraints of the study related to the medication starting 7 days preoperatively, consent and enrollment must be completed at least 7 days prior to the scheduled surgery. If after the initial clinic visit, the patient has another scheduled preoperative clinic visit prior to 7 days preoperatively, then the patient will be given the opportunity to take the consent form home if they so desire, and then signed informed consent will be obtained at the next clinic visit if applicable. If, however, the patient does not have an additional preoperative clinic visit scheduled and needs additional time to consider participation in the study, he or she may bring written materials home and study personnel will follow up via telephone call. If the patient is interested in participating in the study, then a visit will be arranged with the study coordinator (prior to 7 days preoperatively) for the patient to sign the consent form, undergo formal eligibility screening, and complete enrollment.

After enrollment, the subject will fill out the first data collection form, which includes the IPSS survey and questionnaire regarding history of previous urinary retention and urinary tract surgery or procedures. The subject may choose to

decline to answer any of the IPSS survey questions, however, this will result in exclusion from the study, as IPSS score is being used for stratification in the randomization process. Following completion of the IPSS survey, the subject will be randomized by the clinical research pharmacy. The subject will be given a 14-day supply of tamsulosin or placebo, according to randomization, along with instructions for taking the medication.

5.6.3 Treatment period

Treatment will start 7 days prior to scheduled surgery and will continue post-operatively for up to 7 days while the subject is still in the hospital (for a total of 14 doses). A member of the study team will contact the subject via telephone as a reminder on the day that treatment is to be initiated. If a subject discontinues study treatment (chooses to withdraw from the study) prior to their scheduled surgery, the subject will be discontinued and replaced, and reason for withdraw from study will be noted. Data will continued to be collected for these subjects and their data will be included on an intent-to-treat basis, but they will be replaced for sample size. If the subject discontinues study drug any time after their surgery, the subject will be followed with intent to treat and will not be replaced. If a subject's planned surgery is postponed PRIOR to initiation of treatment but is rescheduled to within 30 days of when the subject was randomized, then the subject may stay enrolled in the trial, will keep their same treatment assignment, and will be given a new start date for treatment (7 days before their rescheduled surgery date). If, however, the surgery is postponed or cancelled AFTER initiation of treatment, then the subject will be taken off treatment and discontinued from the study. If the subject has not yet initiated treatment and their surgery is rescheduled to a date that is more than 30 days from the date of randomization, the subject will be discontinued.

Once a subject completes the bladder management protocol (is voiding spontaneously and completely—specifically, 2 consecutive voids with PVR less than 200mL) OR requires replacement of an IUC, the treatment will be discontinued within 24 hours, and the protocol is complete. The protocol may be completed as early as POD#0. The maximum number of days of treatment will be 14 (up until POD#6, i.e. last dose given in the evening of POD#6). No subjects will be discharged from the hospital on study medication.

5.6.4 Follow-up

A member of the study team will contact the subject via telephone approximately 30-40 days after surgery to ask about adverse events and to inquire about urinary tract infection and voiding problems. Subjects will be asked about diagnosis of urinary tract infection since leaving the hospital, and chart review will be performed by study personnel to ascertain the diagnosis of urinary tract infection.

As part of standard of care, most subjects will also have a scheduled post-operative follow up visit in the General Surgery clinic with their surgeon, usually 2-3 weeks following the date of surgery. In general, if a patient is discharged from the hospital

with an IUC, it is standard to have the patient follow up in the Urology Voiding Clinic; however, this would be outside of the scope of this study protocol.

5.6.5 Final study encounter

The final study encounter will be the follow up phone call on or around post-operative day #30 for all subjects (30-40 days after surgery). A study team member will contact the subject via telephone to ask if he/she has been treated for a urinary tract infection since discharge from the hospital (in order to capture UTIs treated outside of the UW system), and to inquire about adverse events since discharge from the hospital.

5.6.6 Early termination visit

If a subject wishes to terminate their enrollment in the study early, no visit will be required, and this decision will have no bearing on the individual's clinical care. If enrollment is terminated after surgery, then the subject will not be replaced. If enrollment is terminated prior to surgery, the subject will be replaced.

6.0 REGISTRATION PROCEDURES

All subjects will be registered prior to beginning the protocol treatment. The following information will be included in registration:

Subject name, address, telephone number, birth date, sex, race
Primary disease site, planned operation
Date on study
Date randomized
Staff physician
Protocol number

7.0 TREATMENT PLAN

7.1 Administration Schedule

7.1.1 Treatment ARM A—tamsulosin:

Tamsulosin 0.4mg capsule orally one time per day, to be taken 30 minutes after dinner or before bed starting 7 days before surgery and continuing for 0-6 days post-operatively. Outline of schedule:

Day 1: tamsulosin 0.4mg in the evening
Day 2: tamsulosin 0.4mg in the evening
Day 3: tamsulosin 0.4mg in the evening
Day 4: tamsulosin 0.4mg in the evening

Day 5: tamsulosin 0.4mg in the evening
Day 6: tamsulosin 0.4mg in the evening
Day 7: tamsulosin 0.4mg in the evening
Day 8: surgery
Day 8: tamsulosin 0.4mg in the evening (same day as surgery) if the subject has not yet completed the bladder management protocol
Day 9-14: tamsulosin 0.4mg in the evening until up to 24 hours after the subject has an indwelling urinary catheter replaced (at which time the protocol stops) or the subject completes the bladder management protocol (has voided twice consecutively with a post-void residual <200mL). The minimum number of total doses is 7; the maximum number of total doses is 14. The 14th dose will be the final dose regardless of bladder function. No subjects will be discharged from the hospital on study medication.

7.1.2 Treatment ARM B—placebo:

Placebo capsule orally dosed exactly as outlined above for Treatment ARM A

7.2 Adverse Event Reporting Requirements

An adverse event log will be maintained for each enrolled subject. Adverse event screening will occur at three time points: 1) on the day of surgery either pre- or post- operatively (in person, in the hospital, via interview of the subject by a study team member), 2) during the postoperative period for the period from surgery until 48 hours after completion of the intervention (via abstraction of AEs from the subject's EMR), and 3) 30-40 days after surgery (via telephone interview of the subject by a study team member). Safety data will be monitored and analyzed by an external Data Monitoring Committee (through ICTR), and unanticipated problems or complications will be reported to the IRB per its reporting guidelines. Unexpected or severe adverse events will also be reported to the PI within 72 hours of identification.

7.3 Dose Modifications

Dose modifications will not be made in this study. If a subject has an intolerable adverse event or side effects related to the study treatment, the drug will be discontinued and the subject will be removed from the protocol. Follow up outcome data will still be collected to allow for intent-to-treat analysis.

7.4 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

7.5 Duration of Therapy

Treatment will be discontinued within 24 hours of the subject's completion of the bladder management protocol with return of normal bladder function (2 consecutive voids with PVR less than 200mL) or requirement of IUC re-insertion for urinary retention. The maximum number of doses (days) of treatment is 14. If ongoing urinary retention is present, further management

will be deferred to the treating physician team. This sometimes involves initiation of a short course of alpha-blockers in conjunction with IUC, followed by a spontaneous voiding trial.

8.0 STUDY PARAMETERS

Component	Description	Timing	Contact points
Pre-screening for eligibility	The electronic medical records of prospective subjects will be pre-screening for eligibility by a study team member.	After the patient is scheduled in the general surgery clinic, prior to actual appointment.	Study team member
Invitation to participate in study	If the patient is eligible based on pre-screening, the patient will be informed about the study and asked about interest in participating.	At initial or subsequent pre-operative general surgery clinic appointment	Surgeon, resident, nurse practitioner, or study team member
Informed consent	If the patient is eligible for the study, he/she will be given a copy of the informed consent and the informed consent process will occur.	Either initial pre-operative clinic visit, or subsequent pre-operative clinic visit if scheduled more than 1 week prior to the date of surgery	Surgeon, resident, or study team member
Formal screening for eligibility	The Eligibility Checklist will be completed by a study team member with the patient. Includes pregnancy test in women of childbearing age and potential.	At initial or subsequent pre-operative general surgery clinic appointment	Study team member
Enrollment	Enrollment in the study and registration.	After informed consent process at preoperative clinic visit.	Study team member
IPSS Survey (R)	Validated survey of lower urinary tract symptoms to be completed by the subject	Pre-operative clinic visit, after enrollment	Study team member

Component	Description	Timing	Contact points
Urinary history questionnaire (R)	Short questionnaire (3 questions) regarding history of urinary retention and prior urinary tract surgery or procedures	Pre-operative clinic visit, after enrollment	Study team member
Randomization	Random allocation by the PRC to either the tamsulosin group or the placebo group	Preoperative clinic visit, after enrollment.	PRC
Reminder phone call (R)	Phone call or text message from study personnel to subject on Study day 1 to remind subject to start taking the drug/placebo	Study day 1	Study team member
Pre-operative treatment with study drug (R)	Dosing of tamsulosin or placebo as described in section 7.1	Study days 1-7	Subject to self-administer at home
Screening for adverse events, time 1 of 3	Study personnel will ask subject about treatment-emergent adverse events occurring during the preoperative phase of intervention	Study day 8, pre or post operatively	Study team member
Operation (SOC)	Elective inpatient complex intra-abdominal surgery as scheduled	Study day 8	Surgeon
Post-operative treatment with study drug (R)	Dosing of tamsulosin or placebo as described in section 7.1	Study days 8-14, or discontinued prior to day 14 based on completion of bladder management protocol or re-insertion of IUC	Administered by subject's RN
Bladder management protocol (see appendix) (SOC)	Monitoring of bladder volume via supra-pubic ultrasound, measurement of post-void residual volume, intermittent catheterization as needed	Postoperatively, while inpatient (Days 8-14)	Subject's RN
Screening for adverse events, time 2 of 3	Study personnel will perform review of the	From day of surgery until 48 hours after	Study team member

Component	Description	Timing	Contact points
	EMR to abstract AEs occurring during the postoperative phase of intervention	completing the intervention	
Final study visit (R)	Telephone call to subject by study team personnel	30-40 days after surgery	Study team member
Screening for adverse events, time 3 of 3 (R)	Study personnel will ask subject about treatment-emergent adverse events occurring during the post-intervention phase of trial (up to 30 days after surgery)	30-40 days after surgery via telephone call, will be combined with inquiry about UTI (see below)	Study team member
Inquiry about diagnosis of UTI (R)	Telephone call to patient 30 days after surgery to inquire about whether the patient has been treated for a UTI since surgery; chart review for UTI diagnosis within our institutional EMR	30-40 days after surgery via telephone call (will be combined with above phone call)/chart review	Study team member

9.0 DRUG FORMULATION AND PROCUREMENT

9.1 Tamsulosin hydrochloride (NDC 0597-0058-01)

9.1.1 Other names: FLOMAX

9.1.2 Classification: alpha$_{1A}$ adrenoceptor antagonist

9.1.3 Mode of Action: Tamsulosin works by blocking alpha$_{1A}$ adrenergic receptors in the prostate, prostatic urethra, and bladder neck, which results in relaxation of the smooth muscles in the bladder neck and prostate, thereby reducing bladder outlet obstruction.

9.1.4 Storage and stability

Stored at 25 degrees Celsius (77 degrees F); excursions permitted to 15 degrees C to 30 degrees C (59 degrees F to 86 degrees F)

9.1.5 Dose specifics: 0.4mg orally dosed one time per day, 30 minutes after a meal, in the evening

9.1.6 Preparation: capsule

9.1.7 Route of administration: orally; capsules should not be crushed, chewed, or opened

9.1.8 Incompatibilities

9.1.8.1 Other alpha-adrenergic blockers

Per package insert: "The pharmacokinetic and pharmacodynamic interactions between FLOMAX capsules and other alpha-adrenergic blocking agents have not been determined. However, interactions may be expected and FLOMAX capsules should NOT be used in combination with other alpha-adrenergic blocking agents." Patients taking concomitant alpha blockers (including verapamil, which has alpha blockade action at therapeutic doses) will be excluded from the study.

9.1.8.2 Cimetidine

Per package insert: "The pharmacokinetic interaction between cimetidine and FLOMAX capsules was investigated. The results indicate significant changes in tamsulosin HCl clearance (26% decrease) and AUC (44% increase). Therefore, FLOMAX capsules should be used with caution in combination with cimetidine, particularly at doses higher than 0.4 mg." Patients taking cimetidine will still be eligible for the study, but will be notified about potential increased risk of side effects.

9.1.8.3 Warfarin

Per package insert: "A definitive drug-drug interaction study between tamsulosin hydrochloride and warfarin was not conducted. Results from limited *in vitro* and *in vivo* studies are inconclusive. Therefore, caution should be exercised with concomitant administration of warfarin and FLOMAX capsules." We will exclude patients taking warfarin.

9.1.8.4 Strong inhibitors of CYP3A4 (boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) and CYP2D6 (bupropion, fluoxetine, paroxetine, quinidine)

It is recommended that doses higher than 0.4mg daily should not be used in combination with strong inhibitors of CYP3A4 or CYP2D6 and that caution should be exercised when using tamsulosin in combination with such drugs. Studies have demonstrated an increased AUC and C_{max} when tamsulosin is taken in combination with strong inhibitors of CYP2D6 or CYP3A4, but these increases have been shown to still fall equivalently or below the higher U.S. dosage of 0.8mg daily. One study specifically examining clinical effects (i.e. orthostasis) of

concomitant tamsulosin/paroxetine and tamsulosin/ketoconazole found no significant clinical effect of these medications being co-administered. Patients taking strong inhibitors of CYP3A4 or CYP2D6 will not be excluded from the study, however they will be advised about potential increased risk of side effects.

9.1.9 Availability: commercially available

9.1.10 Side effects (reported in package insert; data derived from two U.S. clinical trials (US92-03A and US93-01)[7,8]:

	Tamsulosin 0.4mg (n=502)	Placebo (n=493)
Body as whole		
Headache	97 (19.3%)	99 (20.1%)
Infection	45 (9.0%)	37 (7.5%)
Asthenia	39 (7.8%)	27 (5.5%)
Back pain	35 (7.0%)	27 (5.5%)
Chest pain	20 (4.0%)	18 (3.7%)
Nervous System		
Dizziness	75 (14.9%)	50 (10.1%)
Somnolence	15 (3.0%)	8 (1.6%)
Insomnia	12 (2.4%)	3 (0.6%)
Libido decreased	5 (1.0%)	6 (1.2%)
Respiratory System		
Rhinitis	66 (13.1%)	41 (8.3%)
Pharyngitis	29 (5.8%)	23 (4.7%)
Cough increased	17 (3.4%)	12 (2.4%)
Sinusitis	11 (2.2%)	8 (1.6%)
Digestive System		
Diarrhea	31 (6.2%)	22 (4.5%)
Nausea	13 (2.6%)	16 (3.2%)
Tooth disorder	6 (1.2%)	7 (1.4%)
Urogenital System		
Abnormal ejaculation	42 (8.4%)	1 (0.2%)
Special Senses		
Blurred vision	1 (0.2%)	2 (0.4%)

Table reproduced (with modification) from Flomax package insert.

In the two U.S. clinical trials referenced above, symptomatic postural hypotension occurred in 0.2% of men treated with tamsulosin 0.4mg vs. no patients in the placebo groups. Syncope occurred in 0.2% of men treated with tamsulosin 0.4mg vs. 0.6% in the placebo groups. Multiple testing for orthostatic hypotension was also performed in these studies, and demonstrated a 16% rate of at least one positive orthostatic test result in the tamsulosin 0.4mg subjects, vs. 11% rate in the placebo group.[7,8]

No men in the tamsulosin 0.4mg group or placebo group discontinued treatment due to abnormal ejaculation.

In a double-blind RCT comparing tamsulosin 0.2mg to placebo in 140 women over a 4-week period, there were 2 patients out of 70 in the tamsulosin group who had dizziness and asthenia (2.9%) compared to no adverse effects reported in the placebo group.[9]

9.1.10.1 Incidence not known (Post-marketing experience)

9.1.10.1.1 Allergic reactions including skin rash, pruritus, angioedema of tongue, lips and face, urticarial. This has been reported in patients with severe sulfa allergy, and therefore severe sulfa allergy is one of the exclusion criteria for this study.
9.1.10.1.2 skin desquamation
9.1.10.1.3 Priapism (probably less than 1 in 50,000 patients)
9.1.10.1.4 palpitations
9.1.10.1.5 hypotension
9.1.10.1.6 constipation
9.1.10.1.7 vomiting
9.1.10.1.8 Intraoperative Floppy Iris Syndrome (IFIS): This is a clinical syndrome of a flaccid billowing iris, iris prolapse, and pupil constriction that has been described during cataract surgery and has been associated with tamsulosin. This syndrome increases the difficulty of performing cataract surgery and increases the rate of complications associated with cataract surgery.[10] It has been found to occur even up to a year after discontinuation of tamsulosin, and possibly longer.[11] However, one prospective study evaluating outcomes after surgery in which IFIS was present found that when surgeons were aware of prior or current tamsulosin use, they were able to employ compensatory techniques resulting in a low complication rate.[11]

9.1.11 Nursing implications

Nursing staff would administer the study medication when the patient is in the hospital.

10.0 STATISTICAL CONSIDERATIONS

10.1 Randomization and stratification

Subjects will be stratified by gender, pelvic/non-pelvic surgery, and high vs low IPSS score (which “high” defined as >=8, and “low” <=7) prior to randomization. Subjects will be randomized with a 50/50 chance of being allocated to active drug or placebo. Randomization will be performed by the Pharmaceutical Research Center, and the code sheet for randomization will be kept by the PRC. Unblinding of study team members will only occur for

interim data analysis, which will be performed between May 15 and May 30, 2016. Only subjects for who complete data collection (including 30-day postoperative outcomes) has been obtained will be unblinded at that time.

For purposes of stratification, “pelvic” operations include the following: surgery involving the rectum (colorectal anastomosis, ileo-rectal anastomosis, IPAA, proctopexy, proctocolectomy, proctectomy, LAR, and APR).

10.2 Sample size

In this study, we propose to compare a group of subjects given a placebo and a group given tamsulosin in order to prevent postoperative urinary retention. The primary endpoint is need for at least a single intermittent catheterization, treated as a binary outcome. Secondary endpoints include need for indwelling catheter replacement (binary), time until first void (continuous), number of intermittent catheterizations (numeric), post-void residual urine volumes (continuous), UTI rates (binary), and length of stay (continuous). The sample size calculation is based on the primary endpoint. We will employ a two-tailed, two sample test for equality of proportions (chi-squared or Fisher's exact) at a significance level of 0.05 (equivalent to one-tailed alpha of 0.025) in order to compare urinary retention rates as measured by our primary outcome. Based on pilot data and information from the literature, we anticipate that 30% of the placebo group will experience urinary retention, and that the tamsulosin group will see a 50% reduction to a 15% urinary retention rate. In order to achieve at least 80% power for detecting a significant group difference, we will need 134 subjects included in each study arm, or a total of 268 subjects. However, to provide for a 10% drop out rate, we would need to plan to enroll 147 subjects in each arm, yielding an enrollment goal of 294 subjects.

10.3 Error levels

Two-sided type I error level is set at 0.05, and type II error level is 0.20.

10.4 Differences to be detected for comparative studies

Based on institutional urinary retention rates and information from the literature, we anticipate that 30% of the placebo group will experience urinary retention, and that the tamsulosin group will see a 50% reduction to a 15% urinary retention rate. This is the pre-specified difference in the primary outcome that the study is designed to detect at a two-tailed significance level of 0.05 and power of 80%. The secondary outcomes that will be compared include need for indwelling catheter replacement, time until first void, number of intermittent catheterizations, post-void residual urine volumes, UTI rates, and length of stay. These secondary outcomes can be thought of as more hypothesis-generating. We acknowledge that we may not be powered to achieve statistical significance for our secondary outcome measures.

10.5 Estimated accrual rate / study duration

The estimated sample size needed to achieve the pre-specified statistical significance and power is a total of 268 subjects (134 subjects in each arm). Subjects that withdraw from the study prior to surgery will be replaced. We estimate that there will be a 10% drop-out rate, and therefore the enrollment goal to account for drop-outs is estimated to be 294 subjects (147 in each arm) in order to achieve an actual sample size of 268 subjects. We initially predicted that we would need to replace subjects that received epidural anesthesia, but the interim analysis showed no significant difference in response between epidural and non-epidural patients.

The estimated accrual rate is approximately 1-2 subjects per week. In order to enroll a total of 294 subjects, this would take approximately 147-294 weeks, or 2.8-5.7 years. After enrollment of the final subject, data collection will continue for 30 days beyond that subject's date of surgery. Expected study duration is approximately 3-6 years from the time that enrollment begins.

10.6 Stopping rules

The trial will be stopped if at interim data analysis there is a highly significant difference ($p<0.001$) between the tamsulosin group and the placebo group in the primary outcome. Data monitoring will be performed by the ICTR DMC every 6-12 months as needed. The single planned interim data analysis will be performed between May 15 and May 30, 2016, by the PI (Evie Carchman), Greg Kennedy, Christina Papageorge, and Glen Leverson for the purposes of a Master's thesis project. If the rate of either priapism or syncope in the tamsulosin group exceeds that of the placebo group by an absolute value of 10%, then the study will be stopped.

10.7 Primary endpoint for interim and final analysis

The primary endpoint for interim and final analysis is need for any intermittent catheterization after initial IUC removal. This outcome will be compared primarily with an intent-to-treat analysis. However, we will also perform an as-treated analysis. Compliance will be measured based on pill-counts. A subject will be considered "compliant" if greater than or equal to 70% of the pills that were supposed to be taken were actually taken.

10.8 Hypotheses

10.8.1 Primary

10.8.1.1 We hypothesize that subjects treated with tamsulosin will have a decreased need for intermittent catheterization after initial IUC removal compared to those treated with placebo.

10.8.2 Secondary

10.8.2.1 Subjects treated with tamsulosin will have a lower rate of IUC replacement compared to those treated with placebo.

10.8.2.2 Subjects treated with tamsulosin will have a higher incidence of abnormal ejaculation, dizziness, and orthostasis compared to those treated with placebo.

10.8.2.3 Subjects treated with tamsulosin will have a shorter time until first spontaneous void compared to those treated with placebo.

10.8.2.4 Subjects treated with tamsulosin will have a fewer number of total intermittent catheterizations required per subject compared to those treated with placebo.

10.8.2.5 The tamsulosin group will have a smaller average post void residual urine volume after first spontaneous void compared to the placebo group.

10.8.2.6 The tamsulosin group will have a smaller proportion of patients being discharged from the hospital with an IUC compared to the placebo group.

10.8.2.7 The tamsulosin group will have a lower incidence of urinary tract infection diagnosed within 30 days of operation compared to the placebo group.

10.8.2.8 Subjects treated with tamsulosin will have a shorter average hospital length of stay (in days) compared to those treated with placebo.

10.8.2.9 Male gender, high preoperative IPSS score, older age, pelvic operations, larger volume of intraoperative fluids, and epidural anesthesia will be risk factors for POUR.

10.8.2.10 Higher risk patient groups will be most likely to benefit from tamsulosin therapy for the prevention of POUR.

10.9 Maximum number of subjects

We have allowed for a 10% drop out in our enrollment goal calculation. If, however, drop-out rate exceeds the allowed 10%, we will enroll additional subjects to maintain 80% power at a 0.05 significance level. As a contingency plan, the maximum number of subjects we will enroll will be based on a 30% drop out rate. This would yield a maximum number of subjects in each arm of 174, or a total maximum enrollment of 348 subjects.

10.10 Plan for analysis

To analyze differences between the tamsulosin group and the placebo group with regards to the primary outcomes, we will employ a one-tailed, two sample test of proportions (Chi-squared or Fisher's exact) at a two-tailed significance level of 0.05 in order to compare urinary retention rates, as defined by need for at least a single intermittent catheterization. This analysis will be performed primarily with an intent-to-treat analysis. However, we will also perform an as-treated analysis. Compliance for the as-treated analysis will be measured based on pill-counts and subject report. A subject will be considered "compliant" if greater

than or equal to 70% of the pills that were supposed to be taken were actually taken, and crossover from placebo to active drug did not occur. Additionally, this analysis will be performed both including and excluding the subjects who receive epidural anesthesia.

The secondary outcomes will be analyzed using either Chi-squared or Fisher's exact tests for binary outcome measures, and Student t-tests for continuous outcome variables.

The retrospective study to identify risk factors for POUR will be a logistic regression using our primary outcome as the response variable and the various preoperative and operative variables as the predictor variables. We plan to look at risk factors both in the placebo cohort alone and the overall sample of all patients. We will quantify the risks of each variable with odds ratios.

In order to identify groups of patients most likely to benefit from tamsulosin, we will perform chi-squared or Fisher's exact tests on subgroups of patients to identify variables that are associated with POUR, and then create interaction variables between tamsulosin and the key factors identified in the initial analysis. We will also employ binary logistic regression in this analysis to identify odds ratios for the interaction variables.

The interim analysis will be a two-sided two sample test of proportions (Chi-squared or Fisher's exact) at a two-tailed alpha of 0.001 comparing differences in the primary outcome between the tamsulosin and placebo groups. Given the very small p value chosen for interim analysis there will be little to no inflation of the overall type I error for the study.

11.0 RECORDS TO BE KEPT

11.1 Personnel in charge of managing study data

Study data will be primarily managed by the study coordinator and sub investigator.

11.2 Confidentiality

Subjects enrolled in the study will be sequentially assigned a unique 3-digit study identification number, which will be used to identify the subject throughout the course of the study. The link between the subject's identifiers (i.e. name, MRN, birthdate) and the subject ID will be available in the OnCore system. All data exported from the system will only contain the Subject ID number, and will not contain other subject identifiers.

All paper forms containing patient information or data will be kept locked in the offices of the PI or study coordinator.

The data collected during the course of the study will be stored in the OnCore system. OnCore is an electronic data management system that will be used to capture, edit, manage, and export study data for analysis.

Subject identifiable information is restricted at multiple levels. The research team will manage study data through OnCore. Access to the OnCore system is restricted to those that have

been granted access by the software administrators. User access requires supervisor approval, completion of HIPAA and Human Subjects Protection training, and completion of role-based training in the OnCore system. In addition, users' access is limited to protocols for which they have some responsibility of protocol, subject, or data management. Within those protocols, the ability to view and modify data is restricted based on their role in the conduct of the research project (e.g. regulatory staff do not have the privilege to view subject identifiable information).

In addition, the technical components of this software are managed by the UW-Madison's School of Medicine and Public Health Information Technology Office (for server maintenance, software upgrades, etc.), and security and software support is provided by ICTR administrative staff. SMPH IT and ICTR administrative staff are able to access subject information in order to help end users of the software program when questions arise.

All communication between the clients and the OnCore application takes place via Hypertext Transfer Protocol over Secure Socket Layer or HTTPS. HTTPS provide the ability for normal web based communication over an encrypted Secure Socket Layer (SSL) connection. This ensures that data passing between the client and OnCore is protected from unauthorized attempts to access the data.

Data that is exported from the OnCore system will be coded. As is necessary for the completion of remote data analysis and travel to/from conferences where data may be presented, this coded data may be transferred to a limited number of password-protected and encrypted laptops belonging to study staff as necessary. In this case, data would be stored on a password protected and encrypted USB drive in order to transfer data to the laptop. Laptops and USB drives will only contain coded data, and will be used only as necessary as described above. Only study staff will have access to such USB drives and laptops. Laptops and USB drives will not contain the key to the code.

11.3 Data collection methods

Data not readily available in the EMR will be collected using Case Report Forms. Data will be collected from subjects' electronic medical records and subject self-report by a study team member. Prospective data regarding bladder function will be collected by a study team member while the subject is inpatient. Data regarding AEs and UPs will be collected using a form (Adverse Event Log) by a study team member via interview of the subject or abstraction from the EMR. Data regarding treatment for UTI will be collected over the phone by a study team member 30-40 days after the date of surgery and via chart review. Subjects will be identified on the data collection forms by their unique study ID number. Data will be compiled into a single database in OnCore.

11.4 Data management

Online Collaborative Research Environment (OnCore) will serve as the Clinical Trial Management System for this study. ICTR OnCore is supported by the UW School of Medicine and Public Health Information Technology (SMPH-IT) staff and managed by the UW ICTR Clinical Research Infrastructure System (CRIS).

OnCore is a sophisticated, web-based data management system that: a) ensures secure, easy data entry at multiple sites; b) integrates multiple data sources; c) provides controlled, secure access to sensitive data using role-based access control; d) provides workflow automation; and e) allows export and reporting of data for Data and Safety Monitoring Boards and biostatisticians.

This software provides protocol management functions (e.g. subject scheduling; screening, data organization), maintains updated forms, addresses budget development, billing, and fiscal management, generates summary reports, and provides essential links with other research administration and electronic medical records systems. ICTR OnCore eases the burden of the individual researcher and unifies protocol management within research programs and across research sites, enhancing protocol integrity and regulatory compliance efforts.

The ICTR OnCore support team will work with the investigator and study team to ensure that relevant, applicable study data are collected and entered into electronic Case Report Forms (eCRFs) through a secure web-based system with restricted access.

11.5 Duration of study records

Paper study records and the study master list will be destroyed once all data is transcribed into the database, analyzed, and published, no sooner than 7 years after completion of the study. The data in OnCore will remain indefinitely, until the study team requests the data be manually deleted. A de-identified version of the database will be kept indefinitely for possible future studies.

12.0 PATIENT CONSENT AND PEER JUDGMENT

Current FDA, NCI, state, federal, and institutional regulations concerning informed consent will be followed.

Waiver of informed consent will be used for screening review of eligibility for potential subjects. If deemed eligible, the study will be discussed with a prospective subject, and if the subject is interested, the informed consent process will proceed, culminating with signed consent documentation.

Potential subjects will be given written and verbal information about the study, and will be given time to ask any questions, prior to providing signed informed consent. Due to constraints of the study related to the medication starting 7 days preoperatively, consent and enrollment must be completed at least 7 days prior to the scheduled surgery. If after the initial clinic visit, the patient has another scheduled preoperative clinic visit prior to 7 days preoperatively, then the patient will be given the opportunity to take the consent form home if they so desire, and then signed informed consent will be obtained at the next clinic visit. If that clinic visit is the patient's last clinic visit prior to the date of surgery, informed consent will be obtained at that time unless the patient needs additional time to consider participation. If the patient needs additional time to consider participation in the study, he or she may bring written materials home and study

personnel will follow up via telephone call. If the patient is interested in participating in the study, then a visit will be arranged with a study team member (prior to 7 days preoperatively) for the patient to sign the consent form and complete enrollment.

The consent process will occur in a private clinic room or office.

13.0 DATA AND SAFETY MONITORING

An adverse event log will be maintained for all subjects enrolled in the study. A member of the study team will directly inquire about adverse events (via interview of the subject) when the subject reports to the hospital on the day of surgery (after 7 days of taking the study medication). The adverse event log will be updated again based on AEs reported in the EMR from the time of surgery until 48 hours after completion of the intervention portion of the study, and finally a third time via telephone call 30-40 days after surgery. Four study team members (Evie Carchman, Greg Kennedy, Christina Papageorge, and Glen Leverson) will meet between May 15 and May 30, 2016, to perform interim data analysis on primary endpoint data for the purposes of a Master's research project.

13.1 Data Monitoring Committee

We plan to utilize the UW ICTR Data Monitoring Committee (DMC) to oversee the study. The UW ICTR DMC is co-chaired by Dave DeMets and Norm Fost and is comprised of experienced members (core plus ad hoc) with expertise required to oversee this study. The DMC members will review protocol-specific reports created by statisticians using data pulled from the ICTR OnCore clinical research management system. These standard reports will include an overview of study objectives, a review of actual and projected accrual rates, an evaluation of patient demographics for balance of randomization, and a summary of the number and seriousness of adverse events. An interim analysis of study results may be performed and source documents may be reviewed to allow the DMC to independently judge whether the overall integrity and conduct of the protocol remain acceptable based on data provided and reported by the Principal Investigator. The DMC will make recommendations to the Principal Investigator that could include actions of continuation, modification or termination.

In providing oversight for the conduct of this study, the ICTR DMC will meet every 6 months during the 3-year study to review all adverse events. The predefined stopping points for this study will include excess rates of syncope, or priapism requiring medical treatment. The boundary for excess harm will be an incidence of syncope or priapism in the tamsulosin group that exceeds that of the placebo group by an absolute value of 5%, or an observed excess harm which in the judgment of the DMC, is excessive. We will report all serious adverse events to the DMC and the IRB oversight committee, the Health Sciences IRB in accordance with their reporting guidelines.

The individuals responsible for data and safety monitoring are independent of the researchers.

If a subject prematurely withdraws from the study, then a study team member will call the patient (or visit the patient in the hospital) to inquire about adverse events.

Between May 15-30, 2016, unblinding will occur for subjects for which complete data collection (30 days from operation) has been achieved, and interim data analysis will then be performed by Evie Carchman (the PI), Greg Kennedy, Christina Papageorge, and Glen Leverson for purposes of a Master's research project.

13.2 Study Monitoring Service (SMS)

While many institutions involved in clinical research conduct various types of quality assurance reviews and audits, UW ICTR is one of a few institutions to offer Study Monitor of Record services, a robust academic equivalent to the industry Contract Research Organization (CRO) standards for ongoing study monitoring.

The SMS will offer three types of compliance review activities on this study: 1) Study Monitor of Record Reviews; 2) Routine (Random/QA) Reviews; and 3) Directed (For-Cause) Reviews. The Study Monitor of Record activities will be contracted for the proposed study, and will include the conduct and follow-up of monitoring visits throughout the life cycle of the study (e.g., Site Initiation Visit, Interim Monitoring Visits, and Close-Out Visit). Study monitoring visits will occur off-site (remotely) and/or on-site at a frequency necessitated by the protocol risk and complexity.

For this study, UW ICTR SMS personnel will conduct a Site Initiation Visit (SIV) with the UW-Madison research personnel in person after IRB approval is confirmed and before enrollment of any subjects into the study. The SIV will include a detailed review of the protocol, good clinical practice guidelines, and data management expectations of the research team at the study site and the SMS personnel. Following the Site Initiation Visit (SIV), SMS Monitoring personnel will routinely conduct ongoing Interim Monitoring Visits (IMVs) for all data collection sites, either on-site, remotely or a combination of both, following enrollment of the first subject(s) and throughout the duration of the study. During IMVs, the monitors will review study materials, including but not limited to: regulatory files, consent forms, case report forms, and device accountability logs. UW ICTR SMS personnel will conduct a Close-Out Visit (COV) upon completion of the study at the study site.

Monitoring could consist of full or partial review of study records, depending on risk level and observed compliance. As such, during their monitoring activities, UW ICTR SMS personnel plan to review all (100%) of the study-related subject records for 10-20% of the enrolled subjects. The subject records of the first two subjects enrolled will be monitored in their entirety, with the additional number of enrolled subjects to be randomly. SMS personnel could increase the percentage of study or subject records to be reviewed if warranted by the ongoing monitoring findings.

The study monitor(s) will work closely with the ICTR DMC statistician and the study statistician to conduct periodic central data reviews, with follow-up conducted by the study monitors for any data discrepancies identified.

Preoperative tamsulosin for the prevention of postoperative urinary retention: a randomized, double-blind, placebo-controlled trial

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15.0 APPENDIX

ELIGIBILITY CHECKLIST

Any patient being seen in a general surgery clinic at UWHC or the UW Digestive Health Center for possible complex intra-abdominal surgery is a potential subject.

Inclusion criteria:

- >= 18 years of age
- English-speaking
- able to provide informed consent
- scheduled to undergo elective complex intra-abdominal surgery with a planned stay of at least 1 night in the hospital after surgery
- "complex intra-abdominal surgery" includes one of the following operations via ANY transabdominal approach (i.e. open, laparoscopic, hand-assist laparoscopic, single-incision laparoscopic, robotic):

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- Partial colectomy
- Total abdominal colectomy
- Proctocolectomy
- Low anterior resection
- Abdominoperineal resection
- Restorative proctocolectomy/IPAA
- Proctopexy (transabdominal) for prolapse
- Intestinal stricturoplasty
- Lysis of adhesions
- End or diverting colostomy reversal
- Ileostomy reversal
- Closure of enterocutaneous, enteroenteric, or enterocolic fistula
- Partial or complete gastrectomy
- Small bowel resection
- Small bowel diversion/ostomy
- Large bowel diversion/ostomy
- Pancreaticoduodenectomy
- Pancreatectomy
- Hepatectomy
- Gastric bypass
- Sleeve gastrectomy
- Nissen/Dor/Toupet fundoplication
- Transabdominal adrenalectomy
- Splenectomy
- Complex abdominal wall hernia repair (i.e. Rives-Stoppa type repair, large laparoscopic ventral hernia repair)
- Exploratory laparotomy
- Other comparable complex intra-abdominal operation

Exclusion criteria:

- allergy or contraindication to tamsulosin
- serious sulfa allergy
- current use of an alpha blocker (alfuzosin, doxazosin, prazosin, silodosin, terazosin, verapamil, tamsulosin, phenoxybenzamine) or oral alpha agonist (midodrine)
- current warfarin use
- current indwelling urinary catheter, suprapubic catheter, or urostomy
- end stage renal disease or dialysis-dependent
- sitting systolic blood pressure in the upper extremity of less than 100mmHg at time of eligibility screening
- presence of orthostatic hypotension at the time of eligibility screening
    - orthostatic hypotension is defined as a drop in systolic blood pressure of 20mmHg from sitting to standing, or drop in diastolic BP of 10 mmHg from sitting to standing after 2-3 minutes of standing after being in a sitting position
- anticipated inability to take oral medications on post-operative day #0
- anticipated requirement for indwelling urinary catheter beyond post-operative day #2

Preoperative tamsulosin for the prevention of postoperative urinary retention: a randomized, double-blind, placebo-controlled trial

- non-English speaking
- pregnant or breast-feeding women
- lacking capacity to provide informed consent
- unwillingness to answer all 7 questions on the IPSS survey

INSTITUTIONAL BLADDER MANAGEMENT PROTOCOL FOR ADULT SURGICAL INPATIENTS
(Standard of care for post-operative general surgery patients)