A Multi Center Randomized Trial to Study Tamsulosin for Urolithiasis in the Emergency Department STONE

Manual of Operations

Sponsored by:

National Institute of Diabetes and Digestive and Kidney Diseases

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TABLE OF CONTENTS

1 Administration

1.1 Introduction

This manual gives detailed instructions on study procedures for the trial to *Study Tamsulosin for Urolithiasis in the Emergency Department (STONE),* a randomized trial conducted by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). This document is meant to serve as a reference guide for STONE staff, such as investigators, study coordinators, urologists and study nurses.

1.2 Organization

MOMS2 is a cooperative agreement (U01) funded under a multiple PI plan (PIs from the GWU clinical center and coordinating center). The Steering Committee is the policy and decision-making body, and assumes overall responsibility for the management and conduct of the study. The Steering Committee consists of the PI at each of the clinical centers, the PI at the Biostatistical Coordinating Center and the Program Scientist at NIDDK.

1.3 Responsibilities of the Clinical Centers

The minimum staff required at each clinical center are the physician principal investigator (PI) and the study coordinator. Other physicians, study nurses, clerical and secretarial staff may work on study activities.

1.3.1 Principal Investigator Responsibilities

Each PI is responsible for ensuring the proper conduct of the study at his or her site, including recruitment as specified in the protocol, accurate collection of the data and transmittal of data to the Biostatistical Coordinating Center (BCC). Other specific duties include:

1. Applying for IRB approval
2. All study staff are sufficiently trained
3. Any secondary sites are initiated according to procedures outlined in Section 1.7.
4. Obtaining the signed institutional letter authorizing the release of data at the end of the study
5. Notifying all necessary hospital staff of the study, its requirements and medications either contraindicated or not allowed by study protocol such as open-label tamsulosin/flomax, steroids and alpha-blockers.

1.3.2 Study Coordinator Responsibilities

There is <u>one</u> Study Coordinator at each center. This person will be responsible for the day-to-day operations of the study, including data collection and entry processes. This responsibility includes the following:

1. Obtaining a signed informed consent from study participants
2. Serving as primary point of contact for the BCC and disseminating all information to the appropriate staff.
3. Training and certifying staff in data collection, forms completion and data entry and assuring that required back-up security and confidentiality procedures are maintained
4. Organizing and maintaining central records, including the protocol, manual, data forms, reports, correspondence, and study personnel and address lists
5. Maintaining current patient contact information for the duration of the study

1.3.3 Biostatistical Center Responsibilities

The BCC will be responsible for all aspects of biostatistical design, analysis and data management of the study, including maintenance of a central database, performance of interim and final statistical analyses and preparation of publications. The BCC is also responsible for:

1. Maintenance of the study website
2. Coordinating meetings of the study coordinators and the Steering Committee.

1.4 Procedures for Patient Confidentiality

In compliance with federal and IRB regulations, the BCC has ensured that the study data forms and computerized data entry do not include direct patient identifiers such as name, address, social security number, hospital number, date of birth or any other direct personal identifiers. A unique code is used to identify each research subject.

If the BCC requests any other patient medical data, such as charts or ultrasound films, the center must ensure that the identifying tag is the unique patient number and that no specific patient identifiers are present on the shipped materials. For example, the following data, in addition to those mentioned above, must be deleted from patient charts: hospital number, names patient, relatives, or referring physicians, and name or address of patient's employer. The current suggested method is to black out any identifying data with a black magic marker and then make a photocopy to send to the BCC.

If representatives from the BCC or government agencies request to see patient data during a site visit to a center, patient identifying data do not need to be concealed.

1.5 Unmasking

The only indication for unmasking the randomization code is when it is medically necessary to unblind the study drug assignment to be able to treat the patient, such as an allergic reaction or severe side effect that appears to be related to the medication.

For this study, each center will appoint a point of contact. If a patient or non-study physician feels the need to unblind the study medication, the point of contact will be notified. This person will discuss the need with caller. If the caller still feels it is necessary to unblind and the point of contact is not the PI, the center PI will be contacted. The center PI will be the only person who will be able to contact the BCC PI to obtain the treatment group. The BCC PI will contact the requesting physician with the treatment group assignment.

1.6 Informed Consent and IRB Approvals

Each STONE site will develop its own informed consent form(s) according to the requirements of its own institutional review board using the model consent form(s) contained in the protocol. Each center will also develop its own patient research subject authorization form (RSAF), as required by the HIPAA Privacy rule, following the guidelines of its institution. It is highly recommended that a draft of the informed consent form be sent to the BCC prior to submission to the center's IRB. The BCC will check to make sure all the elements, particularly those pertaining to study procedures, confidentiality and data transfer / sharing, are accurate. This is important since multiple centers participate in this trial and contribute to the final data set.

A copy of the IRB approval, along with the center's approved consent form and separate HIPAA form (if required by the center's IRB), must be sent to the BCC where it is kept on file in accordance with federal regulations governing data coordinating centers for multi-center trials.

The PI and nurse coordinator are responsible for ensuring that continuing IRB approval is obtained each year until the study results are published or they are otherwise informed by the BCC. Copies of the

annual IRB approval must be sent to the BCC, in addition to the IRB approval that is obtained when changes are made to the protocol and/or consent form(s).

1.7 Secondary Sites

In order to open a secondary site to the main ED site for STONE, the following protocol will have to be implemented:

- The coordinator at each site will have to be trained by BCC prior to initiation of randomization at the new site.
- If there is potential for medications to be transported from the main site to the secondary site at the time of randomization, a site visit will be conducted to assess the feasibility.
- If the sites are more than a short walk apart (i.e. there is no potential for the study medications to be transported from the main site at the time of randomization), the secondary site will not be allowed to start recruitment until a second packaging and shipment of the study medications is performed.
- It will be necessary to confirm that the listing of patients screened at the main site will be readily accessible by the secondary site and vice versa.

As detailed above, if the coordinator is trained and certified, and a secondary randomization site deemed feasible or additional run of medication received, the secondary site will be able to start recruitment, but not prior.

2 Training and Quality Assurance

2.1 Training

Prior to the start of the trial, research personnel will be trained on all study procedures to ensure that they are applied consistently across the centers. Each center will be required to fulfill certification requirements, including a demonstration of familiarity with the protocol procedures, eligibility criteria and definitions for the case report forms. At a minimum, the study coordinator must be certified. A training session will be held before recruitment starts for coordinators from each center. The purpose of the training workshop is to review the study design, objectives, procedures, form completion and data collection. A quiz and data entry module will be completed before screening of patients can begin. Coordinators are to train any other personnel at their designated center and be responsible for the completion of study forms. The Coordinator may request that research staff who have been designated to work on the study attend in person. In general, this is acceptable, but the BCC should be contacted for permission. Ultimately, however, the coordinators are responsible for training any additional staff assigned to this study.

2.2 Certification

Each clinical center must be certified prior to beginning the study by fulfilling both the center-wide and individual staff requirements. The center-wide requirements consist of:

1. Approval by the PI of the final STONE protocol.
2. Receipt of the final version of the manual of operations, study protocol, and case report forms.
3. Copies of IRB approval and consent forms sent to the BCC and approved by the NIDDK.
4. Identification of the study staff to be certified to complete case report forms.
5. Certification of the coordinator (see below).
6. Receipt of study medications.

The personnel requirements consist of the following:

1. The study coordinator and all staff completing case report forms must successfully complete a study quiz. The study coordinator must be certified in order for the clinic to begin follow-up contacts.
2. The study coordinator must attend a training session at the BCC.
3. The study coordinator and any staff intending to perform data entry must successfully complete data entry certification. At least one study staff member must be certified to perform data entry in order for the clinic to begin follow-up visits.

2.2.1 Approval to Start the Study

The coordinator should date and sign the certification status checklist when all of the requirements have been fulfilled. The completed checklist should be mailed or faxed to the BCC. A formal notification authorizing the center to start recruitment for the study will be issued by Dr. Kusek, NIDDK Program Scientist, and Ms. Katzen Burrows, PI for the BCC.

2.3 Ongoing Requirements

- Copies of annual IRB letters approving renewal of the study should be sent to the BCC.
- Copies of any IRB-approved modified consent should be sent to the BCC.
- New staff should be trained by the coordinator and certification materials submitted to the BCC for approval.
- New coordinators must attend a training session by the BCC.

3 Study Design

The study is a multi-center randomized, placebo-controlled, double-blind clinical trial. Participants are randomized to one of two treatment groups, placebo or active tamsulosin. The primary objective of this study is to test the hypothesis that tamsulosin is clinically useful in the treatment of acute urolithiasis in the Emergency Department. If tamsulosin achieves similar results in a properly conducted placebo controlled trial to those noted in previous smaller pilot studies, we expect to see a significant reduction in days lost from work and decreased morbidity, as well as cost savings resulting from a decreased number of patients referred for the surgical management of retained stones.

3.1 Primary Research Question

Does the administration of tamsulosin after the clinical and radiographic diagnosis of acute urolithiasis produces an increase in the proportion of patients passing their stone at 28 days?

3.2 Secondary Research Questions

The secondary research questions are whether tamsulosin produces a reduction in each of the following:

- Time to passage of stone
- Length of time in pain
- Number of days lost from work
- Need for surgical intervention or lithotripsy
- Overall costs

3.3 Design Summary

The multi-center trial will be conducted in the Departments of Emergency Medicine (ED) at The George Washington University Hospital in Washington D.C, Mercy Hospital of Pittsburgh and Presbyterian-University Hospital, both part of the University of Pittsburgh Medical Center, and the Hospital of The University of Pennsylvania. It is a continuation of the vanguard phase of the study performed solely at The George Washington University Hospital.

This research study is a blinded randomized controlled clinical trial of 400 patients in addition to the 109 enrolled in the vanguard phase. Patients diagnosed with kidney stones via radiographic imaging are approached for screening. Patients who satisfy the eligibility criteria and consent to randomization will be centrally randomized to one of the following two medical protocols, each to be implemented a tablet each day:

a	**The active group who receive 30 tablets of 0.4 mg tamsulosin.**
b	**The placebo group who receive 30 similar inactive tablets.**

3.4 Eligibility Criteria

The study staff will review the informed consent and HIPAA documents with the patient. If the patient refuses consent or is unable to consent due to language barriers, the patient will not be randomized.

3.4.1 Inclusion Criteria

1. Age ≥ 18 years
2. Evidence of ureterolithiasis (i.e. stone is located in ureter, not in bladder) as demonstrated on radiographic studies, specifically non-contrast spiral CT.
3. Willingness to participate and able to proceed with standard outpatient management (no personal or job-related issues, e.g. airline pilot.
4. Has a telephone in order to be contacted for follow-up.

3.4.2 Exclusion Criteria

1. Patient desiring or requiring immediate surgical intervention making then not a candidate for outpatient kidney stone management.
2. Current urinary tract infection based on urine dipstick or micro analysis as admission and urgent procedural management is likely indicated.
3. Known anatomical genitourinary abnormalities or prior GU surgeries.
4. Positive pregnancy test making proper radiological imaging contraindicated.
5. Breastfeeding mothers.
6. History of hypersensitivity to tamsulosin.
7. Current use of alpha blockers or calcium channel blockers.
8. Current use of steroids which may have an independent effect on stone expulsion.
9. Spontaneous stone expulsion prior to enrollment.
10. Largest stone dimension ≥ 9mm assessed using radiologic imaging, being very unlikely to pass spontaneously.
11. Presence of stone outside of the ureters (i.e. within kidney or bladder).
12. Current use of vardenafil which is tamsulosin contraindicated.
13. Ipsilateral, transplanted or solitary kidney as hospitalization may be necessary.
14. Known renal insufficiency (by patient history).
15. Fever defined as >101.5°F which may indicate infection.
16. Floppy iris syndrome which is tamsulosin contraindicated.
17. Planned cataract surgery in the next 60 days which is tamsulosin contraindicated.
18. Prisoners /wards of state.
19. Prior enrollment in STONE.

3.5 Randomization Method and Masking

Consenting patients will be assigned to one of the two treatment groups with a randomization sequence prepared and maintained centrally by the BCC. The active and placebo study medication will be packaged according to the randomization sequence, so that the patient is randomized when he or she is assigned to the next available individual supply of study medication. The study is double masked; neither the patient nor the clinical staff will be aware of the treatment assignment.

The simple urn method will be used to generate the randomization sequences because it provides a high probability of balance in treatment assignments, it is unpredictable, and it allows an explicit randomization analysis, to be conducted with relative ease. Randomization will be stratified by clinical site to assure balance between the two treatment groups with respect to anticipated differences within the clinic populations and possible differences in patient management.

3.6 Patient Re-screening

A patient may be re-screened or screened multiple times, however no patient can be enrolled or randomized to the study more than one time regardless of whether there is a subsequent case of kidney stones. All centers will keep track of the patients identifiers (which will not leave the center) in order to validate whether the patient has been screened (and randomized) prior.

4 Patient Management and Outcome Data Collection

4.1 Contact for Follow-up

The study staff should obtain contact information before discharge and should update it at each contact if necessary. This information should include:

- Names and contact information of friends and family
- All telephone numbers (work, home, cell)
- Patient's urologist, if applicable
- Other physicians or care providers

After study staff has entered the screening data forms for a patient, the follow-up protocol will begin. Each participant will be contacted for interview via phone on days 2, 7, 15, 20, 29 and 90, post randomization. The Follow-up Form (ST10) will be completed at each attempted contact.

4.2 Study Medication

The patient will take one capsule of the study medication each day for 28 days. The medication bottle contains 30 capsules in case one or two are lost. The bottle contains either active tamsulosin 0.4mg or a placebo. Both patient and study staff are blinded to the treatment group.

4.2.1 Receipt and Storage

After study medications are received (initially and for any subsequent shipments), it is important that it be inspected as soon as possible and checked against the listing provided. Any discrepancies will be reported to the BCC immediately.

Study medications will be kept in a double-locked space that is only accessible by study staff with authority to dispense them. A listing of the medications will be kept and maintained to insure the proper sequence of allocation.

4.2.2 Accountability and Dispensing

The only indication for unblinding the treatment group is when it is medically necessary to know the drug assignment to be able to treat the patient, such as an allergic reaction or severe side effect that appears to be related to the medication.

4.2.3 Unmasking Treatment Group

Unmasking the treatment group will only be performed when it is medically necessary to know the drug assignment to be able to treat the patient, such as an allergic reaction or severe side effect that appears to be related to the medication.

The procedure for unmasking depends on the set up at each STONE center. However if the non-study physician still wants to unmask the study medication and the PI concurs, the following procedures will be adhered to. Only the PI at the center will call the BCC PI with the physician's name, contact information and the STONE study number. The BCC PI will then contact the physician with the treatment group.

4.3 Follow-up CT Scan

The patient will have a follow-up CT scan performed at the study ED on day 29 post randomization. This scan can be performed up through day 35; however it cannot be performed sooner than day 29. If a documented CT was done outside the study before 29 days that shows stone passage, it will be reviewed by the PI who will determine if the information is comparable and sufficient for study use. If so, the study CT will not be performed. This scan will be used in conjunction with the follow-up data to confirm stone passage. The results from it will be documented on the study form ST11 as any other study follow-up CT scan.

5 Adverse Event Reporting

Detailed information concerning adverse events will be collected and evaluated throughout the trial. Events should be reported on the ST12, Adverse Event Form, and submitted to the BCC. The BCC will forward all reports of serious events to the NIDDK Program Scientist. The BCC will report adverse events and serious adverse events to the Data and Safety Monitoring Committee (DSMB). The DSMB reviews adverse events, serious adverse events, and other interim safety data and provides a report to the Principal Investigators and the IRBs.

5.1 Definition of Adverse Event

The study definition of an adverse event is any adverse experience, drug reaction, side effect, abnormal laboratory value, hospitalization, other complication or pre-existing conditions that worsened, whether or not considered drug related. Any event that fits the local IRB definition of adverse event should also be reported. Adverse events for the study are events that occur after randomization. Any reports sent to or received by the IRB, will need to be sent to the BCC.

5.2 Assessing Adverse Events

Detailed information concerning adverse events will be collected and evaluated throughout the conduct of the protocol. Results of clinical observations, laboratory tests, and reported events form the basis for evaluating the safety profile of this therapy. At all contacts, patients will be questioned regarding side effects or symptoms associated with the study medication which are as follows:

- Dizziness at rest
- Dizziness on standing (postural hypotension)
- Abnormal ejaculation (in men)
- Gastrointestinal disorder
- Peptic ulcer disease
- Gastrointestinal bleeding
- Urinary tract infections
- Facial flushing
- Headache
- Tachycardia
- Other side effects

The clinical center will report adverse events to the BCC in a timely fashion. The coordinating center will summarize and report adverse events to the DSMB.

5.3 Serious Adverse Events

Additional procedures are warranted for cases of serious adverse events which is defined by the FDA as a patient outcome that is:

- Death
- Life-threatening, i.e., the patient was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the patient's death
- Initiates or prolongs hospitalization
- Disability, i.e., resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life

- Congenital anomaly, i.e., there are suspicions that exposure to a medical product prior to conception or during pregnancy resulted in an adverse outcome in the child;
- Requires intervention to prevent permanent impairment or damage

Serious adverse events will be reported immediately to the BCC and the local IRB. The BCC will notify the NIDDK.

The only indication for unblinding the randomization code is when it is medically necessary to unmask the study drug assignment to be able to treat the patient, such as an allergic reaction or severe side effect that appears to be related to the medication.

6 Data Collection and Management

6.1 Data Collection Forms

Data will be collected on standardized forms on which nearly all responses have been pre-coded. Each form is briefly described below:

- Screening Log lists all patients screened for the study.
- Clinical Screening Form is completed for all randomized patients. This form includes detailed demographic and medical data obtained during screening for the study.
- Eligibility and Randomization Form is completed for all randomized patients and records assigned study drug code number, and information on the study drug administration.
- Screening Radiologic Imaging Form for all randomized patients to document the results of the screening CT scan.
- Follow-up Form for all contact calls for follow-up of randomized patients.
- Follow-up Radiology Form is completed for all follow-up CT scans performed at day 29.
- Adverse Event Form records adverse events reported for randomized patients.

6.2 Web Data Entry System

For this protocol, web data entry screens corresponding to the study forms listed above will be developed and maintained by the staff of the BCC. Clinical center staff will enter data into the database located at the BCC through a web data management system (MIDAS). The data are edited on-line for missing, out of range and inconsistent values. A Users' Manual documenting this system is provided to the centers by the BCC.

6.3 Centralized Data Management System

Daily data conversions from the web database create up-to-date SAS datasets. Data are reviewed weekly using edit routines similar to those implemented on-line during data entry, as well as additional checks for data consistency within or across forms. A database of resulting potential data problems is generated in MIDAS for initial review by BCC staff, who then evaluates the comments keyed in association with edits on missing or unusual values. Valid edits will be flagged in MIDAS for resolution at the clinical centers.

At regular intervals, specialized data reviews comparing data availability and consistency across forms are run by the BCC staff on the entire database or on a specific subset of data. These reports are also submitted to the centers for correction or clarification.

An audit trail, consisting of all prior versions of each data form as entered in the computer for each patient, is maintained so that the succession of corrections can be monitored.

6.4 Performance Monitoring

The BCC will present regular reports to the Steering Committee, and the Data and Safety Monitoring Board. These include:

- Monthly Recruitment Reports - reports of the number of people screened and enrolled by month and by clinical center are provided monthly to the Steering Committee.
- Steering Committee Reports - reports detailing recruitment, baseline patient characteristics, data quality, incidence of missing data and adherence to study protocol by clinical center, are provided the Steering Committee.
- Data and Safety Monitoring Board Reports - for every meeting of the DSMB a report is prepared which includes patient recruitment, baseline patient characteristics, center performance information with respect to data quality, timeliness of data submission and protocol adherence (in addition to safety and efficacy data). The reports also include adverse events, loss to follow-up and all outcome variables as described previously in this protocol.

7 Instructions for Completing Forms

7.1 General Guidelines

The following guidelines apply to all forms used in this study:

- Black ink must be used when completing all data forms, with the exception of the screening logs. If a change is made, line out the old value, write the new value just above the old value, and clearly initial and date. Tape, correction fluid, or erasures should never be used to alter an entry. The original entry should remain legible.
- The centers will keep all original forms and logs, unless otherwise specified.
- Dates should be recorded using an MM/DD/YYYY format, i.e., the date November 2nd, 2007 will be recorded as "11/02/2007".
- If the person completing the form is aware that the value they are writing is 'out of range', they should write their initials and the date alongside the field. The keyer will use those initials to avoid a data check. Concise comments explaining other unusual data should be noted on the bottom of the form, along with the question number (if applicable). These comments can be entered into the database in the comment field provided for each question or the comment field provided for the form.
- The traditional rounding-off rule should be used when necessary (five and up should be rounded up, four and below should be rounded down). For example, a height of "62.65 in" should be rounded up to "63 in". For questions that request a text answer ("specify" or "explain" fields), concise explanations should be entered in the field provided. Do not enter "see comment". Answers that are too long for the "specify" field should be continued in the comment field for that question.
- Patient names, initials, or other personal identifiers should not appear on any form or chart mailed to the BCC.
- The initials recorded on the form should be those of the person who is completing the form, not the person who is entering the data.

7.1.1 Deleting a Form

If a CRF needs to be deleted (usually only because of a misunderstanding or a misidentification problem), keep form in the patient chart with an 'X' through the whole front page, marked 'delete' with initials, date of change and reason why, e.g. "Deleted – form completed but visit never took place". Any such forms must be retained in the patient file so that a complete paper trail exists.

7.2 Missing Data Values

Missing data values should be recorded as follows:

A temporarily missing value is defined as data that is not available when the form is completed but will be available in the future; for example, if a test result has not yet been filed in the patient's medical chart. This should be indicated using a question mark (?). The question mark should be placed beside the box for which the data is unavailable. In addition, in some cases a field may be temporarily unavailable since the keyer cannot read the data field. This can be indicated with an exclamation point (!) beside the box for which the data is unreadable.

A permanently missing value is defined as data that will never be available; for example, results for a test that was never performed. This should be indicated using an asterisk (*). Use of the asterisk in this fashion applies to dates and times as well. A comment should be recorded on the form and keyed into the computer wherever possible to explain why the data are missing.

7.3 Instructions for Completing Form ST01 – Screening Log

Patient Group: All patients presenting to the Emergency Department with possible kidney stone diagnosis.

When completed: When the patient's eligibility criteria to participate in the study are reviewed

Who completes: Certified study coordinator or certified study staff

Related forms: Form ST02, Clinical Screening Form
Form ST03, Radiology
Form ST04, Eligibility and Randomization Form

Special Instructions:

- This form is to be completed in the emergency department by the study nurse when a patient is screened for the study (kidney stone diagnosed or suspected).
- Information for this form is obtained through interview with patient
- Persons screening should be knowledgeable of what medications the patient is currently taking and whether the medication class is exclusionary.
- Patients should only be considered screened if they may be eligible for the STONE study. Patients in the ED who are ordered CT's for such injuries such as trauma, are examples of patients not eligible and should not be reported as a screening.

Center number:

The one digit center number serves as the unique identifying number within a site for the specific center.

1. The George Washington University Medical Center
2. The University of Pennsylvania
3. The University of Pittsburgh Medical Center – Presbyterian Hospital
4. The University of Alabama at Birmingham
5. The University of Pittsburg Medical Center – Mercy Hospital

Screening number:

The four digit screening number will serve as the unique identifying number within a site for the patient until she has been randomized and assigned a STONE identification number. Even though the screening number is preprinted on the form, it must be entered in the computer.

Patient Identifier/ Medical Record Number:

Record the patient's name and chart number. This information is for local record keeping purposes only and is not entered on the computer. If an unusual circumstance arises and a request is made to mail or fax copies of the screening logs to the BCC this field must be covered. Please note this information will not be keyed. The purpose is to track patients who have already been screened or randomized for the study.

Question 1 – Date of screening:

Enter the date that the patient was screened in the Emergency room at any of the three participating Emergency Room center locations. The mm/dd/yyyy format should be used.

Question 2 – Previous screening?

Record YES if the patient was screened at least once before. Record NO if this is the first screening for this patient for STONE.

IF YES,

a. Previous Screening Number:
If the patient was screened for STONE in the past, record the Screening Number used for the first screening.

Question 3 - Gender:

Record the patient's gender. 1= Female and 2= Male

Question 4 - Race:

Code the patient's race as reported by the patient. It should be coded as follows.

1. American Indian / Alaskan Native - Code "1" for patients having origins in any of the original peoples of North, Central, or South America, and who maintain tribal affiliation or community attachment.
2. Asian - Code "2" for patients having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.).
3. Native Hawaiian / Pacific Islander – Code "3" for patients having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
4. Black / African American- Code "4" for patients having origins in any of the black racial groups of Africa. Terms such as "Haitian" can be used in addition to "Black or African American".

5. White - Code "5" for patients having origins in any of the original peoples of Europe, the Middle East, or North Africa
6. Unknowns or Not Reported - Code "6" for patients who are not sure of their ancestry, who refuse to report their ancestry, or whose ancestry does not clearly fall into one of these categories.

Question 5 - Ethnicity:

Record the patient's ethnicity as reported by the patient. The following codes should be used.

1. Not Hispanic / Latino - Code "0" for all others.
2. Hispanic / Latino - Code "1" for all those of Cuban, Dominican, Mexican, Puerto Rican, South or Central America, or other Spanish culture or origin regardless of race.

Question 6 - Screen status code:

Enter the appropriate status code. The 00 format should be used.

1. Eligible, refused consent – Code "1" if the patient has is not known to have any exclusion criteria, the trial is discussed with the patient and she declines to participate in the trial, or refuses to sign the medical records releases.
2. Ineligible – Code "2" if the patient meets any of the exclusion criteria listed below.
3. Randomized – Code "3" if the patient is eligible, the trial is discussed with the patient and she agrees to participate. This status code will need to be changed if the patient subsequently refuses or subsequently found to be ineligible for the trial.

If screen status is Ineligible (2),

a. Reason

If the patient is ineligible (screen status code = 2), provide the reason or exclusion code from the following list. If the patient is eligible, leave this field blank. If more than one exclusion code applies, use the first listed code. For example, if the patient has been admitted to the hospital (code "19") and does not have a phone (code "3"), then code "3" should be recorded.

1. Age <18 – Code "1" if the patient has not turned 18 years of age.
2. No evidence of ureterolithiasis – Code "2 if the CT scan does not indicate a diagnosis of kidney stone. This exclusion criteria should be used if a CT scan does not provide evidence of a stone in the ureters.
    a. If a patient chooses to have an ultrasound instead of a CT, please add a comment to the exclusion criteria indicating 'No CT'.
    b. In addition, if the patient chooses not to have any type of scan performed, this should be documented as 'refused consent' in Question 6. If the patient presents with probable kidney stone and for some reason (other than refusal) does not have a scan performed, this patient should be documented here.
3. No Phone - Code "3"
4. Concurrent UTI – Code "4" using the study definition of UTI which is based on urine dipstick but using clinical judgment. If a dipstick and/or micro urinalysis is performed and is positive, the patient is excluded. If the patient is not treated for a UTI, they are NOT excluded. For example, if there are white cells on the dipstick, but the patient is not treated, this should NOT be considered as a UTI for study purposes and the patient should not be excluded.
5. Prior kidney/ ureter surgery – Code "5"
6. Pregnant – Code "6" if the patient is a female and the HCG testing has confirmed pregnancy or the patient has reported that she is pregnant before the screening

process has progressed to the testing point. All female patients must undergo a pregnancy test unless she has stopped having menstrual periods at least one year after menopause or had a hysterectomy procedure.

7. Anatomical GU abnormality – Code "7" if the patient had any type of GU surgery, such as a stent, that was not accounted for as kidney or ureter surgery (see #5 above. Surgery is defined as a procedure performed using a knife or laser; prior lithotripsy is not exclusion).
8. Ipsilateral or solitary kidney – Code "8" if the there is only one kidney or a horseshoe kidney.
9. Prior renal transplant or donation
10. History of renal insufficiency – Code "10" if there is reason to perform a BUN or creatinine and the results show renal insufficiency OR the patient or chart reports a history of renal insufficiency.
11. Fever – Code "11" if the candidate has a fever $\geq$ 101.5°F in the Emergency Department.
12. History of hypersensitivity to tamsulosin – Code "12" if the patient has a documented hypersensitivity to tamsulosin/Flomax.
13. Taking α-blockers or calcium channel blockers – Code "13" if the patient is taking either an α-blocker or calcium channel blocker. (Please note- tamsulosin is an α -blocker). This code should be used for patients who are put on Flomax in the ED. Some examples of α-blockers, but not all: Cardura, minipress, uroxatral, hytrin, doxazosin, terazosin, alfuzosin. Some examples of calcium channel blockers: Cardizem, diltiazem, cartia, tiazac, nifedipine, procardia
14. Taking vardenafil – Code "14" if the patient is currently taking vardenafil, Levitra, Vivanza or Staxyn. Medications such as Cialis/tadalafil should also be included here.
15. Floppy iris syndrome
16. Cataract surgery within 60 days – Code "16" if the patient has cataract surgery planned within 60 days of the screening.
17. Stone expulsion in the Emergency Department – Code "17" if the patient expels the stone in the
18. Largest stone dimension $\geq$ 9mm – Code "18" if the results from the CT scan show that a stone is greater than or equal to 9mm in diameter.
19. Admitted to the hospital – Code "19" if the patient was admitted to the hospital before randomization. All efforts should be made to figure out if the patient would need to be admitted before randomization.
20. Prisoner of war of state
21. Breastfeeding mother
22. Prior enrollment –Code "22" if the patient was randomized to/enrolled in the STONE study in the past. This includes the pilot study participants at GWU ED.
23. Bladder stone – Code "23" if any of the stones on CT are located in the bladder regardless whether or not there are other stones located elsewhere in the urinary tract. If there are multiple stones and the physician believes that the stone causing symptoms has reached the bladder, the patient will not be eligible for enrollment
24. Taking steroids-Code "24" if the patient is currently taking a steroid medication such as prednisone and medrol. Steroids which are NOT exclusionary are oral contraceptives, topical or inhaled steroids.

25. Non-English speaker-Code “25” if the patient does not speak English or is unable to give consent to the study in English. If the patient is not able to converse in English for the follow-up phone contacts, then they should be excluded as well.
99. Other – Code “99” If the patient is being excluded from the study for another reason (such as intellectual disability) and briefly explain the reason for exclusion in the provided space. If at all possible, always use one of the exclusion codes listed prior to using “99” for other exclusion.

    An example of appropriately using this code is: If a patient has dementia and cannot give consent, they are not eligible for the study.

    Please notify the BCC if exclusion code of “99” is being used.

    If Reason Code is Other (99),

    1) Explain:

    If the patient is eligible for a reason other than those listed in the codes, explain here. As per the example above, “dementia - unable to give consent” would be recorded here.

If screen status is Randomized (3),

b. STONE patient number:

If the patient is eligible for the study (screen status code = 3), record the STONE patient number given at the time of randomization. The STONE patient ID is obtained from the study medication bottle and log.

Question 7 –Initials of person completing form:

Record the initials of the person completing the form. This individual should be a certified study staff member only

7.4 Instructions for Completing Form ST02 – Clinical Screening Form

Patient Group: All patients randomized to the study

When completed: At the time the patient is being screened for eligibility

Who completes: Certified study coordinator or certified study staff

Related forms: Form ST01, Screening Log
Form ST02, Clinical Screening Form
Form ST03, Radiological Follow-Up Form

Special Instructions:

- This form is to be completed after screening has taken place and should only be completed for those patients who have been randomized to the study.

STONE ID number:

Enter the patient's four digit STONE number as assigned when the patient was randomized (from the medication bottle).

Question 1 – Screening Number:

Record the Screening Number for the randomized patient. This Screening Number can be found on the Screening Log (Form ST01).

Question 2 – Date of screening:

Record the date the patient was screened in the Emergency Department. The mm/dd/yyyy format should be used.

Question 3 – Initials of person completing this form:

Record the initials of the person completing the form**.** This individual should be a certified study staff member only.

Demographics and Social Characteristics

Question 4 – Age (not eligible if <18 years):

Record the age of the patient in years. If the patient is younger than 18 years of age, then they are not eligible to participate in this study.

Current Medications

Question 5 – Known allergy to tamsulosin?

Record YES if patient has a documented allergy or hypersensitivity to tamsulosin/flomax and they are not eligible for the study.

Question 6 – Currently taking calcium channel blockers?

Record YES if patient is currently taking calcium channel blockers and they are not eligible for the study.
Some examples of calcium channel blockers: Cardizem, diltiazem, cartia, tiazac, nifedipine, procardia

Question 7 – Currently taking steroids?

Record YES if patient is currently taking any steroids. If the patient is currently on steroids they are not eligible for the study. Examples of excluded steroids are: prednisone and medrol. Steroids which are NOT exclusionary are oral contraceptives. Topical or inhaled steroids are not exclusionary.

Question 8 – Currently taking vardenafil?

Record YES if patient is currently taking vardenafil, Levitra, Vivanza or Staxyn. If the patient is currently on vardenafil, they are not eligible for the study. Medications such as Cialis/tadalafil should be included here.

Question 9 – Currently taking other medications on a regular basis?

Record YES if patient is currently taking any other medication on a regular basis.

IF YES, list current medications (name only)

List all current medications by name only. There is no need to include dose, number of times per day or form. Note, tamsulosin or any other medications reported in questions 6-8 (above) should never be reported in any of these fields.

Current Symptoms

Question 10 – List symptoms:

For questions a-l, answer YES if the patient is experiencing any of the following problems.

a. Increased need to urinate
b. Urinating more often at night
c. Pain when urinating
d. Feeling of not emptying bladder completely
e. Nausea
f. Vomiting
g. Dizziness
h. Chest pain
i. Fever
j. Side/flank pain
k. Lower abdomen pain
l. Scrotum or groin pain

Medical History (by report)

Question 11 – Past history of kidney stones:

Record YES if patient has a past history of kidney stones.

IF YES,

a. How many episodes:

Indicate how many episodes of kidney stone related issues the patient has had in the past (not including the current episode).

b. Date of most recent episode:

Enter the date of the patient most recent kidney stone episode. This should not be the date the current episode started. The mm/yyyy format should be used.

Question 12 – Family history of kidney stones? (Parents/siblings)

Record YES if anyone in the patient's immediate family has a history of kidney stones. .

Initial Vital Signs (at triage)

Question 13 – Blood Pressure:

Enter initial blood pressure recorded at triage.

Question 14 – Heart Rate:

Enter initial heart rate recorded at triage.

Question 15 – Temperature (not eligible if temp >101.5°F):

Enter initial temperature in degrees Fahrenheit recorded at triage. If patient has a fever ≥ 101.5°F in the Emergency Department, they are not eligible for the study.

Urinalysis Results

Dipstick: Dipstick exam does not always need to be completed as long as urinalysis microscopy is done

Question 16 – Glucose:

According to the urinalysis dipstick, indicate the following results:

a. Glucose

Record glucose in mg/ul using the following codes:

0. Normal
1. 50
2. 100
3. 250
4. 500
5. 1000

b. Blood

Record blood analysis using the following codes:

0. Negative
1. Trace
2. About 50
3. About 250

c. White cells (leukocytes)

Record white cells (leukocytes) analysis using the following codes:

0. Negative
1. Trace
2. +
3. ++

Question 17 – Was an HCG done? (necessary for all women of child-bearing age)

Record if an HCG was performed on the patient or if not indicated (e.g. hysterectomy, tubal ligation, post menopause or male). Besides those surgical exceptions listed, an HCG is required for all women of child-bearing age. If the patient is a male, record N/A.

IF YES,

a. **Results positive?**

Record the results of the HCG test. **If results are positive, the patient is not eligible for the study.**

Question 18 – Urinalysis microscopy done?

Record if a urinalysis microscopy was completed. Either dipstick or microscopic urinalysis always must be completed.

IF YES,

Use the scale below to answer questions a-c

0. 0, none, negative, MNL
1. 1-5, trace, rare, present, slight
2. 6-15, moderate
3. 16-30, many, frequent
4. >30, innumerable, TNTC

a. Blood:

b. White cells:

c. Bacteria:

Discharge from ED

Question 19 – Stone expelled in the ED? (Not eligible if expelled)

Record YES if patient expelled the stone while in the emergency department. If YES, the patient is not eligible to participate in this study.

Question 20 – Final primary ED diagnosis:

Indicate what the final primary emergency department diagnosis was from the following options:

1. Renal Colic
2. Stone (includes nephrolithiasis and ureterolithiasis**)**
3. Other

Question 21 – Patient admitted?

Record YES if the patient was admitted to the hospital. This makes the patient not eligible to participate in the study.

IF YES,

a. To which service:

If the patient was admitted to the hospital, indicate from the following for which services.

1. Urology
2. Surgery
3. Medicine
4. Other

7.5 Instructions for Completing Form ST03 – Radiology Screening Form

Patient Group: All patients randomized to the study

When completed: Completed during patient screening process

Who completes: Certified study coordinator or certified study staff

Related forms: Form ST01, Screening Log
Form ST02, Clinical Screening Form
Form ST04, Eligibility and Randomization

Special Instructions:

- Form is to be completed based on the results of the diagnosing CT scan.

STONE ID number:

Enter the patient's four digit STONE number as assigned when the patient was randomized (from the medication bottle).

Question 1 – Date of screening:

Enter the date that the patient was screened in the Emergency Department. The mm/dd/yyyy format should be used.

Question 2 – Initials of person completing this form:

Record the initials of the person completing the form, not the radiologist who read the images. This individual must be a certified study staff member only.

Question 3 – CT Result:

Record the results of the CT scan result using one of the following codes:

0. No stones
1. Single Stone
2. Multiple Stone
3. Bladder stone(s)

No stones (0) or bladder stones (3), patient is ineligible to be randomized and SKIP to question 13.

Question 4 – Side of symptomatic stone:

Record the side of stone causing symptoms from the following options:

1. Left
2. Right

Question 5 –Location of symptomatic stone:

Indicate the location of the symptomatic stone only.

1. Renal pelvis
2. Proximal ureter
3. Mid ureter
4. Distal ureter
5. UVJ

Question 6 – Diameter of symptomatic stone:

Record the largest stone diameter in millimeters for the symptomatic stone.

If the diameter of this stone is greater than or equal to 9mm, the patient is not eligible. If stone is a punctate stone, record '1' for the size and make a comment to indicate "punctate stone(s)".

Question7 – Hydronephrosis:

Record YES if hydronephrosis is reported in the CT results.

Question 8 –Stranding:

Record YES if there is a diagnosis of stranding on the CT report.

If Single stone (1), SKIP to Question 13.

If Multiple stones (2), CONTINUE.

Question 9- Number of stones:

Record the number of stones reported on the CT report.

Question 10 – Side additional stone(s)

Record the side or sides of the additional stone(s). This should not include the symptomatic stone.

1. Left
2. Right
3. Bilateral

Question 11 –Location of additional stone(s):

Record YES if the patient had any additional stone(s) in each of the locations noted. Do not include the symptomatic stone.

a. Renal pelvis
b. Proximal ureter
c. Mid ureter
d. Distal ureter
e. UVJ
f. Kidney

Question 12- Is the symptomatic stone the largest stone?

Record YES if the symptomatic stone is the largest stone.

If NO,

a Diameter of largest stone

Record the diameter in millimeters of the largest stone if it is not the symptomatic stone. If the diameter of any stone is greater than or equal to 9 mm, the patient is not eligible. If stone is a punctate stone, record '1' for the size and make a comment to indicate "punctate stone(s)".

Question 13 –Initials of radiologist reading images:

Record the initials of the radiologist who read the images, not the person completing the form.

7.6 Instructions for Completing Form ST04 – Eligibility and Randomization

Patient Group: All patients randomized to the study

When completed: Soon after screening and randomization process

Who completes: Certified study coordinator or certified study staff

Related forms: Form ST01, Screening Log
Form ST02, Clinical Screening Form
Form ST03, Radiology

Special Instructions:

- The eligibility criteria should be reviewed again prior to giving the patient the first study medication dose.
- The answers to the questions on this form will be documented elsewhere on the prior screening forms (ST01, ST02 and ST03).

STONE ID number:

Enter the patient's four digit STONE number as assigned when the patient was randomized (from the medication bottle).

Question 1 – Date of screening:

Enter the date that the patient was screened in the Emergency Department. The mm/dd/yyyy format should be used.

Question 2 – Initials of person completing this form:

Record the initials of the person completing the form**.** This individual must be a certified study staff member.

Eligibility Inclusion Criteria (All criteria must be answered YES in order for a patient to be eligible)

Question 3 –Signed informed consent?

Record YES if patient signed the informed consent form.

Question 4 – Age ≥ 18 years?

Record YES if patient is age 18 or older.

Question 5 – Evidence of acute nephrolithiasis?

Record YES if there is evidence of acute nephrolithiasis by clinical diagnosis, based on history, physical, urinalysis, and radiographic studies.

Question 6 – Has a phone?

Record YES if patient has access to a telephone.

Eligibility Exclusion Criteria (All criteria must be answered NO in order for a patient to be eligible)

Question 7-Requires immediate stenting or other surgical intervention?

Record YES if patient requires immediate stenting or other surgical intervention. Other surgical interventions could include: lithotripsy, ureteroscopy, and laparoscopy.

Question 8 – Urinary tract infections (UTI)?

Record YES if patient has a current urinary tract infection (UTI).

Question 9 – Prior surgery involving kidneys or ureters, or known urological anatomical abnormality?

Record YES if patient has had prior surgery involving kidneys or ureters, or unknown urological anatomical abnormalities.

Question 10 – Currently pregnant?

Record YES if patient is currently pregnant. Answer N/A if patient is a male.

Question 11- Currently Breastfeeding?

Record YES if the patient is currently breastfeeding.

Question 12 – History of hypersensitivity to tamsulosin?

Record YES if patient has a history of hypersensitivity to tamsulosin.

Question 13 – Currently taking tamsulosin or other alpha-blocker or calcium channel blockers?

Record YES if patient is currently taking tamsulosin or other alpha-blocker or calcium channel blockers.

Question 14- Currently taking steroids?

Record YES if the patient is currently taking any steroid medication

Question 15 – Spontaneous stone expulsion in the ED (i.e. the patient urinated the stone out while in the ED)?

Record YES if patient spontaneously expelled stone in the Emergency Department

Question 16 – Largest stone dimension ≥ 9mm?

Record YES if the dimension of the largest stone is 9mm or greater.

Question 17 – Stone is located in the bladder?

Record YES if the CT imaging identified any stone located in the bladder.

Question 18 – Concurrent use of vardenafil?

Record YES if patient is currently taking of vardenafil, Levitra, Vivanza or Staxyn.

Question 19 – Known ipsilateral, transplanted or solitary kidney (includes a kidney donor)?

Record answer YES if patient has had known ipsilateral, transplanted or solitary kidney. This includes if the patient has been a kidney donor.

Question 20 –Fever > 101.5° F at any time during ED stay?

Record YES if patient at any time in the ED has had a fever greater than 101.5° F.

Question 21- Floppy iris syndrome?

Record YES if patient has been diagnosed with floppy iris syndrome.

Question 22- Cataract surgery is planned in the next 60 days?

Record YES if patient is planning cataract surgery in the next 60 days following the visit date.

Questions 23-Prisoners or ward of state?

Record YES if patient is a prisoner or ward of the state.

Question 24- Prior enrollment in STONE study?

Record YES if patient has had prior enrollment in the STONE study. This includes any participants in the pilot study performed at George Washington University Emergency Department prior to the multi-center trial.

Question

Affix label of drug bottle dispensed to the patient BELOW.

Question 25 - Initials of individual dispensing study medication:

Regardless of who screened the patients, who completed the case report forms, record the initials of the person who dispensed the study medication. This individual must be a certified study staff member.

7.7 Instructions for Completing Form ST10 – Follow-Up Form

Patient Group: All randomized patients to the study

When completed: At each of the follow-up contacts at days 2, 7, 15, 20, 29 and 90 post randomization.

Who completes: Certified study coordinator or certified study staff

Related forms: Form ST11, Radiological Follow-Up Form

Special Instructions:

- All randomized patients at day(s) 2, 7, 15, 20, 29 and 90 after randomization.
- Please note: this form obtains some information that is specified as (since the last contact).
- Persons completing this form should be knowledgeable of what medications the patient is currently taking and what drug class the medication is under in the event it is an exclusionary medication.
- Coordinators should try to hone down on any requested dates (ex. Date of last episode of previous stone, date of last medication dosage). A comment can be put in MIDAS to indicate if a date is a patient's or study staff's estimate.
- Even if a patient reports passing a stone, follow-up calls still need to occur on the designated protocol days. There is always the possibility that there is another stone(s), that the patient only passed part of the stone or that the patient will continue to have pain and/or side effects. The study medication should continue to be taken.

STONE ID:

Enter the patient's four digit STONE ID number as assigned on the Screening log (ST01) and Eligibility and Randomization Form (ST04).

Question 1- Post ED day:

Enter the post ED day visit. ED visit is day 0 and scheduled follow up calls are on days 2, 7, 15, 29 and 90. The 00 format should be used.

Question 2 – Date of contact:

Enter the date of contact. The mm/dd/yyyy format should be used.

Question 3 – Initials of person completing this form:

Record the initials of the person completing the form. In most cases, this will be the person contacting the patient. This individual must be a certified study staff member.

Question 4 – Patient reached?

Record YES the patient was able to be reached by phone for follow up.

If YES, CONTINUE.
If NO, STOP.

If the patient is unable to be reached, Question 4 should be answered NO. This will mark completion of the form for that call day. The coordinator should try to continue to call the following day and subsequent days and not wait until next scheduled call.

If Day 90 contact, SKIP to question 12.

Question 5 – Have you taken the study medication since the last contact?

Record YES if patient has taken the study medication since the last contact.

If YES,

a. How many doses since the last contact:

Indicate how many doses of the study medication the patient has taken since the last contact. The '00' format should be used.

Question 6- Have you taken any open label tamsulosin/Flomax since the last contact?

Record YES if patient has taken any **open label** tamsulosin/Flomax since the last contact. Any ingestion of open label tamsulosin/Flomax would indicate medication crossover.

If YES,

a. How many doses since the last contact?

Indicate how many doses of open label tamsulosin/Flomax the patient has taken since the last contact. The '00' format should be used.

- For all crossovers to open label tamsulosin/Flomax, an ST13 (Protocol Violation/Deviation Form) needs to be completed, AND all follow-ups will continue as scheduled.

Question 7 – Are you taking an NSAID?

Record YES if patient is currently taking a non-steroidal anti-inflammatory drug (NSAID). Examples of NSAIDs are: ibuprofen, Advil, Aleve, Ketorlac, Toradol, and Naproxen. Note that acetaminophen is NOT an NSAID.

If YES,

a. What dose?

Indicate what dose of the NSAID reported above from the following options:

1. 200mg
2. 400mg
3. 600mg
4. 800mg
5. Other

b. How many pills have you taken since the last contact?

Indicate how many pills of the NSAID reported above have been taken since the last contact.

Question 8 – Are you currently taking Percocet?

Record YES if patient is currently taking Percocet.

If YES,

a. Dose per day:

Indicate the dose per day of Percocet from the following options:

1. 1 tablet
2. 2 tablets
3. 3 tablets
4. Other

Question 9-Are you currently taking any other analgesic?

Record YES if the patient is currently taking any analgesic **other than Percocet**. If the patient is taking an additional NSAID, the second NSAID should be reported here. Do not report any NSAIDs already reported in question 6 or Percocet (reported above).

If YES.

a. Type of analgesic:

Record the type of analgesic from the following options:

1. Acetaminophen
2. Demerol
3. Other

If Other (3)

1) Specify:

Record only the name of the other type of analgesic indicated above.

b. What dose:

Record the dose per day of the "other" analgesic reported above.

c. How many pills have you taken since the last contact:

Record the number of pills of the analgesic reported above that the patient has taken since the last phone contact.

Question 10- Have you taken a steroid medication since the last contact?

Record YES if the patient has taken a steroid medication since the last contact.

Question 11- Have you taken a contraindicated medication since the last contact?

Record YES if the patient has taken any contraindicated medications since the last contact. Coordinators should ask if the patient is taking any new medications, only recording new medications not previously recorded.

Examples of contraindicated medications are:

- Steroids (Prednisone, Medrol)
- Alpha-blockers (Cardura, Flomax, Minipress, Uroxatral, Hytrin)
- Calcium channel blockers (Cardizem, Diltiazem, Cartia, Tiazac)
- Vardenafil, Levitra, Vivanza

An ST13 (Protocol Violation/Deviation Form) needs to be completed for this patient, AND all follow-ups will continue as scheduled.

Question 12- Are you employed?

Record YES if the patient is currently employed regardless of whether or not they have returned to work.

IF YES,

a. Have you returned to work?

Answer YES if the patient has returned back to work since their visit to the ED and enrollment in STONE.

Question 13- Side effects-Have you experienced…..

Record Yes or No to indicate experiencing any of the side effects:

a. Dizziness at rest
b. Dizziness when standing up
c. Abnormal ejaculation - If the patient is a female, circle 'female' on the form.
d. Stomach upset, nausea or vomiting (gastrointestinal disorder)
e. Bloody/black stool, or bloody vomiting (gastrointestinal bleeding)
f. Abdominal pain or a stomach ulcer
g. Urinary tract infection(s)
h. Facial flushing
i. Headache(s)
j. Tachycardia or fast heart rate

Question 14- Have you had a follow-up visit with any doctor for the stone?

Record YES if the patient has had a follow-up visit with any doctor for the stone since the last contact. This does not include visits to the Emergency Department.

If YES,

Name and phone of MD:

Record the name of the physician the patient saw in the visit reported above. If available, record the contact phone number of the physician reported above. Note this identifying information will not be keyed for data entry. This information is recorded in case the study staff needs to contact the doctor for information.

a. Date of visit:

Enter the date that the patient had a follow up visit with a doctor for the stone indicated above. The mm/dd/yyyy format should be used.

b. Specialty:

Record the specialty of the physician the patient had a follow up visit with for the stone from the following options:

1. Primary care physician (PCP)
2. Urologist
3. Nephrologist
4. Other

If Other (4), **Specify**:

1) Specify the specialty of the physician.

Question 15- Have you returned to the ER because of the stone(s)?

Record YES if the patient has returned to the ER because of the stone since the last contact.

If YES,

a. How many visits?

Record the number of visits the patient has made to the ER since the last contact.

b. Date of most recent visit:

Enter the date of the most recent ED visit for the stone. The mm/dd/yyyy format should be used.

ER?

Record the name of the emergency department that the patient visited. Note that this data is not entered in the database. It is recorded in case the study staff needs to contact the facility for information.

c. CT performed:

Answer YES if a CT scan was performed during the time the patient was in the ED.

d. Ultrasound performed:

Answer YES if an ultrasound was performed during the time the patient in the ED.

Question 16- Have you been hospitalized because of the stone(s)?

Record YES if the patient has been hospitalized because of the stone. This does not include Emergency Department visits documented above in Question 15.

If YES,

a. How many hospitalizations?

Record the number of the hospitalizations. The "00" format should be used.

b. Date of most recent hospitalization:

Record the date that the patient was hospitalized. The mm/dd/yyyy format should be used.

Hospital:

Record the name of the hospital the patient was admitted. Note, this information will not be keyed for data entry. It is recorded in case the study staff needs to contact the facility for information.

c. How many nights did you spend in the hospital?

Record the number of nights the patient spent in the hospital. The 00 format should be used.

Question 17- Have you expelled the stone:

Record if the patient has expelled the stone using the following options

0. No
1. Seen
2. Captured

For patients that physically feel the stone pass, coordinators should record 'NO' on the follow-up form and a comment should be made to indicate the patient felt the stone pass. The same procedure should be used if the patient "thought" the stone(s) passed, but did not see or capture it.

If SEEN (1) or CAPTURED (2),

a. Date

Record the date that the patient expelled the stone and it was either seen or captured. The mm/dd/yyyy format should be used. If the patient had a single stone and previously reported passage, confirm documented date of passage since the last call. If a patient had multiple stones and has passed a new one since the last call, confirm subsequent date of passage.

Question 18- Have you expelled multiple stones?

Record YES if the patient has expelled multiple stones.

If YES,

a. How many stones?

Record the number of stones that have been expelled.

Question 19- Have you had or been scheduled for surgical intervention for stone?

Record if the patient has had or been scheduled for surgical intervention for the stone from the following options:

0. No
1. Yes, Scheduled
2. Yes, already done

If YES, scheduled (1) or performed (2),

a. Type of procedure

Record the procedure performed from the following options:

1. Lithotripsy
2. Ureteral stent
3. Ureteroscopy
4. Laser blast
5. Other

If a patient had two or more procedures, document the procedure they had first. A comment should be added indicating all other procedure with dates. Please note- All comments should clearly indicate any additional procedures other than the first as being secondary. Be sure all comments are clearly noted and entered into MIDAS.

b. Date:

Record the date that the surgical intervention procedure was performed or is scheduled to be performed. The mm/dd/yyyy format should be used

Question 20- Have you experienced any adverse events not mentioned above:

Record YES if the patient has experienced any adverse events not mentioned.
Please complete the Adverse Event Form (ST12) for any adverse experience reported by the participant that is serious or not captured on this form. Adverse events may include, but are not limited to: drug reaction, side effect (not listed above), abnormal laboratory value, hospitalization, other complication or pre-existing condition that worsened.

7.8 Instructions for Completing Form ST11 – Radiological Follow-Up Form

Patient Group: All randomized patients who have a follow-up CT scan

When completed: Complete this form after follow-up CT results are available.

Who completes: Certified study coordinator or certified study staff

Related forms: Form ST10, Follow-Up Form

Special Instructions:

- This form is completed for all follow-up scans.
- The scan can take place at a non-study location. If a documented CT was done outside the study before 29 days that shows stone passage, it will be reviewed by the PI who will determine if the information is comparable and sufficient for study use. If so, these results should be documented on this form.

STONE ID:

Enter the patient's four digit STONE ID number as assigned on the Screening log (ST01) and Eligibility and Randomization Form (ST04).

Question 1- Follow-up CT performed?

Record if a follow-up CT was performed.

If NO,

a. Reason:

Record the reason for follow-up not being completed.

1. Refused – Patients, who indicate being 'too busy/no time' or 'traveling/could not get CT' should be recorded here as they are essentially refusing to come back for a CT.
2. Captured/seen stone – If this reason is used, it should correlate with data reported on form ST10.
3. CT or scan already done – If this reason is used, it should correlate with data reported on form ST10.
4. Urologist recommendation
5. Radiation exposure
6. Surgical intervention – If this reason is used, it should correlate with data reported on forms ST10 and ST13.
9. Other – Please contact BCC if this reason is being used.

If study CT performed, CONTINUE.
If no study CT performed, STOP.

Question 2 – Date of scan:

Enter the date that the patient received a CT scan. The mm/dd/yyyy format should be used.

Question 3 – Initials of person completing this form:

Record the initials of the person completing the form, not the radiologist who read the images. This individual must be a certified study staff member.

Question 4 – Performed follow-up CT for study:

Record if the CT scan was completed as a day 29 follow-up scan for the study.

Question 5 – CT Result:

Record the results of the CT scan result using one of the following codes:

0. No stones
1. Single stone
2. Multiple stones

If there are no stones (0) SKIP to question 10

Question 6 – Number of stones:

Record the number of stones found on the CT scan.

Question 7 –Side of stone(s):

Record the side of the stone(s) location. There could be more than one stone which should be reflected in the response.

1. Left

2. Right
3. Bilateral

Question 8 – Location of additional stone(s):

Record the location of any stones in the following locations:

a. Renal pelvis
b. Proximal ureter
c. Mid ureter
d. Distal ureter
e. UVJ
f. Kidney

Question 9 – Diameter of largest stone:

Record the diameter of the largest stone in millimeters. If stone is a punctate stone, record '1' for the size and make a comment to indicate "punctate stone(s)".

Question 10 – Hydronephrosis:

Record YES if there is any indication of hydronephrosis reported.

Question 11 –Stranding?

Record YES if there is any indication of stranding reported.

Question 12 –Initials of radiologist reading images:

Record the initials of the radiologist who read the images, not the person completing the form.

7.9 Instructions for Completing Form ST12 – Adverse Event Form

Patient Group: Any randomized patients who have experienced an adverse event after randomization.

When completed: Within 48 hours after notification of an event occurring.

Who completes: Certified Study Coordinator or Certified Study Staff

Related forms: None

Special Instructions:

- The NIDDK Project Officer and the BCC will be notified within 48 hours of any adverse events that are serious or considered related to the study procedures.

- For **Question 5**: There is no need to include information captured elsewhere on this form in the response (e.g. the relationship to the event, the treatment). Answers should be concise and should not include dates or doses of medications. Please use only very standard abbreviations. A separate page may be attached if additional space is needed to explain further only if absolutely necessary.

- If two events (with different symptoms. treatments and resolutions) result from the same procedure, two separate Adverse Event forms should be completed.

- An AE report, form ST12 should be completed any time a patient is experiencing side effects that are considered clinically significant. The Steering Committee will assess the frequency of side effects being reported at a later time and examiner if reporting these issues should continue.

- If voluntary information is provided by the patient which resolves or updates a previously completed AE, coordinators should contact the BCC to figure out next steps. This will be handled on a case by case basis.

STONE ID:

Enter the patient's four digit STONE ID number as assigned.

Question 1 – Date of contact:

Enter the date that the patient was contacted. The mm/dd/yyyy format should be used.

Question 2 – Event number:

Record the event number for the follow-up call date. Note: event number only refers to events reported on the specific date of contact. It does not track all adverse events over time. For example, if the patient has pain and dizziness, the events are documented as 1 and 2 with order of no relevance. If only one event is reported on the call, it is documented as event 1.

Question 3 – Initials of person completing this form:

Record the initials of the person completing the form. This individual must be a certified study staff member

Question 4 – Date of onset:

Record the date of the onset of the adverse event. The mm/dd/yyyy format should be used.

Question 5 – Brief description of adverse event:

Briefly describe the adverse event that has occurred**.** If additional space is needed, continue description at the bottom of page two. Answers should be concise and should not include dates or doses of medications.

Question 6 – Taking study medication at the time of the event?

Record YES if the patient had taken study medication within 24 hours before the time of the onset of the event.

If YES,

a. Study medication stopped?

If the patient was taking study medication, record YES if it was discontinued.

Question 7 – Treatment:

Record treatment using the following codes:

0. None
1. Self- treatment/OTC
2. Outpatient/med changes
3. Outpatient procedure
4. Hospitalization

Question 8 – Serious (definition also includes death document in question 8)

More than one may apply.

Record the appropriate answer to indicate whether each part of the FDA definition of serious is applicable. More than one question can apply:

a. Life-threatening
b. Required or prolonged hospitalization
c. Disability
d. Congenital anomaly
e. Required intervention to prevent one of the above or death

Question 9 – Relationship of event of study medication (Principal Investigator's assessment):

Record the Principal Investigator's assessment of the relationship of the adverse event to the study intervention using the following convention:

0. Not related – Record "1"
1. Unlikely – Record "2"
2. Possibly – Record "3"
3. Probably – Record "4"
4. Definitely – Record "5"
5. Not assessable – Record "6"

Question 10 – Current status or outcome:

Record the current status of the patient or outcome of the event using the convention below.

1. Complete recovery – Record "1"
2. Partial recovery – Record "2"
3. Persistent – Record "3"
4. Death – Record "4"
5. Unknown – Record "5"

If (1), Complete recovery,

Item a – Date resolved:
Record the date the adverse event resolved. The mm/dd/yyyy format should be used.

If (4), Death,

Item b – Date of death:
Record the date of the patient's death. The mm/dd/yyyy format should be used.

Item c – Cause of death:
Specify the reason the patient died.

Question 11 – Final Diagnosis:

Report the diagnosis, not necessarily the final diagnosis as per discharge summary.

Question 12 – Date of completion of form:

Enter the date that the form was completed. The mm/dd/yyyy format should be used.

Name of research investigator:

Record the name of the Principal Investigator.

Signature of research investigator:

The signature of the Principal Investigator should be recorded.

7.10 Instructions for Completing Form ST13 – Violation/Deviation Form

Patient Group: Any randomized patients who have experienced violation/deviation from the study protocol.

When completed: Within 48 hours after notification of an event occurring.
Who completes: Certified Study Coordinator or certified study staff

Special Instructions:

- The BCC will be notified within 48 hours of any violation/deviation. A copy of the ST13 will be sent to the BCC along with any reports sent to or received from the center's IRB.
- ST13 should be completed for any patient randomized to the STONE study who should not have been randomized based on protocol inclusion/exclusion.
- Study Coordinator should contact the BCC as well as the IRB. A copy of any reports sent to the IRB must also be sent to the BCC.

Definitions for Violation/Deviation Form should adhere to the following definitions:

Screening/Randomization

- **Screened**-Patient is considered for the study based on diagnosis of ureterolithiasis. Patient has been given a screening number. A screened patient may or may not be randomized.
- **Randomized**- Patient has met all inclusion criteria, has not met any exclusion criteria, has been given a STONE Study number and study medications. All randomized patients are contacted for follow-up.

Note, the term **"Enrolled"** is used outside of STONE in several different ways, and due to the high possibility of miscomprehension, the GWU Biostatistics Center generally does not use this term.

After Randomization

- **Refusal**- The patient has refused to participate in an aspect of the study (for follow-up CT, this includes someone who lives far and is not willing to return). Refusal may be verbal or simply by lack of reason for participation.
- **Crossover to open label medication**- Patient has taken open-label Flomax/tamsulosin during the study. Upon crossing over to open-label medication, study medication should be discontinued as it would be contraindicated.
- **Crossover to surgical procedure**- Patient has undergone a surgical intervention for the current kidney stone(s) during the study.
- **Treatment non-compliance**- A patient who has been randomized and has refused to adhere to the treatment (i.e. taking the study medication).

- **No further contact** - A patient who has been randomized and subsequently decides they no longer want to participate in the study which includes no further contact including calls. As per most consent forms, the patient might need to submit in writing this request to the PI.
- **Lost to Follow-Up** - Any randomized patient for whom primary outcome was not obtained and study contacts/visits were not completed. This category includes those who have requested no further contact (see above) AND those who became unreachable at some point during the study, did not complete follow-up and primary endpoint was not assessed.

Note, the term **"Withdrawal"** is used outside of STONE in several different ways, and due to the high possibility of miscomprehension, the GWU Biostatistics Center generally does not use this term.

STONE ID:

Enter the patient's four digit STONE ID number as assigned.

A. Screening/ Randomization

Question 1 – Should the patient have been randomized?

Record whether the patient should or should not have been randomized. An example of a patient that should not have been randomized is one who met exclusion criteria prior to randomization (i.e. currently taking Flomax, or have a stone >9mm), but was randomized.

If NO, **continue.**

If YES, skip to section B.

Question 2 – Inclusion criteria met?

Record whether or not the patient met inclusion criteria prior to randomization.

If NO, complete questions 2a, b and c:

a. <u>Age <18 years?</u>

If the patient was less than the age of 18 at randomization, record YES.

b. NO evidence of ureterolithiasis on CT?

If there was no evidence of ureterolithiasis on CT prior to randomization, record YES. This could mean either of the following:

- There was no CT performed (no scan of any type done or a scan other than CT done)
- A CT was performed, however there was no kidney stone or none that met study criteria (e.g. only a stone in the bladder)

c. NO telephone?

If the patient did not have access to a phone to be contacted for follow-up, record YES

Question 3 – Should the patient have been excluded from the study?:

Record YES if the patient should have been excluded from the study prior to randomization and then record the appropriate responses to each of the exclusion criteria detailed below.

If YES,

a. Desiring/requiring immediate surgical intervention?

b. Current urinary tract infection?

c. Known anatomical genitourinary abnormalities or prior GU surgeries?

d. Positive pregnancy test?

e. Breastfeeding mother?

f. History of hypersensitivity to tamsulosin?

g. Stone expulsion before randomization?

h. Largest stone dimension ≥ 9mm ?

i. Presence of any stone in bladder (or kidney only)?

j. Ipsilateral, transplanted or solitary kidney ?

k. Known renal insufficiency ?

l. Fever defined as >101.5°F?

m. Floppy iris syndrome?

n. Planned cataract surgery?

o.. Prisoner/ward of state?

p Prior enrollment in STONE?

If YES,

1) – Patient Number:

Record the patient number of prior enrollment.

q. – Exclusionary medication?

Record YES if the patient was taking an exclusionary medication prior to randomization. Exclusionary medications include tamsulosin, vardenafil and similar medications, steroids, alpha blockers (including tamsulosin) or calcium channel blockers..

B. Follow-Up

Question 4 – Incorrect study medication dispensed?

Record whether or not incorrect study medication was dispensed to the patient. This includes study medication dispensed out of randomization order.

If YES, briefly explain

Please provide a brief and detailed explanation summarizing how and why incorrect study medication was dispensed.

Question 5– Crossover to open label Flomax/tamsulosin:

Record whether or not the patient crossed over to open label Flomax. This data should correlate with information reported on form ST10.

Question 6 – Addition of contraindicated medication?

Record if the patient began taking a contraindicated medication after randomization. An example of contraindicated medication is Vardenafil. This information should correlate with data captured on form ST10.

If YES, specify:

Please provide a brief and detailed explanation summarizing.

Question 7 – Crossover to surgery before stone passage or 29 days:

Record here any surgery before stone passage or 29 days after randomization. Examples of surgical procedures include lithotripsy, ureteral stent, ureteroscopy, and laser blast.

If YES, briefly explain

Please provide a brief and detailed explanation to explain reason for crossover to surgery before stone passage or 29 days after randomization.

Question 8 - Patient request no further contact?

Record any patient requesting no further contact. Patients will probably need to submit a written letter to the center PI expressing the desire no further contact with their signature as per IRB request.

If YES,

a. Specify date:

Record the date the patient requested no further contact.

Question 9 - Study follow-up completed?

This question has been added as of September 2015 to identify patients for which primary endpoint has not been assessed. Patients who are lost to follow-up as per their own request (see question 8 above) are not reported here.

If YES,

a. Specify date of last contact:

Record the last date of contact with this patient, regardless of how much data was captured.