YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Biomedical Research
100 FR1 (2015-2)

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: *Toradol to Reduce Ureteroscopic Symptoms Trial (TRUST)*			
Principal Investigator: Piruz Motamedinia		**Yale Academic Appointment:** **Assistant Professor of Urology**	
Department:			
Campus Address: Po Box 208058 New Haven, CT 06520-8058			
Campus Phone: 2037852815	**Fax:** 2037378035	**Pager:**	**E-mail:** Piruz.motamedinia@yale.edu
Protocol Correspondent Name & Address (*if different than PI*):			
Campus Phone:	**Fax:**	**E-mail:**	
Yale Cancer Center CTO Protocol Correspondent Name & Address (*if applicable*):	**Campus Phone:**	**Fax:**	**E-mail:**
Business Manager: Kevin Vest			
Campus Phone :203-785-4371	**Fax :**	**E-mail: Kevin.vest@yale.edu**	

Faculty Advisor:(required if PI is a student, resident, fellow or other trainee) ☒ **NA**		**Yale Academic Appointment:**	
Campus Address:			
Campus Phone:	**Fax:**	**Pager:**	**E-mail:**

Investigator Interests:

Does the principal investigator, or do any research personnel who are responsible for the design, conduct or reporting of this project or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual's role and

degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

See Disclosures and Management of Personal Interests in Human Research
http://www.yale.edu/hrpp/policies/index.html#COI
❑ Yes ❑**x** No

Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?
❑ Yes ❑**x** No

If yes to either question above, list names of the investigator or responsible person:

The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current financial disclosure form on file with the University's Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as co-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form: http://www.yale.edu/coi/

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. **Whether or not they are required to maintain a disclosure form with the University's Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.**

SECTION II: GENERAL INFORMATION

1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

a. Internal Location[s] of the Study:

☐ Magnetic Resonance Research Center (MR-TAC)
☐ Yale Cancer Center/Clinical Trials Office (CTO)
☐ Yale Cancer Center/Smilow
☒ Yale-New Haven Hospital
☐ Cancer Data Repository/Tumor Registry
☐ Specify Other Yale Location:
☐ Yale University PET Center
☐ YCCI/Church Street Research Unit (CSRU)
☐ YCCI/Hospital Research Unit (HRU)
☐ YCCI/Keck Laboratories
☐ Yale-New Haven Hospital—Saint Raphael Campus

b. External Location[s]:

☐ APT Foundation, Inc.	☐ Haskins Laboratories
☐ Connecticut Mental Health Center	☐ John B. Pierce Laboratory, Inc.
☐ Clinical Neuroscience Research Unit (CNRU)	☐ Veterans Affairs Hospital, West Haven
☐ Other Locations, Specify:	☐ International Research Site (Specify location(s)):

c. Additional Required Documents *(check all that apply)*: ☒ N/A

☐ *YCCI-Scientific and Safety Committee (YCCI-SSC)	Approval Date:
☐ *Pediatric Protocol Review Committee (PPRC)	Approval Date:
☐ *YCC Protocol Review Committee (YRC-PRC)	Approval Date:
☐ *Dept. of Veterans Affairs, West Haven VA HSS	Approval Date:
☐ *Radioactive Drug Research Committee (RDRC)	Approval Date:
☐ YNHH-Radiation Safety Committee (YNHH-RSC)	Approval Date:
☐ Yale University RSC (YU-RSC)	Approval Date:
☐ Magnetic Resonance Research Center PRC (MRRC-PRC)	Approval Date:
☐ *Nursing Research Committee	Approval Date:
☐ YSM/YNHH Cancer Data Repository (CaDR)	Approval Date:

☐ Dept. of Lab Medicine request for services or specimens form

☐ Imaging on YNHH Diagnostic Radiology equipment request form (YDRCTO request) found at http://radiology.yale.edu/research/ClinTrials.aspx)

Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.
   The expected duration of the project including all follow-up and data analysis is 48 months from trial initiation.

3. **Research Type/Phase: (Check all that apply)**
   a. **Study Type**
   ☒ Single Center Study
   ☐ Multi-Center Study
   Does the Yale PI serve as the PI of the multi-site study? Yes ☐ No ☒
   ☐ Coordinating Center/Data Management
   ☐ Other:

   b. **Study Phase** ☒ **N/A**
   ☐ Pilot ☐ Phase I ☐ Phase II ☐ Phase III ☐ Phase IV
   ☐ Other (*Specify)*

4. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

☒ Clinical Research: Patient-Oriented
☐ Clinical Research: Epidemiologic and Behavioral
☐ Translational Research #1 ("Bench-to-Bedside")
☐ Translational Research #2 ("Bedside-to-Community")
☐ Clinical Research: Outcomes and Health Services
☐ Interdisciplinary Research
☐ Community-Based Research

5. Is this study a clinical trial? Yes ☒ No ☐

NOTE the current ICMJE (International Committee of Medical Journal Editors) definition of a clinical trial: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events"

If yes, where is it registered?

Clinical Trials.gov registry ☐
Other (*Specify*)

*Registration of clinical trials **at their initiation** is required by the FDA, NIH and by the ICMJE.*

If this study is registered on clinicaltrials.gov, there is new language in the consent form and compound authorization that should be used.

For more information on registering clinical trials, including whether your trial must be registered, see the YCCI webpage, http://ycci.yale.edu/researchers/ors/registerstudy.aspx or contact YCCI at 203.785.3482)

6. Does the Clinical Trials Agreement (CTA) require compliance with ICH GCP (E6)?
Yes ☐ No☒

7. Will this study have a billable service? *A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.*

Yes ☐ No☒

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

8.. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes _x__ No ___ *If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? **Yes**

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? **No**

c. Will a novel approach using existing equipment be applied? **No**

If you answered "no" to question 8a, or "yes" to question 8b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. ***By signing this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH****.*

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

1. **Funding Source:** Indicate all of the funding source(s) for this study. Check all boxes that apply. Provide information regarding the external funding source. This information should include identification of the agency/sponsor, the funding mechanism (grant or contract), and whether the award is pending or has been awarded. Provide the M/C# and Agency name (if grant-funded). If the funding source associated with a protocol is "pending" at the time of the protocol submission to the HIC (as is the case for most NIH submissions), the PI should note "Pending" in the appropriate section of the protocol application, provide the M/C# and Agency name (if grant-funded) and further note that University (departmental) funds support the research (until such time that an award is made).

PI	Title of Grant	Name of Funding Source	Funding	Funding Mechanism

Piruz Motamedinia, M.D.	*Toradol to Reduce Ureteroscopic Symptoms Trial (TRUST)*	Yale Department of Urology	☐ Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For Profit ☒ Other	☐ Grant-M# ☐ Contract# ☐ Contract Pending ☒ Investigator/Department Initiated ☐ Sponsor Initiated ☐ Other, Specify:
			☐ Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For Profit ☐ Other	☐ Grant-M# ☐ Contract# ☐ Contract Pending ☐ Investigator/Department Initiated ☐ Sponsor Initiated ☐ Other, Specify:
			☐ Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For Profit ☐ Other	☐ Grant-M# ☐ Contract# ☐ Contract Pending ☐ Investigator/Department Initiated ☐ Sponsor Initiated ☐ Other, Specify:

IRB Review fees are charged for projects funded by Industry or Other For-Profit Sponsors. Provide the Name and Address of the Sponsor Representative to whom the invoice should be sent. ***Note: the PI's home department will be billed if this information is not provided.***

Send IRB Review Fee Invoice To:

Name:
Company:
Address:

2. **Research Team:** List all members of the research team. Indicate under the affiliation column whether the investigators or study personnel are part of the Yale faculty or staff, or part of the faculty or staff from a collaborating institution, or are not formally affiliated with any institution. **ALL members of the research team MUST complete Human Subject Protection Training (HSPT) and Health Insurance Portability and Accountability Act (HIPAA) Training before they may be listed on the protocol. See NOTE below.**

	Name	**Affiliation: Yale/Other Institution (Identify)**	**NetID**
Principal Investigator	Piruz Motamedinia MD	Yale University Urology	Pm639

Role: Data Analysis, Data Collection, Manuscript Preparation	Jamil Syed	Yale University Urology	Js3569
Role:			
Role:			

NOTE: The HIC will remove from the protocol any personnel who have not completed required training. A personnel protocol amendment will need to be submitted when training is completed.

SECTION IV: PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR AGREEMENT

As the **principal investigator** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean's Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital, or have a faculty advisor.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities.

_____ _____

PI Name (PRINT) and Signature Date

As the **faculty advisor** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- This project has scientific value and merit and that the student or trainee investigator has the necessary resources to complete the project and achieve the aims.
- I will train the student investigator in matters of appropriate research compliance, protection of human subjects and proper conduct of research.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- The student investigator will obtain approval for this research study and any subsequent revisions prior to initiating the study or revision and will obtain continuing approval prior to the expiration of any approval period.
- The student investigator will report to the HIC any serious injuries and/or other unanticipated

Department Chair's Assurance Statement

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a sponsoring company, patents, licensure) associated with this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC.)
☐ No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC)
☐ No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

_____ _____ _____

Chair Name (PRINT) and Signature Date

_____

Department

YNHH Human Subjects Protection Administrator Assurance Statement

Required when the study is conducted solely at YNHH by YNHH health care providers.

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:

- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to notify the IRB if I am aware of any real or apparent institutional conflict of interest.
- The principal investigator of this study is qualified to serve as P.I. and has the support of the hospital for this research project.

_____ _____ _____

YNHH HSPA Name (PRINT) and Signature	Date

SECTION V: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

The objective of this study is to evaluate the effect of a single intraoperative ketorolac injection on intra-operative narcotic use, postoperative pain and narcotic use, and hospital readmission rates in patients who undergo retrograde ureteroscopy for kidney and/or ureteral stone management.

2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

   The incidence and prevalence of urolithiasis in the United States has risen considerably over the past few decades.(1) Treatment for ureteral stones can include expectant therapy for asymptomatic and small stones,, shock wave lithotripsy (SWL) or ureteroscopy (URS) with lithotripsy for obstructing or symptomatic stones up to 15-20mm, and percutaneous nephrolithotomy for larger more complex stones.

   Historically, SWL offered a non-invasive and effective intervention for the treatment of most symptomatic stones and was the preferred therapy. However, with advancement in ureteroscopic digital optics, miniaturization of scope caliber, improved flexibility and durability, and recognized better stone free rates, utilization of URS has steadily grown and is overtaking SWL as the preferred treatment modality for kidney stones. URS is accepted as the treatment of choice for lower ureteral stones and is associated with stone free rates of up to 100% by post-operative day 2.(2)

   One limitation of URS is that post-operative pain due to intra-operative instrumentation and the common utilization of temporary ureteral stents can be challenging to manage. The complication rate for URS requiring postoperative hospital admission has been reported at up to 14%, with pain being the predominant complication.(4) This temporary post-operative pain and stent related colic is perhaps the greatest barrier, aside from surgeon skill, to the wider utilization of this URS over SWL, which has less efficacy but can be better tolerated. In addition to improving URS as a technology, we as physicians must improve the tolerance of URS for the patients.

   Ketorolac is a non-steroidal anti-inflammatory drug (NSAID) available in oral or parenteral formulations. It is a highly effective analgesic with comparable potency to narcotics, non-

habit forming, and without the gastro-intestinal (e.g. nausea, ileus, constipation) or neurologic side effects seen with narcotics. Ketorolac use is generally safe for short durations limited to less than 5 days. Contraindications including NSAID allergy, renal insufficiency, NSAID induced asthma, peptic ulcer disease, bleeding diathesis, pregnancy/breast feeding, or advanced age. The peri-operative use of ketorolac had been limited due to bleeding concerns. However, surgical studies have shown that its use in appropriately selected patients does not result in increased clinically significant bleeding but does improve pain control over placebo with reduced narcotic use. (6)

It has been previously shown that in-patients who undergo ureteral stent placement following SWL, the use of ketorolac as an intravesical agent significantly decreased discomfort 1hour after treatment in comparison to patients who did not receive the treatment.(5) The safety of this was also confirmed as there were no postoperative side effects from the instillation.(5)

Currently, there is currently no consensus on standard of care regarding intraoperative analgesia for ureteroscopy. A ureteral stent is utilized in about 90% of patient. Patients are discharged with a prescription for oral narcotics and stents are usually removed on post-operative day 5-7.

To the best of our knowledge there have not been any prospective studies that have evaluated the use of intraoperative ketorolac in patients who undergo URS, regardless of stent placement, to minimize postoperative pain. We hypothesize that patients who receive intraoperative ketorolac during URS will have improved outcomes with regards to postoperative pain assessment as well as decreased pain related hospital admissions in comparison to patients with no treatment.

3. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths**. Describe the setting in which the research will take place.

This is an investigator-initiated, single-center, prospective randomized clinical trial evaluating the efficacy of intraoperative Ketorolac on post-operative pain in patients undergoing ureteroscopy at Yale-New Haven Hospital.

The study population will include anyone between the age of 18-80 who is undergoing elective ureteroscopy for management of stone disease without contraindication to ketorolac.

Patients who are being consented to undergo a ureteroscopy with Dr. Motamedinia will be asked to participate in this study. There is currently no consensus on standard of care regarding intraoperative analgesia for ureteroscopy. There is wide variability in practice, some clinicians choose to administer intraoperative analgesia while others rely only on the sedation effects of general anesthesia. This study is being carried out to see if administration of Ketorolac during ureteroscopy provides a post-operative benefit in pain scores when compared to no treatment.

The intervention group in this study will receive a one time dose of Ketorolac 30mg intravenously after undergoing general anesthesia. Because they will be under general anesthesia, they will not know if they received the medication. Following the procedure, the intervention group may continue to use Ketorolac as needed to manage pain. The only difference between the intervention group and the non-intervention group is the one time dose of intraoperative ketorolac.

The FDA approves Ketorolac as a nonsteroidal anti-inflammatory drug (NSAID), indicated for the short-term (up to 5 days in adults) management of moderately severe acute pain that requires analgesia at the opioid level.

Following assessment of eligibility and documentation of consent to participate in the study, patients will be randomized to receive intraoperative Ketorolac Tromethamine (Toradol®) or not. In the no-treatment group, participants will not receive a dose of intra-operative Ketorolac. Pain will be managed in the standard way with post-operative Ketorolac as needed. In the treatment group, participants will receive one dose of Ketorolac IV 30mg during the procedure. Randomization will occur by the attending anesthesiologist.

For this trial the investigators, surgical team, and patients will be blinded to the administration of the agent, which is given as an IV Push of 30mg. For patients who are older than 65 years or weight less than 50kg the dose will be adjusted to 15mg to minimize the risk of bleeding. The anesthesiologist will not be blinded as he/she will deliver the agent and because the use of ketorolac may alter their usage of other intra-operative agents and post-operative agents. The surgical team will be un-blinded post-operatively.

Following the procedure, patients will rate their pain using a visual pain assessment scale at 1 hour postoperatively and at the time of discharge from the recovery room. Once the patient is at home, they will fill out a validated survey that has questions related to pain. This will be filled out once a day for a total of 7 days following the procedure. In addition, we will provide a medication utilization diary sheet for the patient to record daily use of prescribed narcotic and other as needed over the counter medications such as acetaminophen and ibuprofen.This will also be done daily for a total of 7 days. The patient will be surveyed at their one-week postoperative visit using the same assessment. All adverse drug reactions will be recorded from time of administration to initial follow-up. The following is the study schedule:

Study Schedule	*Preop*	*Intraop*	*1hr post op*	*2 hr post op*	*1 week*
Assessments					
Consent	*x*				
History and Physical	*x*				
Urine Culture					
Post URS medication record			*x*	*x*	
Pain Questionnaire	*x*		*x*	*x*	*x*
Adverse Events		*x*	*x*	*x*	*x*

4. **Genetic Testing N/A ☒**
   A. Describe
      i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned
      ii. the plan for the collection of material or the conditions under which material will be received
      iii. the types of information about the donor/individual contributors that will be entered into a database
      iv. the methods to uphold confidentiality

   B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects?
   C. Is widespread sharing of materials planned?
   D. When and under what conditions will materials be stripped of all identifiers?
   E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?
      i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)?

   F. Describe the provisions for protection of participant privacy
   G. Describe the methods for the security of storage and sharing of materials

5. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

Only patients with the following indications for URS will be included: All patients who are undergoing elective ureteroscopy for management of stone disease without contraindication to ketorolac.

6. **Subject classification:** Check off all classifications of subjects that will be <u>specifically recruited for enrollment</u> in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐ Children	☒ Healthy	☐ Fetal material, placenta, or dead fetus
☐ Non-English Speaking	☐ Prisoners	☐ Economically disadvantaged persons
☐ Decisionally Impaired	☐ Employees	☐ Pregnant women and/or fetuses
☐ Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #4 for further requirements)

7. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

Inclusion criteria

Kidney Stones requiring surgery
Ureteral stones requiring surgery
Able to undergo general anesthetic
Willing and able to consent to treatment
Willing and able to complete all questionnaires
18 years of age and older

Exclusion criteria

Solitary Kidney
Anatomic Bladder or ureteral abnormality
Previous urinary diversion
Interstitial cystitis
Pregnancy
Ectopic kidney
Renal failure
Coagulopathy
Neurogenic bladder
Transplanted kidney
Indwelling foley catheter or suprapubic tube
Chronic narcotic use
Known contraindications to agent (NSAID allergy, renal insufficiency, NSAID induced asthma, peptic ulcer disease, bleeding diathesis, pregnancy/breast feeding, or advanced age)

8. How will **eligibility** be determined, and by whom?

Eligibility will be determined based on URS indications and inclusion and exclusion criteria. All patients will be determined eligible by Dr. Motamedinia

9. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

Additional risks from participating in this trial include those associated with the use of ketorolac. This includes but is not limited to bruising at place of injection, indigestion, allergic reactions including anaphylactic shock, abdominal pain, abnormal bleeding, vomiting, diarrhea, constipation, gas, bloating, dizziness, drowsiness, sweating, nausea, ringing in the ears, & headaches.

The delivery of pain medications during ureteroscopy require the use of an intravenous (IV) line. This is a safe procedure used in every surgery requiring general anesthesia. There is a slight chance that multiple needle-sticks will be needed to make sure the IV is placed correctly. The subject might feel a small amount of pain when the IV is placed but it does not last very long. A bruise or a minor infection might develop where the IV is placed. A bruise will go away by itself and it might help if you wrap a warm towel around your arm. Infections can also be treated if necessary.

10. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

The above mentioned risks will be minimized as a thorough medication history for each patient will be assessed. Those who are previously known to have adverse events with NSAIDS or specifically ketorolac will be excluded. In addition, medication dosing will be in compliance with federal drug administration recommendation. For severe allergic reactions such as anaphylaxis, all patients will be under monitored anesthesia care during the procedure and immediately postoperatively and as such under the care of indivdiduals trained to recognize and treat this. Patients who are older than 65 may be more sensitive to the effects of ketorolac and clear the drug more slowly, so for this population we will dose reduce to 15mg. In addition, abdominal pain, nausea, vomit- ing, hyperventilation, peptic ulcers and/or erosive gastritis and renal dysfunction which have been associated with single dose ketorolac have resolved with medication discontinuation and for the purposes of this study, participants will only receive one dose and subsequently be discontinued on it.

A bruise from the IV will go away by itself and it might help to wrap a warm towel around the arm. Infections can also be treated with antibiotics if necessary.

11. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.

a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Greater than Minimal risk

b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? n/a

c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for

i. Minimal risk

ii. Greater than minimal

1. Personnel responsible for the safety review and its frequency:

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator, or the IRB have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed greater than minimal for the following reasons: (choose those that apply)

1. We do not view the risks associated with the _use of Ketorolac as minimal risks.

Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

3. Attribution of Adverse Events:
Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator *Piruz Motamedinia* according to the following categories:

Possible: *bruising at place of injection, indigestion, allergic reaction, abdominal pain, abnormal bleeding, vomiting, diarrhea, constipation, gas, bloating, dizziness, drowsiness, sweating, nausea, ringing in the ears, & headaches*may be related to intraoperative Toradol use.

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event- Abdominal pain (mild), headache, gas, bloating, indigestion, nausea
2. Moderate adverse event- Abdominal pain (mild), bruising at place of injection, sweating, diarrhea, dizziness, drowsiness, ringing in the ears
3. Severe- allergic reaction leading to anaphylaxis, abnormal bleeding

5. Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events:
In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death;

2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR
5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE.

6. Plan for reporting UPIRSOs (including Adverse Events) to the IRB

The principal investigator will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. ***Please note*** that adverse events are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented**.** In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

☒ All Co-Investigators listed on the protocol.

☐ Yale Cancer Center Data and Safety Monitoring Committee (DSMC)

☐ National Institutes of Health

☐ Food and Drug Administration (Physician-Sponsored IND #_____)

☐ Medical Research Foundation (Grant_____)

☐ Study Sponsor

☒ Other Data Safety Monitoring Board (DSMB) or Committee (DSMC)

The principal investigator Piruz Motamedinia will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

d. For multi-site studies for which the Yale PI serves as the lead investigator: This is a single site study

i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed?
ii. What provisions are in place for management of interim results?
iii. What will the multi-site process be for protocol modifications?

12. **Statistical Considerations:** Describe the statistical analyses that support the study design.

All data will be collected prospectively. Preoperative data will include patient demographics, number of previous URS, baseline medications including analgesics, urine culture, stone size and location, and pain questionnaire scores. Mean scores will be calculated and compared between groups stratified by follow-up time. The number of adverse events and hospital admissions related to pain will recorded and described as counts and percentages.
The primary outcome that will be used to estimate effect size is mean post-operative pain.

Our study is set up as two independent groups with a continuous outcome (Pain measured on a 1-10 scale) and an enrollment ratio of 1. We anticipate mean post-operative pain in the non-intervention group to be 7 with a standard deviation of 2. We aim to detect a 10% difference in pain, in the intervention arm. With an alpha of 0.05 and a power of 80% we will need to enroll 63 patients in each arm.

SECTION VI: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, state N/A and delete the rest of the section.

A. DRUGS, BIOLOGICS and RADIOTRACERS

1. **Identification of Drug, Biologic or Radiotracer:** What is (are) the **name(s)** of the drug(s) biologic(s) or radiotracer(s) being used? Identify whether FDA approval has been granted and for what indication(s).

Name of Drug: Ketorolac Tromethamine.
It has FDA approval as a nonsteroidal anti-inflammatory drug (NSAID), indicated for the short-term (up to 5 days in adults), management of moderately severe acute pain that requires analgesia at the opioid level.

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

Ketorolac has been used for roughly the past 20 years as an alternative to opiates for parenteral pain management. Limiting the duration of use to 5 days or less has been shown to reduce the adverse effects associated with long-term use (8). The adverse effects of ketorolac are similar to other NSAIDs, including gastrointestinal bleeding, peptic ulcers, renal failure in patients with chronic kidney disease, and bleeding due to platelet enzyme inhibition (9). To minimize the risk of bleeding, it is recommended not to administer ketorolac along with warfarin, heparin, or other NSAIDs (7).

The effects of analgesia with IV and IM administration of ketorolac is generally observed within 10 minutes, with peak pain control at 75-150 minutes. Current dosing recommendations for patients is 30 mg for a single dose, with totally daily dosages totaling less than 60 mg. Age related dosing for patients >65 years is generally accepted to be half of the dosage used for patients <65 years (7, 10).

Studies assessing the use of pre-operative IV administration of ketorolac demonstrated that 15-30 mg of ketorolac did not increase operative times or estimated blood loss, and also did not

significantly affect renal function. Ketorolac also decreased the use of morphine in the experimental group (11).

Other studies assessing the risk of bleeding in patients with concomitant use of ketorolac and anticoagulants failed to demonstrate any enhanced risk of operative site bleeding (8). There was a small risk of gastrointestinal bleeding noted in elderly patients who had used ketorolac more than 5 days with dosages exceeding 105 mg/day; however, use in patients younger than 65 years with dosages less than 105 mg/day, and usage for 5 days or less failed to show any increased risk of GI bleeding (12).

Bleeding risk with ketorolac has been established in spinal surgeries, where a single IV intra-operative dose of 30 mg failed to induce any significant changes in gross or surgical site bleeding (13).

3. **Source:** a) Identify the source of the drug or biologic to be used.

   b) Is the drug provided free of charge to subjects? ☐ Yes ☐ No
   If yes, by whom? This drug is routinely covered as a cost by insurance as part of pain management for outpatient procedures.

4. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity. This drug is routinely utilized by Yale-New Haven hospital and is subjected to the same standards of storage and handling as other commonly utilized post-operative pain medication.

   Check applicable Investigational Drug Service utilized:

   ☐ **YNHH IDS**
   ☐ **CMHC Pharmacy**
   ☐ **PET Center**
   ☐ **Other:**
   ☐ **Yale Cancer Center**
   ☐ **West Haven VA**
   ☒ **None**

   Note: If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.

5. **Use of Placebo: ☒ Not applicable to this research project**
   If use of a placebo is planned, provide a justification which addresses the following:
   1. Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this.
   b. State the maximum total length of time a participant may receive placebo while on the study.
   c. Address the greatest potential harm that may come to a participant as a result of receiving placebo.
   d. Describe the procedures that are in place to safeguard participants receiving placebo.

6. **Use of Controlled Substances:**
   Will this research project involve the use of controlled substances in human subjects?

☐ Yes ☒ No *See HIC Application Instructions to view controlled substance listings*.

If yes, is the use of the controlled substance considered:
☐ Therapeutic: The use of the controlled substance, within the context of the research, has the potential to benefit the research participant.
☐ Non-Therapeutic: *Note, the use of a controlled substance in a non-therapeutic research study involving human subjects may require that the investigator obtain a Laboratory Research License. Examples include controlled substances used for basic imaging, observation or biochemical studies or other non-therapeutic purposes. See Instructions for further information.*

7. **Continuation of Drug Therapy After Study Closure** ☒ **Not applicable to this project**
Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?
☐ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access.

☐ No If no, explain why this is acceptable.

B. DEVICES

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☒No *If Yes, please be aware of the following requirements*:

SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

a. targeted for enrollment at Yale for this protocol 126
b. If this is a multi-site study, give the total number of subjects targeted across all sites N/A

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☐ Flyers	☐ Internet/Web Postings	☐ Radio
☐ Posters	☐ Mass E-mail Solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center Website	☐ Television
☐ Medical Record Review	☐ Departmental/Center Research Boards	☐ Newspaper
☐ Departmental/Center Newsletters	☐ Web-Based Clinical Trial Registries	
☐ YCCI Recruitment database	☐ Clinicaltrials.gov Registry (do not send materials to HIC)	

☒ Other (describe): *Patients will be recruited at time of consultation for URS*

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.
Subjects will be identified at time of consultation for URS
b. Describe how potential subjects are contacted.
Subjects are contacted in person at consultation
c. Who is recruiting potential subjects?

The principle investigator

4. Screening Procedures

a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☐ Yes ☒ No

b. If yes, identify below all health information to be collected as part of screening and check off any of the following HIPAA identifiers to be collected and retained by the research team during this screening process.

HEALTH INFORMATION TO BE COLLECTED:

HIPAA identifiers:

☐ Names

☐ All geographic subdivisions smaller than a State, including: street address, city, county, precinct, zip codes and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly-available data from the Bureau of the Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people, and (2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.

☐ Telephone numbers

☐ Fax numbers

☐ E-mail addresses

☐ Social Security numbers

☐ Medical record numbers

☐ Health plan beneficiary numbers

☐ Account numbers

☐ All elements of dates (except year) for dates related to an individual, including: birth date, admission date, discharge date, date of death, all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older

☐ Certificate/license numbers

☐ Vehicle identifiers and serial numbers, including license plate numbers

☐ Device identifiers and serial numbers

☐ Web Universal Resource Locators (URLs)

☐ Internet Protocol (IP) address numbers

☐ Biometric identifiers, including finger and voice prints

☐ Full face photographic images and any comparable images

☐ Any other unique identifying numbers, characteristics, or codes

5. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☒ Yes, all subjects

☐ Yes, some of the subjects

☐ No

If yes, describe the nature of this relationship.

All patients that are recruited into the study will be patients of the Principle Investigator (Piruz Motamedinia) and have a direct clinical relationship with him. Recruitment and data collection will be done through clinical visits.

6. **Request for waiver of HIPAA authorization:** (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

   Choose one:
   ☐ For entire study
   ☐ For recruitment purposes only
   ☐ For inclusion of non-English speaking subject if short form is being used

   i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data;
   ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data;

   By signing this protocol application, the investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

   Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

7. **Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:
   ☒ Compound Consent and Authorization form
   ☐ HIPAA Research Authorization Form

8. **Consent Personnel:** List the names of all members of the research team who will be obtaining consent/assent.
   Dr. Piruz Motamedinia will be obtaining consent/assent

9. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

The PI routinely consults with patients regarding urinary stones. During the initial outpatient consultation with the PI, patients who are candidates for ureterscopic management and are in agreement to this surgical method will be recruited to participate in the study. These are all patients being seen in the outpatient clinic prior to surgery and are not under any acute distress/pain.
The investigator will explain the research study to the participant and answer any questions that may arise. The participants will sign the informed consent document prior to any procedures being done specifically for the study. The participants will have sufficient opportunity to discuss the study and process the information in the consent process prior to agreeing to participate. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.
The acquisition of informed consent will be documented in the participant's medical records. The informed consent form will be signed and personally dated by the participant and the person who conducted the informed consent discussion. The original signed informed consent form will be retained in the medical chart and a copy will be provided to the participant

10. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

The PI performs a mental status exam as part of every physical exam during clinic visit. This exam assesses the subjects thought process, cognition, insight, and judgement. In addition to using this routine exam, the PI will assess the subject's ability and capacity to consent by asking questions during the consent process to gauge whether they have an understanding of the study. If the subject does not fully understand the study as it is described, he/she will not be enrolled.

11. Documentation of Consent/Assent: Consent form and pain assessment questionnaire will be used during the consent/assent process. Copies are attached

12. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

We will not be recruiting non-English speaking patients in this trial.

12(a) As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment?
YES ☐ NO ☐

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are found on our website at: http://www.yale.edu/hrpp/forms-templates/biomedical.html. If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via amendment prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

13. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☒ **Not Requesting a consent waiver**
☐ **Requesting a waiver of signed consent**
☐ **Requesting a full waiver of consent**

A. Waiver of **signed** consent: (Verbal consent from subjects will be obtained. **If PHI is collected, information in this section must match Section VII, Question 6**)

☐ **Requesting a waiver of signed consent for Recruitment/Screening only**

If requesting a waiver of signed consent, please address the following:
a. Would the signed consent form be the only record linking the subject and the research?
☐ Yes ☐ No
b. Does a breach of confidentiality constitute the principal risk to subjects?
☐ Yes ☐ No

OR

c. Does the research activity pose greater than minimal risk?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

☐ **Requesting a waiver of signed consent for the Entire Study (**Note that an information sheet may be required.)

If requesting a waiver of signed consent, please address the following:
a. Would the signed consent form be the only record linking the subject and the research?
☐ Yes ☐ No

b. Does a breach of confidentiality constitute the principal risk to subjects?
☐ Yes ☐ No

OR

c. Does the research pose greater than minimal risk? ☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** ☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

B. **Full waiver** of consent: (No consent from subjects will be obtained for the activity.)

☐ **Requesting a waiver of consent for Recruitment/Screening only**

a. Does the research activity pose greater than minimal risk to subjects?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☐ No
b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No
c. Why would the research be impracticable to conduct without the waiver?
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

☐ **Requesting a full waiver of consent for the Entire Study (Note: If PHI is collected, information here must match Section VII, question 6.)**

If requesting a full waiver of consent, please address the following:

a. Does the research pose greater than minimal risk to subjects?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.***
☐ No
b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No
c. Why would the research be impracticable to conduct without the waiver?
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

SECTION VIII: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

Patient name, age and medical record number will be collected.

b. How will the research data be collected, recorded and stored?

Participants' signed consent forms will be contained in a secure location separate from the questionnaires – within a locked file cabinet in the principle investigators office. The questionnaires will not have any identifying information on them. All data will be accessible only to the researcher(s) and the research advisor.

c. How will the digital data be stored? ☐ CD ☐ DVD ☐ Flash Drive ☐ Portable Hard Drive ☐ Secured Server ☒ Laptop Computer ☐ Desktop Computer ☐ Other

d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

The investigators will ensure that the subject's anonymity is maintained. Subjects will not be identified in any publicly released reports of this study. All records will be kept confidential to the extent provided by federal, state and local law. The study monitors may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records. The investigator will inform the subjects that the above-named representatives will review their study-related records without violating the confidentiality of the subjects. All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified only by a coded number in order to maintain subject confidentiality. All records will be kept in a password protected computer. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB.

Do all portable devices contain encryption software? ☒ Yes ☐ No
If no, see http://hipaa.yale.edu/guidance/policy.html

c. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured. A*nonymized data will be kept through the course of the study and upon completion of manuscript after which it will be destroyed.*

d. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)

Only the specified research team will have access to the PHI.

g. If appropriate, has a Certificate of Confidentiality been obtained?

h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview -incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported.

We do not anticipate that any of the study procedures will yield information subject to mandatory reporting requirements

SECTION IX: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

The treatment group may experience decreased postoperative pain and decreased risk of needing hospital readmission. The results of this study may be useful for guiding treatment strategies for other institutions involved in URS procedures. In the event that no-benefit is noted (negative study) these findings would discourage the ineffective use of a medication which is cost saving and limit potential drug related side effects.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research? Alternatives include no additional pain medication intraoperatively.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

   There will be no payments made to subjects of this trial.

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.
   Ketorolac is commonly used in the peri-operative setting. Costs of the drug are bundled into the billed amount for the specific procedure performed.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.
   a. Will medical treatment be available if research-related injury occurs? Yes medical treatment will be available for research-related injury, this will be coordinated by the PI.
   b. Where and from whom may treatment be obtained? The surgical team will routinely evaluate the patient during their operative stay and consult the appropriate specialty service should an injury occur.
   c. Are there any limits to the treatment being provided? No
   d. Who will pay for this treatment? This will be under the same coverage of the patients insurance for the procedure.
   e. How will the medical treatment be accessed by subjects? Patients may present to Yale-New Haven Hospital for medical assistance that is required as part of this research project.

1. Scales CD, Jr. Practice patterns in the management of urinary lithiasis. Current urology reports. 2013;14(2):154-7.
2. Peschel R, Janetschek G, Bartsch G. Extracorporeal shock wave lithotripsy versus ureteroscopy for distal ureteral calculi: a prospective randomized study. J Urol. 1999;162(6):1909-12.
3. Pearle MS, Calhoun EA, Curhan GC. Urologic diseases in America project: urolithiasis. J Urol. 2005;173(3):848-57.
4. Bromwich EJ, Lockyer R, Keoghane SR. Day-case rigid and flexible ureteroscopy. Annals of the Royal College of Surgeons of England. 2007;89(5):526-8.
5. Beiko DT, Watterson JD, Knudsen BE, Nott L, Pautler SE, Brock GB, et al. Double-blind randomized controlled trial assessing the safety and efficacy of intravesical agents for ureteral stent symptoms after extracorporeal shockwave lithotripsy. Journal of endourology / Endourological Society. 2004;18(8):723-30.
6. Gobble RM, Hoang HL, Kachniarz B, et al. Ketorolac does not increase perioperative bleeding: a meta-analysis of randomized controlled trials. *Plast Reconstr Surg*. 2014; 133: 741–755.
7. Vadivelu, N., Gowda, A. M., Urman, R. D., Jolly, S., Kodumudi, V., Maria, M., Taylor, R. and Pergolizzi, J. V. (2015), Ketorolac Tromethamine – Routes and Clinical Implications. Pain Pract, 15: 175–193.
8. Jung D, Mroszczak E, Bynum L. Pharmacokinetics of ketorolac tromethamine in humans after intravenous, intra- muscular and oral administration. Eur J Clin Pharmacol. 1988;35:423–425.

9. Litvak KM, McEvoy GK. Ketorolac, an injectable nonnarcotic analgesic. Clin Pharm. 1990;9:921–935.

10. He A, Hersh EV. A review of intranasal ketorolac tromethamine for the short-term management of moderate to moderately severe pain that requires analgesia at the opioid level. Curr Med Res Opin. 2012;28:1873–1880.

11. Chow GK, Fabrizio MD, Steer T, et al. Prospective double-blind study of effect of ketorolac administration after laparoscopic urologic surgery. J Endourol. 2001;15:171– 174.

12. Strom BL, Berlin JA, Kinman JL, et al. Parenteral ketorolac and risk of gastrointestinal and operative site bleeding. A postmarketing surveillance study. JAMA. 1996;275:376–382.

13. Chin KR, Sundram H, Marcotte P. Bleeding risk with ketorolac after lumbar microdiscectomy. J Spinal Disord Tech. 2007;20:123–126.