Narcotic-Free Percutaneous Nephrolithotomy
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PI: Mantu Gupta, MD
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NARCOTIC-FREE PERCUTANEOUS NEPHROLITHOTOMY

Protocol Number: STUDY-23-00206

Principal Investigator: Mantu Gupta, MD

Funded by: Icahn School of Medicine at Mount Sinai

28 April 2023

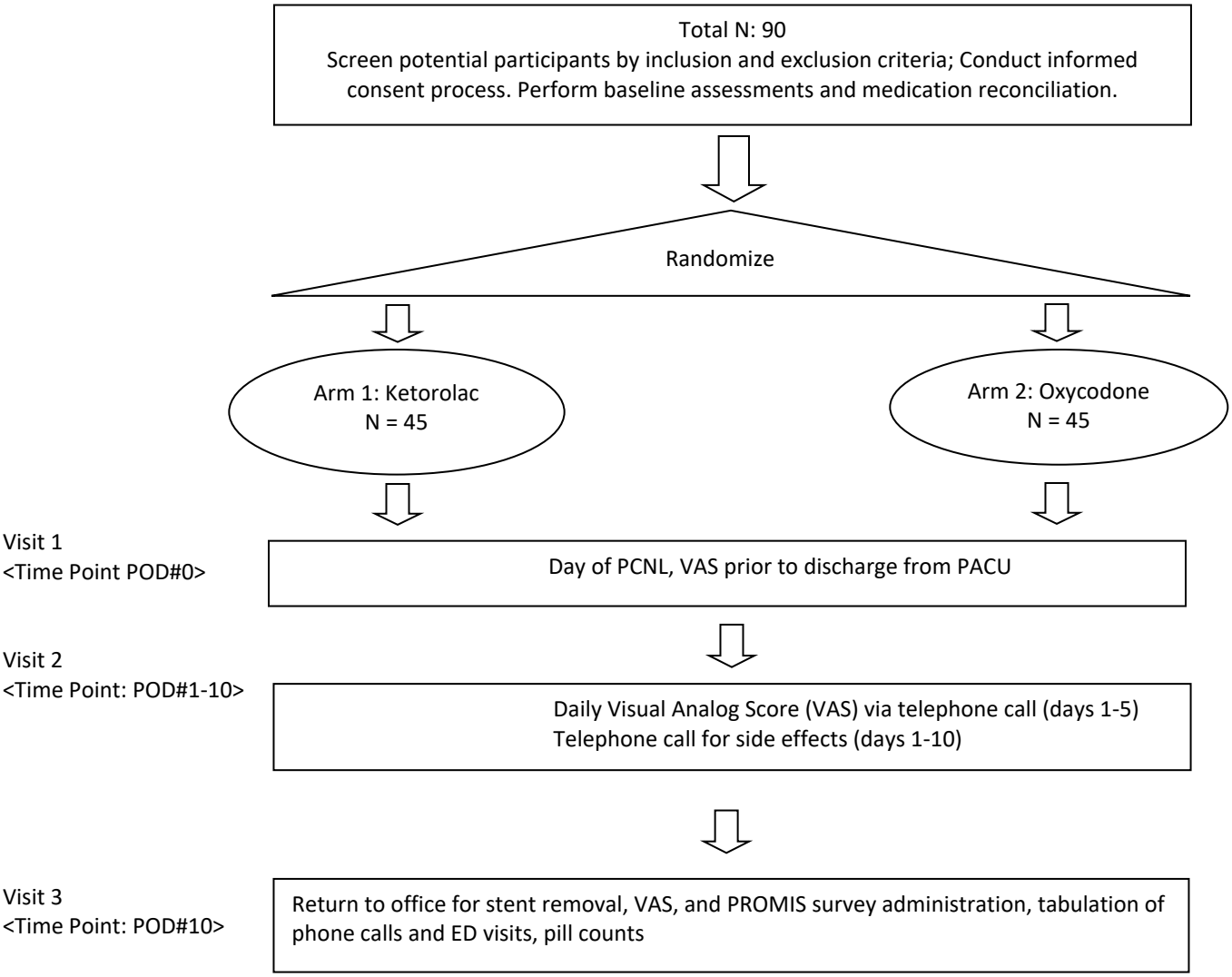
Effective Date: 4/9/2024
End Date:4/8/2025

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Narcotic-free Percutaneous Nephrolithotomy
Grant Number:	*N/A*
Study Description:	This is a randomized control trial comparing oral ketorolac and opioid medication for the use of post-operative analgesia.
Objectives:	**Primary Objective:** 1. To establish the non-inferiority of oral NSAIDs compared with oral opioids for post-operative pain control after percutaneous nephrolithotomy (PCNL) **Secondary Objectives:** 1. To establish a standard of care pathway for post-PCNL pain control 2. To quantify average number of pills of pain medication required after PCNL
Endpoints:	**Primary Endpoint:** ● Visual analog scale pain scores **Secondary Endpoints:** ● Pill counts ● patient-related outcome survey (PROMIS) scores ● Emergency room visits ● Patient telephone calls
Study Population:	Adult patients 18 years and older with a planned standard percutaneous nephrolithotomy procedure
Phase* or Stage:	N/A
Description of Sites/Facilities Enrolling Participants:	Written consent will be obtained at the approved clinic sites where the Principal Investigator sees patients (425 W. 59th Street, Suite 4F & 625 Madison Ave, 2nd floor). Participants will undergo surgery at Mount Sinai West Hospital. Follow up will also occur at the aforementioned clinic sites.
Description of Study Intervention/Experimental Manipulation:	Patients undergoing PCNL will be randomized to receive either oxycodone or ketorolac for post-operative pain control
Study Duration*:	*18-24 months*
Participant Duration:	*10 days*

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES

Outcome	POD#0	POD#1	POD#2	POD#3	POD#4	POD#5	POD#6	POD#7	POD#8	POD#9	POD#10
VAS Score (max and average)	X	X	X	X	X	X					X
PROMIS											X
Pill count											X
Side effect Telephone Call	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	X

2 INTRODUCTION

2.1 STUDY RATIONALE

In the literature, there lacks a consensus on the utility of narcotics for post operative pain relief during percutaneous nephrolithotomy (PCNL). Physicians and surgeons have been entrusted with devising effective and strategic methods for lowering opioid prescription in light of the present national opioid epidemic. In place of opioid-based pharmaceuticals, urologists are increasingly recommending nonsteroidal anti-inflammatory drugs for postoperative analgesia due to encouraging findings, albeit anecdotal. We intend to conduct a prospective randomized study to demonstrate the noninferiority of NSAIDs (especially Ketorolac) against opioid-based medications.

2.2 BACKGROUND

Percutaneous Nephrolithotomy (PCNL) is the gold standard therapy for kidney stones larger than 2 cm, with a higher stone-free rate and fewer re-do procedures than ureteroscopic and shockwave procedures. Postoperative pain is a common concern for patients and a challenge for surgeons, since it is one of the most frequent reasons for hospital readmission. Pain following PCNL should be regarded as a result of the technique. Smaller diameter tracts and alternative postoperative renal drainage have been studied as potential pain-relieving strategies, but only for simple cases. Post-PCNL pain is largely controlled with analgesic medicines, in particular narcotics and recently non-steroidal anti-inflammatory drugs (NSAIDs) in order to limit opioid consumption. In urological operations, it has been demonstrated that patients are routinely over prescribed opioid pills. The greatest issue with narcotics is their abuse, which may lead to addiction and deadly overdoses, and evidence indicates that even short-term usage of opioids for post-operative pain can lead to long-term use. This opioid crisis is a significant concern presently with astounding figures. While both narcotics and NSAIDS are both commonly prescribed after PCNL, no standard of care has been established.

Recently, the use of NSAIDs has been promoted because prostaglandin inhibition in ureteral smooth muscle may be advantageous for both renal colic and postoperative pain. There is data that indicates the non-inferiority and safety of NSAIDs (mostly Ketorolac) compared to opioids in kidney stone (ureteroscopy and PCNL) post-operative therapy, indicating lower peak pain intensity and lower average pain levels in comparison to the narcotics control group. The average pain intensity and pain score were also evaluated one week following the surgery in another study that assessed pain one week later. A comparative examination of the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids is required to better establish the value of NSAIDs in post-operative PCNL care, resulting in the use of narcotics only when medically necessary and preventing potential addiction.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Side effects associated with Ketorolac include:

- Gastrointestinal and bleeding risks: nausea, vomiting, diarrhea, gas, peptic ulcers, gastrointestinal bleeding, and/or perforation of the stomach or intestines
- Cardiovascular risks: serious cardiovascular thrombotic events, myocardial infarction, stroke, hypertension
- Renal (kidney) risks: renal impairment (although this risk is low because eligible subjects must have documented eGFR < 60 mL/min).
- Other risks: dizziness, drowsiness, mental/mood changes, allergic reactions

Risks associated with oxycodone include constipation, nausea, vomiting, headache, pruritus (itchy skin), insomnia (trouble sleeping), dizziness, asthenia (weakness/tiredness), and somnolence (drowsiness).

Subjects will be counseled to call our office (24-hour line) if they experience any side effects so that they can discuss this with a provider.

2.3.2 KNOWN POTENTIAL BENEFITS

Given the duration of study and the "as needed" nature of post-operative analgesia, the prescription is for a limited number of days. We do not anticipate any further benefit to the study participants aside from adequate postoperative pain control.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Study participants will be exposed to commonly prescribed analgesic medication. Medication overuse will be minimized as no more than 3 days of 'as needed medication" would be prescribed.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
To establish the non-inferiority of oral NSAIDs compared with oral opioids for post-operative pain control after percutaneous nephrolithotomy (PCNL)	The primary endpoint will be determination of visual analog scale (VAS) pain scores on POD#0-5, and again on POD#10	VAS score is the most accurate representation of quantifiable pain post-operatively	*N/A*
Secondary			

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OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
1. To establish a standard of care pathway for post-PCNL pain control 2. To quantify average number of pills of pain medication required after PCNL	1. Pill counts performed on POD#10 (at time of stent removal) 2. Determination of number of pain-related office phone calls and ED visits	Pill counts and pain-related office phone calls/ED visits will allow us to determine the feasibility of establishing a non-opioid pathway after PCNL	*N/A*
Tertiary/Exploratory			
N/A	N/A	N/A	N/A

4 STUDY DESIGN

4.1 OVERALL DESIGN

The proposed study will be a randomized controlled trial (RCT) designed to assess the non-inferiority of non-opioid pain management after PCNL. Patients who are scheduled to undergo PCNL (see inclusion/exclusion criteria) will be randomized in a 1:1 ratio into one of two groups: 1) an opioid group, in which patients will be discharged home with 12 tablets of oxycodone (5mg, Q6 PRN) in addition to the standard post-procedural, stent-related medications of oxybutynin and phenazopyridine. 2) an NSAID group, in which patients will be discharged home with 12 tablets of ketorolac (10mg Q6 PRN) in addition to the standard post-procedural, stent-related medications of oxybutynin and phenazopyridine. While both oxycodone and ketorolac are both commonly prescribed after PCNL, no standard of care has been established. Block randomization will take place prior to study initiation and surgeons will be blinded to each patient's allocated study group before and during surgery. After informed consent, patients will then undergo PCNL as per standard of care in our practice. A 6Fr silicone stent will also be placed at the end of the procedure as is the standard of care in our practice.

Patients will be asked to provide their VAS pain score at multiple time points including POD#0 (just prior to discharge from hospital), and POD#1-5 (via telephone call). At each of these time points, maximum and average VAS scores for the preceding 24 hours will be provided. Patients will also be asked if they are experiencing any side effects on POD #1-10 via telephone call. As is our routine practice, patients will have their stents removed on POD#10 in the office. During this office visit, patients will again provide a VAS pain score, and will complete the PROMIS survey (see attachment). Pill counts will be performed of all prescription medications and tabulation of pain-related office phone calls and ED visits will also be performed. Thus, patients will be enrolled for a total of 10 days.

Patients will be instructed to call our 24-hour phone number if they run out of medication, are experiencing pain, or are experiencing side effects. The surgeon will evaluate the patient's pain intensity. If the patient's pain is controlled while on the allocated medication and has ran out of medication, the doctor will refill the same medication. However, if the patient's pain is not being controlled adequately or if they are not tolerating the medication/experiencing side effects, the surgeon will prescribe the other medication and they will cross over to the other study group.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

In this study, the group receiving opioids (oxycodone) will be considered our control group. This is still considered the standard of care in parts of the world. Our comparison group has been chosen to receive ketorolac for several reasons. First, NSAIDs such as ketorolac provide analgesic and anti-inflammatory pathways that have both been shown to reduce renal- and stent-related colic. Second, ketorolac (and NSAIDs in general) have been demonstrated to be non-inferior in terms of pain control during ureteroscopic laser lithotripsy, a less invasive type of surgery for kidney stones.

Opioids have gained worldwide attention in recent years due to their potential for abuse, addiction, in addition to their other side effects of nausea, vomiting, constipation, and altered mental status. In this regard, ketorolac has no known potential for addiction or abuse, and has a relatively favorable side effect profile.

4.3 JUSTIFICATION FOR INTERVENTION

Both post operative medications are commonly prescribed but a head-to-head comparison of their efficacy has not been studied in a prospective randomized study. Study participation requires no additional visits or excessive effort placed upon the study participants as standard of care intervention and follow will be the same regardless of study participation or not.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the baseline assessment, provided VAS pain scores on POD#1-5 via phone call, and returned for stent removal on POD#10, at which time pill counts and PROMIS survey will be performed.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet the following criteria:

1. Undergoing scheduled unilateral standard (24Fr), PCNL with at least 2cm stone burden, with expected single access

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Pregnant women
2. History of chronic opioid abuse
3. Allergy, hypersensitivity, or other contraindication to NSAID usage such as
    - eGFR < 60 mL/min
    - Peptic ulcer disease or history of gastric bypass
    - Concurrent use of antiplatelet or anticoagulation therapy (including aspirin)
    - Thrombocytopenia
    - Suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic diathesis, incomplete hemostasis, and those at high risk of bleeding.
    - Concomitant medications:
        - Other NSAIDs
        - Antiplatelet or anticoagulation medications
        - Probenecid
        - Pentoxifylline
4. Allergy, hypersensitivity, or other contraindication to opioids:
    - Current opioid prescription/usage for any reason, including active treatment with suboxone or methadone
    - Respiratory depression
    - Patients with acute or severe bronchial asthma or hypercarbia
    - Patients who have or is suspected of having paralytic ileus as PCNL done under general anesthesia
    - Patients with hepatic Impairment
    - Concomitant medications:
        - Monoamine Oxidase Inhibitors (MAOIs)
        - Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics
5. Diagnosis of chronic pain disorder
6. Reduced sensation of abdomen or pelvis (e.g. patients with spinal cord injury)
7. Pre-existing stent or nephrostomy tube
8. Urinary tract anomalies such as urinary diversion, horseshoe kidney, solitary kidney, urinary stricture disease, ureteropelvic junction obstruction, pelvic kidney, stone in calyceal diverticulum)
9. Pulmonary disease
10. Liver disease
11. Seizure disorders
12. Subjects taking nephrotoxic medications
13. Subjects taking medications that can increase sedation risk (benzodiazepines or other sedative hypnotics)

5.3 LIFESTYLE CONSIDERATIONS

If the subject can possibly get pregnant, they must agree to use at least two forms of contraception. All subjects that can get pregnant will be given a pregnancy test on the day of the procedure in the pre-operative area.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened.

Examples of screen failures specific to this trial include:

1. Intraoperative determination of need for more than 1 access tract
2. Significant renal pelvis perforation and/or urinary extravasation

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients will be recruited from the practices of Dr. Mantu Gupta and Dr. Atallah. Dr. Gupta and Dr. Atallah have one of the busiest kidney stone practices in the area providing ample patients to recruit into the study. We do not anticipate any issues with retention as patient involvement will occur at two visits. The first visit on the day of the surgical intervention. The second visit takes place during an obligatory outpatient follow up visit. The follow up visit is considered obligatory as patients will have their ureteral stents removed at this visit.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

Randomization will occur preoperatively. All subjects will undergo surgical interventions that abide by broadly accepted guidelines and standards of care, allowing for slight variations in technique as seen necessary by the attending surgeon Dr. Gupta and Dr. Atallah.

Subjects are assigned to receive either Oxycodone or Ketorolac postoperatively.

6.1.2 ADMINISTRATION AND/OR DOSING

Oxycodone dose: 12 tablets of 5mg, Q6 PRN

Ketorolac dose: 12 tablets of 10mg, Q6 PRN

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization in this study will be performed prior to initiation of patient enrollment via computer-based algorithm. All study staff members who are active participants in patient care (e.g. surgeons) will be blinded to the allocated study sequence before and during surgery. After surgery, the surgeon will prescribe the allocated medications.

Subjects will not be blinded to their study group.

6.3 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

In order to remain active in the study, participants will receive a phone call once daily for the first 5 days after surgery (POD#1-5). During this phone call, VAS pain scores will be assessed, and participants will be reminded to adhere to the prescribed study medications to the extent possible.

6.4 CONCOMITANT THERAPY

For this protocol, participants may use non-opioid analgesics for pain control, including over-the-counter medications such as acetaminophen (in both groups) and over-the-counter NSAIDs (in the opioid group), and prescribed medications. Participants in the ketorolac group will be advised not to take additional over-the-counter NSAIDs (e.g. ibuprofen). Medication usage will be assessed at each study visit and documented.

6.4.1 RESCUE THERAPY

Rescue therapy will not routinely be prescribed at study initiation. Participants have access to a physician within the study group at all times via telephone call. If pain control is inadequate with study medications, participants who call may be prescribed additional rescue medication. If the patient's pain is controlled while on the allocated medication and has ran out of medication, the doctor will refill the same medication. However, if the patient's pain is not being controlled adequately or if they are not tolerating the medication/experiencing side effects, the surgeon will prescribe the other medication and they will cross over to the other study group.

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

Discontinuation of study medication will take place if the patient has any adverse effects or allergic reactions to the medication. Patients will be instructed to call the study team if any adverse effects occur. Additionally, a member of the study team will screen for any adverse events during the phone calls on POD'S 1-5.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Patients will be considered enrolled in the study once consent has been signed. Participants may discontinue or withdraw from the study for any reason and at any point in time through the conclusion of the study.

7.3 LOST TO FOLLOW-UP

A single follow up visit is required to complete enrollment criteria for this study. Participants who fail to show up to their first follow up appointment for stent removal will be automatically withdrawn from the study and previously collected urine samples will be discarded as above.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.1.1 DEFINITION OF ADVERSE EVENTS

Any untoward medical occurrence, unintended sign, symptom, illness or disease temporally associated with the study protocol regardless of the suspected cause.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An Adverse Event that is considered "serious" if it meets at minimum one of the three Seriousness reporting criterions below:

1. Led to death,
2. Led to a serious injury which:
    a. Resulted in a life-threatening illness or injury, or
    b. Resulted in a permanent impairment of a body structure or a body function, or
    c. Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function

8.1.3 CLASSIFICATION OF AN ADVERSE EVENT

8.1.1.1 SEVERITY OF EVENT

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".]

8.1.1.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All AEs will be assessed for relationship to the study protocol based on the following definitions:

Not Related: There is no clear evidence that the AE has a relationship to the study protocol and can be attributed to an underlying or concurrent illness/clinical condition or an effect of another device, drug or treatment.

Related: There is a clear causal relationship of the AE to the marketed device or procedure beyond reasonable doubt.

8.1.2 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

All enrolled subjects will be monitored for adverse events by review of the medical record on a monthly basis by Dr. Gupta. Subjects will have routine follow up scheduled 10 days postoperatively at which time in-person visit will be performed and assessment of adverse events may be performed.

8.1.3 ADVERSE EVENT REPORTING

Adverse events must be reported to the IRB as soon as possible and no later than **2 working days** after the PI first becomes aware of the event. The PI or designee must record all AE information that can be gathered within the reporting timeframe and enter it onto the AE eCRF.
Relevant follow-up information should be submitted to the IRB as soon as it becomes available and/or upon request.

8.1.4 SERIOUS ADVERSE EVENT REPORTING

Serious adverse events must be reported to the IRB as soon as possible and no later than **2 working days** after the PI first becomes aware of the event. The PI or designee must record all AE information that can be gathered within the reporting timeframe and enter it onto the AE eCRF.
Relevant follow-up information should be submitted to the IRB as soon as it becomes available and/or upon request.

8.1.5 REPORTING EVENTS TO PARTICIPANTS

All SAE's or AE's will be reported to affected participants by the principal investigator directly.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Null Hypothesis: There is no difference in post operative pain control between NSAIDS and narcotics

Alternative Hypothesis: There is a difference in post operative pain control between NSAIDS and narcotics

9.2 SAMPLE SIZE DETERMINATION

To obtain a statistical power of 80% with a 5% significance level (alpha), with a 2.5 standard deviation of the outcome, a sample size of 80 subjects would be required to run a non-inferiority study between the two arms. A noninferiority limit of 1.4 was chosen based on prior literature appropriate to this study population.

To account for the possibility of screen failures (intraoperative determination of need for more than 1 access tract, renal pelvis perforation, and/or urinary extravasation), 10 patients have been added which equals 90 patients total enrolled.

9.3 POPULATIONS FOR ANALYSES

We will be performing an intention-to-treat analysis, and all enrolled subjects will be included for analyses.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Survey, quantitative, and qualitative variables will be presented as medians, interquartile ranges, and percent, respectively. The p-value to be used for statistical significance is 0.05 (two-tailed).

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Visual analog scale pain scores will be analyzed using t-tests to compare medians.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Pill counts and patient-related outcome survey (PROMIS) scores will be analyzed using t-tests to compare medians.

Emergency room visits and patient telephone calls will be analyzed as categorical outcomes using Chi-squares.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

The standard informed consent process for research outlined in SOP HRP-090 will be followed.

10.1.1.1 CONSENT PROCEDURES AND DOCUMENTATION

Subjects will be recruited from Dr. Mantu Gupta's and Dr. William Atallah's practice. Patients will be recruited during initial presentation to the office. Consent will be obtained at the initial office visit when decision to proceed to surgery has been made.

Potential subjects will be informed of the study at their preoperative visit (see above point) and may sign the consent at that time if they feel comfortable. If subjects require time for further contemplation, the consent may be signed on the day of surgery in the preoperative area (prior to administration of any anesthesia). This gives potential subjects at least 24 hours to consider the study and review the consent form.

We anticipate that no more than 5-10 minutes will generally be required to explain the consent form. However, longer and more extensive discussions will be available to those who request or require. All potential subjects will be verbally informed that their participation is completely optional and that their decision of whether or not to participate does not impact their care in any manner. Subjects will be asked to verbally repeat and summarize their involvement in the study. A copy of the consent form will be provided to the subject directly after signing the form.

10.1.2 CONFIDENTIALITY AND PRIVACY

All data will be housed in Mount Sinai's REDCap database. The data is will be deidentified and stored with protected passwords. The data will be reported to the sites in aggregate. The publication will also not mention any center by name. The results in the publication will be in aggregate form and anonymous.

Urine samples will be kept in a secure freezer in the Mount Sinai West pathology lab. Only study staff will have access to these samples.

10.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

The data will be deleted 6 years after publication, per regulations. Data will not be shared with any outside organizations.

10.1.3.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the research staff at the site under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the electronic data capture (EDC) system, a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

The data safety will be monitored by the PI.

10.1.3.2 STUDY RECORDS RETENTION

Study documents will be retained until at least 6 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the principal investigator.

10.1.4 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonization Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations will be addressed in study source documents.

Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements.

The PI will be responsible for any vigilance and monitoring of the data.