PROTOCOL TITLE:
Oral Ketorolac as an Adjuvant Agent for Postoperative Pain Control following Arthroscopic Rotator Cuff Repair

PRINCIPAL INVESTIGATOR:
Name Robert Gillespie, M.D.
Primary Department Orthopaedic Surgery
Telephone Number 216-844-7200
Email Address Robert.Gillespie@uhhospitals.org

UH FACULTY ADVISOR:
If the principal investigator's primary role at UH is resident, fellow or student, identify a faculty advisor.
Name N/A
Primary Department N/A
Telephone Number N/A
Email Address N/A

OTHER DEPARTMENTS INVOLVED IN THIS STUDY (IF APPLICABLE):
N/A

VERSION NUMBER:
Version 5.

DATE:
2/19/2019

Indicate the origin of this protocol (who conceived of and leads the development of the protocol regardless of funding):
☒ Investigator initiated *(Investigator(s) developed protocol, regardless of funding)*
☐ Industry *(Pharmaceutical, Device, etc.) (Industry developed protocol)*
☐ Federal *(NIH, DOD, etc.)*
☐ Cooperative Group *(SWOG, GOG, etc.)*
☐ Other - *Please specify:*

Funding
There is no funder for this study. The UH Department of Orthopaedic Surgery will cover any necessary costs for this study.

Objectives

1. We aim to examine the use of IV and oral ketorolac as an adjunctive agent to the standard of care pain protocol for postoperative pain control following arthroscopic rotator cuff repair.

2. We hypothesize that the use of IV and oral ketorolac in addition to the standard of care pain protocol will reduce postoperative opioid consumption following arthroscopic rotator cuff repair.

Background

The utilization of arthroscopy to treat rotator cuff tears has continued to increase in recent years, partly due to an aging population and improved technology and technique. In addition, there has been a push for this procedure to be performed in an outpatient surgery setting.[5] In contrast to many arthroscopic orthopaedic procedures, arthroscopic rotator cuff repairs are associated with substantial postoperative pain. Traditionally, oral narcotic agents have been the preferred analgesic postoperatively in orthopaedic surgery. However, these agents are associated with several side effects, including nausea/vomiting, constipation, and somnolence. In addition, opioid agents have a significant potential for abuse in comparison to non-narcotic analgesics. In light of the rising opioid epidemic and nationwide initiatives to limit narcotic usage, surgeons must explore alternate pain modalities in the acute postoperative period. Ketorolac (trade name: Toradol) is an NSAID with analgesic and anti-inflammatory properties.[6] Multiple prior studies have examined the beneficial effect of oral and IV ketorolac as an analgesic in the postoperative period.[1-3, 6] However, the beneficial effects of this agent following arthroscopic rotator cuff repair have not been described.

Inclusion and Exclusion Criteria

At University Hospitals, patients in the practices of the orthopaedic investigators meeting the below inclusion and exclusion criteria will be eligible for enrollment in this investigation. Patients will be evaluated for potential inclusion in the office setting during pre-operative discussion. Patients will be evaluated for exclusion criteria before enrollment. The patient's past medical history will be evaluated for contraindications to ketorolac and the other exclusion criteria. A patient's medical record and the pre-operative history form will be reviewed to ensure the patient does not meet any of the exclusion criteria. The patient will also be questioned prior to enrollment about having any of the conditions in the exclusion criteria using the questions on the patient enrollment form created for this study (see "Other Documents" in Sparta submission).

	Inclusion Criteria
1.	Patients between the ages of 18 and 89 years old, male or female
2.	Patients undergoing primary shoulder arthroscopic rotator cuff repair
3.	
4.	

	Exclusion Criteria

1.	Patients below the age of 18 or above the age of 89
2.	Illiterate or non-English speaking patients
3.	Patients with contraindications to Ketorolac
4.	History of alcohol of drug abuse
5.	Chronic use of analgesic or psychotropic drugs
6.	Known peptic ulcer disease or bleeding diathesis
7.	Renal dysfunction

Number of Research Participants

We are seeking to enroll 43 patients in this single-center study.

Vulnerable Populations

1. Indicate specifically if you will include each of the following special populations by checking the appropriate box:
   - ☐ **Adults unable to consent**
   - ☐ **Minors (infants, children, teenagers)**
     - ☐ Wards of the state
     - ☐ Foster Children
   - ☐ **Pregnant Women**
   - ☐ **Neonates**
   - ☐ **Neonates of Uncertain Viability**
   - ☒ **Employees of CWRU or UHHS**
   - ☐ **Prisoners**
   - ☐ **Illiterate Individuals**
   - ☐ **Non-English Speaking**
   - ☐ **University Students**
   - ☐ **None**

2. If excluding pregnant women, illiterate or non-English speaking individuals, provide a scientific rationale for the exclusion. Inconvenience or cost is not an acceptable rationale.

   Pregnant women are unlikely to undergo any elective operative procedures, as such the authors do not believe they will encounter pregnant patients during the study. In order to appropriate study data collection, patients must have the ability to comprehend the study procedure as defined in the consent form, while being able to objectively identify their pain and record analgesic requirements in the post-operative period. Due to concern that patients may not fully understand study procedure or the requirements for post-operative pain control recording, illiterate and non-English speaking study subjects will be excluded.

3. If the research involves individuals that are included in a vulnerable population, describe the additional safeguards included to protect the rights and welfare of the individuals for

each population indicated.

There is minimal risk and no conflict of interest identified in this study in utilizing employees of University Hospitals or Case Western Reserve University or students of Case Western Reserve University. Supervisors of participating employees or students will not be informed as to whether they participated in the study and no negative impact will result from employee or student refusal to participate. As such, employees and students will be included as study candidates.

Recruitment Methods

Note: Attach all applicable recruitment materials to the last section of the Smart form under "Recruitment Materials."

1. Which of the following methods will be used to recruit research participants. *– Select all that apply*
   - ☐ Email
   - ☐ Phone call
   - ☐ Letter
   - ☐ Advertisement (e.g., poster, flyer, etc.)
   - ☐ Social media
   - ☒ Other. *Please specify:*

   Patients will only be approached about study enrollment in the outpatient clinics of the orthopaedic investigators after they have agreed to undergo arthroscopic rotator cuff surgery as part of the standard of care for their rotator cuff pathology.

2. Describe when, where, and how potential research participants will be recruited.

   Following appropriate referral to one of the orthopaedic investigators, patients will be evaluated in the clinic setting. Appropriate imaging will be obtained and then reviewed to determine if the patient's pathology meets appropriate criteria to be treated using a shoulder arthroscopic rotator cuff repair and if the patient meets appropriate inclusion/exclusion criteria. These interactions will all occur in the pre-operative period.

3. Describe the source (e.g., from what department, EMR, etc.) of the research participants.

   The source of patients will be from the practices of the Drs. Gillespie, Karns, Voos, and Salata.

4. Describe the methods that will be used to **identify** potential research participants.

   Patients will be evaluated for potential inclusion in the research study based on meeting the above inclusion/exclusion criteria. Patient must be between the ages of 18 to 89, and presenting with shoulder pathology amendable to shoulder arthroscopic rotator cuff

repair. Patients with a history of prior surgery to the shoulder will be excluded as no revision procedure will be included in the investigation.

5. Describe the feasibility of recruiting the required number of suitable research participants within the agreed recruitment period. For example, how many potential research participants do you have access to?

   The orthopaedic investigators included in this investigation receives dozens of consults every week for orthopaedic injuries to the shoulder and pain secondary to rotator cuff disease that require operative intervention. As such, the investigators will have access to more than the required number of research participants required to appropriately power this investigation.

Setting

The research will be conducted at University Hospitals Ahuja Medical Center, UH Westlake Health Center, UH Cleveland Medical Center, and UH Richmond Medical Center. Recruitment will occur in the office setting of the orthopaedic investigators in outpatient clinics. The primary research location for University Hospitals will be at UH Cleveland Medical Center (11100 Euclid Ave., Cleveland, OH, 44106), UH Ahuja Medical Center (3999 Richmond Road., Beachwood, OH, 44122) or UH Westlake Health Center (960 Clague Road., Westlake, Ohio 44145).

Consent Process

1. Indicate whether you will be obtaining consent:

☒ Yes ☐ No

If yes, answer the following questions:

1. Describe where the consent process will take place:

2. The time that will be devoted to the consent discussion:

3. Any waiting period available between informing the prospective subject and obtaining the consent:

4. Steps that will be taken to ensure the research participants' understanding:

5. Any process to ensure ongoing consent:

6. The role of the individuals listed in the application as being involved in the consent process:

7. Steps that will be taken to minimize the possibility of coercion or undue influence to the subjects:

Consent will take place in the office setting prior to surgery at one of respective locations listed above. Prior to discussion of the investigation, the patient and family will be asked if they require time to discuss with others their desire to participate in the study. No coercion will be encountered by the patients to serve as a research subject, as patients will be fully able to refuse. Patient may be free to refuse participation at any point in the study. At University Hospitals, and all participating institutions, only IRB-approved study personnel will all be a part of obtaining consent in the clinic setting. All will be up to date on their CITI training. The authors anticipate 10 minutes to discuss the study and patient involvement, with 5 minutes to answer questions regarding study participation, resulting in a total of 15 minutes. Patients will be informed that the decision to enroll in the study is entirely dependent on their willingness to participate and that no changes in their medical care will be experienced based on their decision to participate or not. An unsigned consent will signify that the patient is not interested in enrollment in the study investigation. Again, it will be emphasized to the patients that no changes during surgery or in medical management during the post-operative time will be experienced based on the patient's decision. Investigators obtaining consent will ensure adequate understanding by asking patients if they have any questions or concerns and if they understand the investigation being performed. All patients who enroll in the study will sign their consent form in the presence of a UH IRB-approved study team member.

2. Indicate if you will be asking for a waiver or alteration of consent process or documentation (consent will not be obtained, written consent will not be documented)

☒ Yes ☐ No

If yes, indicate which part of the consent process you are requesting to be waiver or altered and the rationale for requesting the waiver or alteration.

☐ I will obtain consent, but not participant's signature

☒ I will obtain consent, but request a waiver for pre-screening purposes

☐ I will obtain consent, but request a waiver of some of the elements of consent (e.g. use of deception)

☐ I will not obtain consent and I am requesting a full waiver of consent

1. Give the rationale for the request of a waiver or alteration of the consent process or documentation:

A consent waiver is requested for prescreening purposes, only. Subjects will sign a consent form to participate in the research study.

2. Explain how the research involves no more than minimal risk

The risks to patients enrolled in this study are minimal. All patients scheduled for elective shoulder arthroscopic rotator cuff repair undergo pre-operative testing to

ensure they are medically optimized for surgery. Patients with contraindications to Ketorolac will not be enrolled in the study. However, enrollment in the investigation does increase the risk for breach of confidentiality during subject enrollment in study.

3. Explain why the waiver or alteration of consent will not adversely affect the rights and welfare of the participants:

   All patients who enroll in the study will sign a consent form to participate. The waiver is requested for screening the patients to ensure they satisfy the inclusion criteria and do not meet any of the exclusion criteria.

4. Explain why the research could not practicably be carried out without the waiver or alteration of consent.

   Patients will eventually sign a consent to formally enroll in the study. However, the investigators need to be able to evaluate patients' eligibility for the study before discussing the procedures of it with them to obtain consent. Specifically, the investigators will pre-screen patients to ensure they are a candidate for arthroscopic rotator cuff surgery, do not have contraindications to ketorolac, and fulfill the inclusion criteria of the study.

5. If you will obtain consent, but not document consent in writing (e.g. over the phone, verbally, electronic survey, etc.), please describe and provide a rationale.
   ☒ N/A

6. Describe how you will be documenting that a research participant has consented:

   They will be signing a consent form to participate. All of the consent forms for patients from this study will be stored in the office of the Principal Investigator, Robert Gillespie, M.D., Hanna House 6, Room 542, 11100 Euclid Ave. Cleveland, Ohio.

   **Be sure to upload a consent script or information sheet with your study protocol*

Additional Considerations for Consent Process with Adults
Non-English Speakers *(Please select one)*

☒ I am **not** enrolling non-English speaking individuals in this research study. The following is justification for why non-English speaking individuals cannot be enrolled:

Due to concern that non-English speakers may not have a reliable, medically trained and approved interpreter present, the study will not involve non-English speakers as it is the preference of the investigations that all patients have a comprehensive understanding of the study

procedure and post-operative requirements. As none of the investigators speak Spanish or any other language fluently, only English speaking patients will be enrolled.

☐ I will be targeting non-English speaking adults

1. Describe the process to ensure that the oral and written information provided to those research participants will be in that language during initial consent as well as throughout the study.

2. List the language(s) other than English that will be targeted:

☐ I am **not** targeting non-English speaking individuals. If a non-English speaking individual is eligible for the trial, we will use the following procedures to enroll:

1. Describe the process to ensure that the oral and written information provided to those research participants will be in that language during initial consent as well as throughout the study.

2. List the language(s) other than English that will be targeted:

Adults Unable to Consent

☒ I am **not** enrolling adults unable to consent in this research study – *please leave the rest of this section blank.*

☐ There is an anticipated direct benefit to the subject. Explain:

☐ There is NOT an anticipated direct benefit to the subject. Explain:

1. Describe the process to determine whether an individual is capable of consent.

2. List the individuals from whom permission will be obtained in order of priority (e.g. durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child).

3. For research conducted outside of the state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in the research.
   ☐ N/A

4. Describe the process for assent of the research participants. Indicate:
   - Which subjects that are unable to consent will be required to give assent? If not all, explain why.

- Describe whether assent of the research participants will be documented and the process to document assent.

☐ The subject will be informed about the research to the extent compatible with the subject's understanding.
☐ Subjects will be closely monitored.
☐ The subject will be withdrawn if they appear unduly distressed.

Research Participants Who Are Not Yet Adults (infants, children, teenagers)

☒ I am not enrolling participants who are not yet adults in this research study. *– please leave the rest of this section blank*

1. Will parental permission be obtained from:
   - ☐ One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child
   - ☐ Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child
   - ☐ Waiver of parental permission

2. Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals' authority to consent to each child's participation in research.

3. Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent.

4. When assent of children is obtained, describe how it will be documented.

5. For children who are pregnant, describe how assent and permission are obtained.
   ☐ N/A

6. Describe how the risk is justified by the anticipated benefit to the subjects.

7. Describe how the anticipated risk-to-benefit ratio is at least as favorable to the subjects as that presented by currently available alternative approaches.

Sharing of Results with Research Participants

☒ Results will **not** be shared with research participants
☒ Results will **not** be shared with research participants' doctors

Study Design

This is a prospective randomized clinical study that involves studying ketorolac as an adjuvant pain medication for arthroscopic rotator cuff surgery patients. All patients enrolled in this study will receive the standard pain control protocol before, during, and after surgery. This includes a 1) a regional block during the pre-operative period, 2), IV Dexamethasone and IV Odansetron during surgery, and 3) analgesics (as directed by the anesthesiologist) in the PACU. Both groups will also receive the standard of care discharge pain medication for arthroscopic rotator cuff repair: oxycodone-acetaminophen 5-325 (1-2 tablets PO q4-6h PRN for moderate to severe pain #28 tabs).

Patients will be randomized into one of two groups. Group 1 will receive standard of care pain protocol, including a prescription for oxycodone-acetaminophen 5-325 on discharge. Group 2 will also receive the standard of care pain protocol before, during, and after surgery but will also receive an intraoperative dose of IV ketorolac at the completion of the procedure and oral ketorolac on discharge (10mg PO q6 x3 days). Patients will record their pain levels, oxycodone-acetaminophen 5-325 consumption, and pain medication side effects in a diary three times per day for the first five days after surgery. The patient will return the completed diary to their surgeon at the first post-operative appointment. Participation in this study will not require any additional visits to the surgeon's office or hospital outside of the standard pre- and post-operative appointments.

Study Procedures

1. All patients scheduled to undergo elective shoulder arthroscopic rotator cuff repair identified in the office of one of the orthopaedic investigations will undergo the process of obtaining consent prior to surgery. The consent form will be reviewed in depth with an IRB approved-member of the research team, all questions answered, and written consent obtained by the patient after all questions have been answered and the patient demonstrates a full understanding of the investigation and their role in the study. The patient's home medications will be reviewed, and any potential drug-drug interactions will be discussed with the patient.

2. As part of the standard of care, patients undergoing elective shoulder arthroscopic rotator cuff repair will undergo pre-operative testing to ensure patients are optimized for surgery from a medical perspective. During the pre-operative testing period, the standard blood draw taken as part of the standard of care, utilizing no more of the patient's time or blood than generally performed if the patient were not enrolled in the investigation. Before surgery patients will fill out the following patient reported outcome metrics: Visual Analogue Score (VAS), American Shoulder and Elbow Surgery (ASES), and Single Assessment Numeric Evaluation (SANE). These questionnaires should only take patients 5 to 10 minutes to complete.

3. Patients will be re-identified in the preoperative holding area. Both Group 1 and Group 2 will receive the standard of care pain protocol for arthroscopic rotator cuff repair surgery, which consists of: 1) a regional block during the pre-operative period, 2), IV Dexamethasone and IV Odansetron during surgery, and 3) analgesics (as directed by the anesthesiologist) in the PACU. Both groups will also receive the standard of care discharge pain medications for arthroscopic rotator cuff repair: oxycodone-acetaminophen 5-325 (1-2 tablets PO q4-6h PRN for moderate to severe pain #28 tabs). Group 1 will receive only the standard of care pain protocol on the day of their surgery and discharge pain medications. Group 2 will receive the standard of care pain protocol on the day of surgery and an intraoperative dose of IV ketorolac at the completion of surgery (dosing individualized by patient age and weight). Group 2 will also receive the standard of care discharge pain medications and scheduled oral ketorolac (10mg PO q6 x3 days). In addition, Group 2 will receive a prescription for omeprazole (20 mg PO, once per day x3 days) to take for 3 days after surgery to decrease their risk of developing stomach ulcers. A 1:1 randomization ratio will be used (an equal number of patients will be placed in each group). Patients will then undergo standard shoulder arthroscopic rotator cuff repair with one of the surgical investigators. Prior to discharge, all patients will be provided a handout on safely using opioids. Patients in both Group 1 and Group 2 will receive all their medications on the day of surgery.

4. Following discharge from the ambulatory surgery center, patients in Group 1 and Group 2 will be asked to document their VAS pain scores at 6 hour intervals (morning, afternoon, and evening) for five days in a journal administered to them at the time of study enrollment. They will also be asked to record the number of oxycodone-acetaminophen 5-325 pills they take during this time interval in their journal. At the end of each day, patients will be asked to document the following adverse effects: nausea, vomiting, somnolence, dizziness, headache, pain, pruritis, other in their journal. All patients in Group 2 will be instructed to take ketorolac every 6 hours for pain every day for the first 3 days after surgery. Thus, patients in Group 2 will not be required to record the number of ketorolac pills they take each day. To ensure safety, all patients assigned to Group 2 will receive a form outlining the common and serious side effects of Ketorolac and specific instructions for when they should call their doctor or go to the emergency room. All patients who receive rotator cuff repair surgery at UH are instructed to call their surgeon's office if they feel their pain is not controlled at home after surgery.

5. Patients in Group 1 and Group 2 will receive a phone call from a member of the study team on Day 2 after surgery to see if they have any questions and to ensure they are filling out their journal. Patients in Group 2 will also be asked if they are experiencing any of the side effects from ketorolac. Patients in Group 2 will be given two educational handouts on taking Ketorolac at home and the side effects of ketorolac when they are discharged from the hospital.

6. Patients will follow up in clinic on a routine basis based on the recommendations of the surgeon, typically at 2 weeks, 6 weeks, 3 months, 6 months and 1 year following surgery. During these follow up appointments, patients will be screened per standard of care for range of motion to the operative shoulder, pain levels, strength and questioned regarding functionality of the operative shoulder. In the setting of a complication (wound breakdown, infection), patient information will be recorded and communicated using university password protected email to

communicate with the primary investigator. At the first and second follow-up clinic appointments after surgery patients will fill out the following patient reported outcome metrics: VAS, ASES, and SANE questionnaires. The first appointment is about 2 weeks after surgery and the second appointment is about 6-8 weeks after surgery. Filling out these questionnaires should only take you 5-10 minutes to complete at each clinic visit. At the 6 month clinic visit, a follow-up MRI will be obtained. In the event that a patient cancels due to the recent coronavirus outbreak, we will contact the patient by phone or email for follow-up information. In this setting, the post-operative questionnaires will either be administered verbally over the phone or transmitted through email, based on patient preference.

7. After 1 month from their surgery date, patients will receive a phone call from a member of the study team to ask how many refills they have received for their prescription for oxycodone-acetaminophen 5-325. Once the patient has attended their 6 month post-operative appointment their participation in the study will be complete.

8. The investigators will also review the patient's medical record up to 6 months after surgery to determine if they have had any post-operative complications (wound breakdown, infection) and if they had been re-admitted to the hospital during that time.

Study Timeline

Patients are evaluated in the orthopaedic investigators' outpatient clinics for shoulder pathology. If a patient's condition is amenable to arthroscopic shoulder surgery and they elect to undergo the procedure they will be approached for participation in this study. This evaluation and discussion of the surgical procedure should take 10-15 minutes. The time for enrolling a patient should take 10 minutes with 5 minutes for patients' questions. Therefore, an outpatient visit for a patient enrolling this study would take 25-30 minutes. This will be the only visit before surgery. After the surgery, patients will complete their pain diaries at home each day, which should take about 5 minutes each day to fill in. They will bring these completed diaries to their first post-op visit and return it to the study team. At their first and second post-op visits they will fill out pain and function questionnaires. At one month after surgery patients will receive a phone call asking them how many refills they have received for their prescription pain medication. Patients will be asked to complete a follow-up MRI at six months postoperative.

Radiation and Radioactive Substances

1. Does the research involve the use of radiation or radioactive substances?
   ☐ Yes ☒ No – *you may delete the rest of this section*

If yes, answer the following questions.

2. Is the radiation use only for the purposes of the research study (e.g. over and above standard of care)
   ☐ Yes ☐ No

Please note that if you are using radiation or radioactive substances for research purposes you must receive Radiation Safety Committee (RSC) approval. You can obtain RSC approval by completing the form titled: "Radiation Safety Committee Application" which can be found in the templates section of SpartaIRB. Then use the "Manage Ancillary Reviews" button to send to "Radiation Safety." You can find the template section of SpartaIRB by going to your homepage, clicking on "Library" and then clicking on the "Templates" tab.

3. Does the protocol use radionuclides?
   ☐ Yes ☐ No

4. Provide justification for the additional risk associated with the research radiation use.

ClinicalTrials.gov Information

There are no plans to register this study on ClinicalTrials.gov because it does not involve clinical investigation of an experimental therapy.

List of Data to be Collected

Note: If using REDCap, all selected identifiers below must be indicated as PHI.

- Indicate what identifiers you will collect
  - ☒ Name
  - ☐ Address *(e.g., Zip code, other geographical designation, etc.)*
  - ☒ Dates related to an individual *(e.g., Date of admission, birth, surgery, etc.)*
  - ☒ Telephone number
  - ☐ Fax number
  - ☒ Email address
  - ☐ Social security number
  - ☒ Medical record number
  - ☐ Health plan beneficiary number
  - ☐ Account number
  - ☐ Certificate/license number
  - ☐ Any vehicle or other device serial
  - ☐ Device identifiers or serial numbers
  - ☐ Web URL
  - ☐ Internet protocol (IP) address
  - ☐ Finger or voice prints
  - ☐ Photographic images
  - ☐ Other: *Any characteristic that would uniquely identify the individual*

- List all other data to be collected for the research study *(e.g. laboratory values, physician notes, length of stay, etc.)*
- Pre-operative diagnosis

- Mechanism of injury/disease, if relevant
- Narcotic pain medication and side effects in patient journal (number of opioid pills consumed at six hour intervals for five days postoperative)
- Pre- and post-operative scores for the following
    a. Patient-Reported Outcomes Measurement Information System (PROMIS)
    b. Visual Analog (VAS)
    c. American Shoulder and Elbow Surgery (ASES)
    d. Single Assessment Numeric Evaluation (SANE)
- Complications after surgery, such as wound breakdown, infection, etc.
- If the patient was re-admitted to the hospital after surgery
- Post-operative MRI results

Data Analysis Plan

Statistically significant differences in patient demographics and comorbidities between Group 1 and Group 2 will be determined initially with univariate analysis. Students t-test will be utilized to compare the differences in mean VAS scores and narcotics utilization between the two groups at each time point. Linear regression models will be utilized to identify trends over time. Descriptive analyses (e.g., percentages) will be used to report qualitative data as appropriate.

The minimal clinically important difference in VAS scores is 13 in patients with rotator cuff disease.[4] A prior study by White et al. comparing oxycodone-acetaminophen versus oral ketorolac for analgesia following arthroscopic tubal ligation, the common standard deviation in VAS scores was 11 points.[6] Using this data, our power analysis showed that, with an alpha of 0.05 and 90% power, we would need 34 patients, or 17 per group, to achieve adequate power. However, to account for a 20% dropout rate we will recruit for 43 patients. Power analysis was performed using G*Power 3.1.9.2.

The primary endpoint of this study is VAS pain scores and number of narcotic medications consumed. Secondary scores include PROIS, VAS, ASES, SANE scores.

Confidentiality of Specimens and Banking

Are you storing the specimen(s) for future use for other research projects?

☒ I am **not** collecting specimens in this research project – *you may delete the rest of this section*

☒ I am **not** storing specimens in this research project – *you may delete the rest of this section*

☐ Yes

☐ No

If yes, describe:

1. The source of the specimens:
2. Where the specimens will be stored:
3. How long the specimens will be stored:
4. How the specimens will be labeled:

5. How the specimens will be accessed:
6. Who will have access to the specimens:
7. When and how will the specimens be destroyed:
8. How will the specimens be transported? (Please note if transporting specimens, a Material Transfer Agreement (MTA) is required)

9. The procedures to release specimens including:
   - The process to request a release:
   - Approvals required for a release:
   - Who can obtain specimens:
   - The data to be provided with specimens, including if the data will be identifiable to others:

☐ For genomic data, please check the box to attest there is no master list and no attempt will be made to re-identify the specimens.

Confidentiality of Data

1. To maintain the confidentiality of the data:
   ☒ I will use a unique study identifier (not derived from the participants' personal identifiers) to code individuals' data and I will store this ID log separate from study data.
   ☒ Other *(please explain)*

Data collected from subjects participating in the study will be immediately protected as each subject will be assigned a number based on their enrollment and the institution in which they were enrolled that will in no way correspond to any pertinent data relating to the subject's protected health information. Following the results of lab studies and follow up appointments, all data will be entered electronically into RedCap software. Electronic copies of any documentation will be stored in the UH Secure Network drive while any physical documentation be placed within the locked file cabinets located within the institution's investigators office. Data will be accessed by only approved study personnel. Data will be assessed for completeness, accuracy and per strict adherence to the approved protocol by the orthopaedic resident (LS) and during bi-monthly meetings with the investigative team who will be responsible for data protection using files on only protected hospital computers. In addition, monitoring of the data by the entire investigative team will be conducted frequently during these bi-monthly meeting in which the standards and rules of the protocol will be reviewed to ensure that all regulations set forth in the confidentiality agreement are met and complete. Following the complete data transfer electronically, all documentation will be properly disposed of to ensure complete participant protection of information. Following the conclusion of the study, all documentation will be disposed of while maintaining patient confidentiality for 3 years following study closure per UH policy.

2. How are you storing your electronic data?
   ☒ UH Redcap

☐ CWRU Redcap
☐ CWRU's SRE (Secure Research Environment)
☐ CWRU Box
☐ OnCore
☒ UH Secure Network Drive
☐ CWRU Secure Network Drive
☐ Other - *List storage method and provide justification:*

3. ☒ I acknowledge that paper research data and documents will be stored in a double-locked secure environment in the following location:

   Location: ☐ The Office of Robert J. Gillespie, Hanna House 6, Room 542, 11100 Euclid Ave. Cleveland, Ohio.

4. Will data be shared?
   ☐ N/A
   ☒ No
   ☐ Yes
   - List the exact data elements that will be shared:
     1.
   - Describe how data will be sent:

(Please note: if sharing data, please contact your Grants and Contracts Specialist to ensure the proper contracts are in place.)

No data will be shared outside of the IRB-approved investigators.

HIPAA Authorization

If you are going to be accessing PHI (Protected Health Information), indicate how HIPAA authorization will be obtained (check all that apply):

☐ HIPAA authorization is in the consent form
☒ Requesting a full or partial waiver of HIPAA for prescreening
☐ Requesting a full or partial waiver of HIPAA

1. Describe why the study cannot be completed without the specified identifiable information.

   In addition to measuring patient's pain levels in response to the intra-operative pain control protocol we are investigating, a central aim of the study is to follow these patients during their post-operative course and track their clinical progress and any complications that would arise. Therefore, patients' identifiable information to follow their outcomes post-operatively is necessary.

2. If the identifiable information will be used or disclosed by anyone other than the research team, please state who those individuals/entities are and provide justification for the disclosure.
   - ☒ Identifiable information will **not** be used or disclosed by anyone other than the research team
   - ☐ Identifiable information will be used or disclosed to:

3. Describe how long identifiers will be kept for in relation to study length and data collection and analysis.

   3 years per UH policy

☒ I assure that protected health information collected for purposes of this research study will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use of disclosure of protected health information for which an authorization or opportunity to agree or object is not required by 45 CFR 164.512

Risks to Research Participants

1. List the reasonably foreseeable risks such as breach of confidentiality, discomforts, hazards, or inconveniences to the research participants related to their participation in the research. Include a description of the probability, magnitude, duration, and reversibility of the risks. Include the physical psychological, social, legal, and economic risks.

All patients scheduled for elective shoulder arthroscopic rotator cuff repair undergo pre-operative testing to ensure they are medically optimized for surgery. Patients with contraindications to Ketorolac will not be enrolled in the study:

- Previous allergic reaction to Ketorolac
- History of any of the following: peptic ulcer disease, gastrointestinal bleeding, or perforation of the stomach or bowel
- Having experienced an asthma, urticarial, or a allergic-type reactions after taking aspirin or other NSAIDs
- History of kidney disease or kidney failure
- History of a brain bleed
- History of a bleeding disorder
- Currently taking the medication probenecid
- Currently taking the medication pentoxifylline

The investigators will ensure no patient with contraindications to Ketorolac are enrolled via the following: 1) the patient's past medical history in their electronic medical record and pre-operative history form will be evaluated for contraindications to ketorolac, and 2) the patient will be questioned prior to enrollment about having any of the conditions that are contraindications to

Ketorolac using the patient enrollment form created for this study (see "Other Documents" in Sparta submission).

Common non-serious side effects of Ketorolac:

- Nausea, stomach pain, indigestion, diarrhea
- Dizziness, drowsiness
- Headache
- Swelling

Serious side effects of Ketorolac:

- Gastrointestinal problems: ulcers, bleeding, or peforation
- Hemorrhage
- Impaired renal function
- Impaired liver function
- Allergic or anaphylactoid reaction
- Anemia
- Ketorolac, like other NSAIDs, may cause serious cardiovascular side effects, such as myocardial infarction or stroke, which may result in hospitalization and even death

All patients that receive ketorolac will be monitored in the PACU for side effects to Ketorolac after receiving an IV dose at the end of their surgery, and will be given two informative handouts on taking ketorolac and its side effects (see "Other Documents" in Sparta submission). These handouts also have instructions for when patients should call their surgeon's office or seek immediate medical assistance. In addition, all patients enrolled in this study will receive a phone call on Day 2 after surgery to ensure they are filling out their pain diary. Patients who received ketorolac will also be questioned about having any side effects of ketorolac.

Patients who receive Omeprazole will only be taking it for 3 days after surgery while they are taking Ketorolac. There are no known interactions between Omeprazole and Ketorolac.

Common non-serious side effects of Omeprazole:

- Headaches
- Vomiting
- Diarrhea
- Stomach pain
- Constipation
- Fatigue

Serious side effects of Omeprazole:

- Serious allergic reaction – skin rash, wheezing, throat swelling, trouble breathing,
- Liver problems – yellow skin, dark urine, and fatigue

Also, enrollment in the investigation does increase the risk for breach of confidentiality during subject enrollment in study.

MRI risks:
A known risk is that the magnet could attract certain kinds of metal that may cause injury to the subject. Subjects will be asked about metal within their body (this includes certain dyes used in tattoos and body piercings). If there is any question about potentially hazardous metal within their body, they will not be able to participate in this portion of the research study. We will also keep the MRI room locked so that no one carrying metal objects enters the room while the scan is being performed. In addition, the MRI scanner makes a loud buzzing noise that could affect hearing ability. Subjects will be provided with earplugs and assistance in their use in order to protect hearing.

2. If applicable, indicate which experimental procedures may have risks to the research participants that are currently unforeseeable.
   ☒ N/A

No unforeseen risks are anticipated outside of the risks documented in the prior section.

3. If applicable, describe the risks to others who are not research participants.
   ☒ N/A

No risks are anticipated to individuals outside of the research investigation.

4. Describe the availability of medical or psychological resources that research participants might need.
   ☐ N/A

No such resources are likely to be required, however patients will be instructed to call the office of the operative surgeon with any questions or concerns during the study period, however this is standard of care based on whether the patient is involved in the research study or not.

Additional Considerations for Pregnant Women:

5. Indicate which procedures may have risks to an embryo or fetus should the research participant or their partner be or become pregnant.
   ☒ N/A

   ☐ Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.
   ☐ No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
   ☐ Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
   ☐ Individuals engaged in the research will have no part in determining the viability of a neonate.

Provisions to Protect the Privacy Interests of Research Participants

Privacy of the study subjects will be protected throughout all phases of the research study. Consent will be obtained by only a member of the investigative team and patients will be given the opportunity to discuss participation with an investigator out of the room, allowing the patient to remain alone or with family. During the study period, all subject data will be protected through careful handling of patient information by assigning each subject a research number. After completion and collection of all study documents, all documentation will then be securely transported back to the appropriate investigators office securely locked away after being entered electronically after the identifiable information is converted to a study number which will not contain any protected health information. All patient information will be stored confidentially on protected hospitals computers and files using RedCap software to ensure added protection. Following conclusion of the study, all hard documentation will be stored within the locked file cabinet in the investigators office after being transferred onto electronic files protected by RedCap. All documentation will be disposed of at the end of the study to ensure confidentiality is maintained. In addition, participants and their information will not be discussed in any public areas or with any medical or non-medical personnel not directly involved with and approved as an active investigative member of the research study.

Potential Benefit to Research Participants

☒ There is potential benefit to research participants.

1. Describe the potential benefits that individual research participants may experience from taking part in the research. Include the probability, magnitude, and duration of the potential benefits.

   There is no guaranteed direct benefit from participating in the study. All subjects undergoing surgery will benefit from the known effects of shoulder arthroscopic rotator cuff repair following surgery whether or not they are enrolled in the study. Possible benefit of the research is patients could experience increased pain relief, compared to standard pain control protocols, after surgery from receiving intra-operative IV and PO Ketorolac. This will make their post-op period more comfortable.

☐ There is **no** direct benefit to research participants.

2. If no direct benefit, state the potential benefit to society or others. *Do not list compensation.*

Withdrawal of Research Participants

☐ N/A

Patients can withdraw at any point during the study period. Patients will be withdrawn if they fail to appropriately follow up in the post-operative period. If a patient withdraws from the study before their surgery, they will proceed with their shoulder arthroscopic rotator cuff repair and clinical follow-up, and no further data will be collected on them. If a patient withdraws during the post-operative period, then no more follow-up data will be collected past their withdrawal date.

Alternatives to Participation

☐ The alternative is for research subjects not to participate.

Patients may elect to proceed with arthroscopic shoulder rotator cuff repair with the standard of care postoperative pain regiment oxycodone-acetaminophen 5-325 (1-2 tabs PO q4-6h PRN moderate to severe pain #28 tabs))

Arthroscopic repair is a well-established treatment option for patients with rotator cuff pathology. Therefore, if their surgeon has recommended they receive arthroscopic repair, it will be because the surgeon believes it is the best treatment option for their condition, not for research purposes. If a patient elects to withdraw from the Ketorolac arm, they will simply be asked to discontinue use of Ketorolac and continue with the use of oxycodone-acetaminophen 5-325. Since this is the standard of care there is no alternative treatment to list in the consent.

Costs to Research Participants

☐ There are **no** costs to research participants or their insurance companies (there are no clinical visits or billable procedures). *– You may delete the rest of the section.*

1. Describe what costs research participants will be responsible for as a result of their participation in the research, including but not limited to: clinical services required by the protocol deemed billable to insurance, transportation to study visits, parking, costs of drugs, cost of therapy, lost broken or stolen devices, etc.
2. Explain who will be responsible for payment of provided services in the event of insurance denials.
3. List what procedures, drugs, devices, supplies will be paid by the study sponsor or covered by other funding. List the other funding source.

There are not sufficient funds within our department to cover the cost of ketorolac and omeprazole for patients randomized into Group 2. As such, the patient's insurance company will be responsible for the cost of ketorolac and omeprazole. However, ketorolac is a generic drug that is commonly utilized both within and outside of Orthopaedics. Patients will ultimately be responsible if the insurance company does not pay, and for any associated co-pay. Paying for Ketorolac and Omeprazole will be discussed with the patient in clinic during the consent process. The six-month MRI costs will be covered through the research fund of the principal investigator.

Research Participant Compensation

☒ There is **no** compensation or reimbursement for research participants.

☐ There is compensation for research participants.
Describe the schedule, payment method, and payment total of any incentives or compensation that research participants will receive for participation in the research (e.g., gift cards or cash with amount, t-shirts, devices, bags, swag, etc.)

☐ There will be reimbursement for research participants.

Describe the schedule, payment method, and payment total of any reimbursement that research participants will receive for participation in the research (e.g., gift cards or cash with amount, etc.)

Compensation for Research Related Injury

Describe who will pay for the costs of medical treatment and/or compensation in the event of a research related injury:

- ☐ Funding agency is providing some/all payment for injury
- ☒ Funding agency is providing no payment for injury
- ☐ N/A

Provisions to Monitor the Data to Ensure the Safety of Research Participants

1. Describe how often the data will be monitored for completeness, accuracy and adherence to the protocol.

   Data collected from subjects participating in the study will be immediately protected as each subject will be assigned a number that will in no way correspond to any pertinent data relating to the subject's protected health information. Following collection of data from questionnaires and pain journals, the orthopaedic resident will collect all documentation and after being entered electronically behind RedCap software, will be placed within the locked file cabinets located within the primary investigators office. Data will be accessed by only approved study personnel. Data will be assessed for completeness, accuracy and per strict adherence to the approved protocol by the orthopaedic resident and during bi-monthly meetings with the investigative team who will be responsible for data protection using files on only protected hospital computers. In addition, monitoring of the data by the entire investigative team will be conducted frequently during these bi-monthly meeting in which the standards and rules of the protocol will be reviewed to ensure that all regulations set forth in the confidentiality agreement are met and complete. Following the complete data transfer electronically, all documentation will be properly disposed of to ensure complete participant protection of information. Following the conclusion of the study, all information and hard copies will remain stored in a locked file cabinet located within the primary investigators office per UH policy.

2. Indicate if there will be a Data and Safety Monitoring Board or Committee:
   ☒ There will **not** be a formal Data and Safety Monitoring Board/Committee.

   ☐ There will be a formal Data and Safety Monitoring Board/Committee.

   Provide information about the DSMB/C including the contact information of the committee member(s) (as applicable); whether it is independent from the study sponsor; how often it meets; the type of data that will be used; written reports, etc.

As stated above, data will be monitored during a bi-monthly research meeting with the investigative team.

Drugs or Devices

☐ This is **not** a drug or device study. The protocol is considered non-therapeutic (non-therapeutic is defined as research not intended to diagnose, prevent, cure, mitigate, treat, etc. a disease or condition) by the FDA. *– You may delete the rest of this section.*

OR

☒ This is a drug or device study. The protocol is considered therapeutic (research intended to diagnose, prevent, cure, mitigate, treat a disease or condition) by the FDA.

1. Is there an active IND (Investigational New Drug) or IDE (Investigational Device Exemption) for the proposed clinical research study?
   - ☐ Yes, provide an official letter of support or proof of approval which identifies the IND/IDE holder and IND/IDE number. *Please attach this in the SpartaIRB smartform*
   - ☒ No, *see question below:*

2. Is the drug IND exempt *OR* is the device (and its use) a non-significant risk device for the proposed study design?
   - ☐ Yes, *please identify the authorized party who made the determination and provide supporting documentation as applicable.*
   - ☒ No *NOTE: either an active IND/IDE or an exemption would be required for investigational product use in a therapeutic protocol.*
   - ☐ N/A

Ketorolac is an FDA-approved drug for pain relief.

3. If the research involves drug(s) or device(s), describe your plans to store, handle, administer and track those drug(s) or device(s) to ensure that they will be used only on research participants and be used only by authorized investigators.

Patients will be provided IV and oral ketorolac during the study. The IV ketorolac will be provided by the anesthesia team in the operating room at the conclusion of the study. The study investigators will provide patients with a prescription for the oral ketorolac, which they may fill at a pharmacy of their choice.

Additional Information

Directions: If you have any additional information regarding your study not covered in the template, please include it here.

Community-Based Participatory Research

☒ This is **not** a community-based participatory research project – *please leave the rest of this section blank*

☐ This is a community-based participatory research project
Describe the involvement of the community in the design and conduct of the research.

Note: Community based research is research that is conducted as an equal partnership between academic investigators and members of a community. In Community Based Participatory Research (CBPR) protects, the community participates fully in all aspects of the research process.

International information

☒ This is **not** an international study – *you may delete the rest of this section.*

☐ We will be conducting this research at the following international sites:
1.

☐ We are recruiting participants outside of the US from the following locations:
1.

☐ We are sending data outside of the US to the following locations:
1.

☐ We are receiving data from outside of the US from the following locations:
1.

MULTI-SITE RESEARCH (when UH or CWRU is the IRB of Record)

Does this project have multiple sites?

☐ **Yes**

☒ **No** – *please leave the rest of this section blank*

Non-Local Site Information for Multi-Site Studies
*If this is a multi-site study where you are the **lead investigator,** list the following information for each relying site:*

1. Name of site:
2. PI of relying site:
3. Name of IRB contact:
4. Phone number of IRB contact:
5. Email address of IRB contact:

Non-Local Recruitment Methods for Multi-Site Studies
*If this is a multi-site study and research participants will be recruited by methods **not under the control of the local site** (e.g. call centers, national advertisements) describe those methods. Local recruitment methods are described above.*

1. *Describe when, where, and how potential research participants will be recruited.*

2. *Describe the methods that will be used to identify potential research participants.*

3. *Describe the materials that will be used to recruit research participants.*

Multi-Site Research Communication Plan (when you are the lead investigator)

*If this is a multi-site study where you are the **lead investigator**, describe the processes to ensure communication among sites including:*

☐ *All sites will have the most current version of the protocol, consent document, and HIPAA authorization*

☐ *All required approvals (initial, continuing review and modifications) have been obtained at each site (including approval by the site's IRB of record)*

☐ *All modifications have been communicated to sites, and approved (including approval of the site's IRB of record) before the modification is implemented*

☐ *All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies*

☐ *All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies*

☐ *All local site investigators conduct the study in accordance with applicable federal regulations and local laws*

☐ *All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy*

*If this is a multi-site study where you are the **lead investigator,** describe the method for communicating to engaged participant sites the following:*

1. *Problems:*
2. *Interim results:*
3. *The closure of the study:*

References

1. Barber FA, Gladu DE. Comparison of oral ketorolac and hydrocodone for pain relief after anterior cruciate ligament reconstruction. *Arthroscopy.* 1998;14(6):605-612.

2. Gebuhr PH, Soelberg M, Strauss W. A multiple-dose, double-blind comparison of intramuscularly and orally administered ketorolac tromethamine and Ketogan in patients with pain following orthopaedic surgery. *J Int Med Res.* 1994;22(4):202-217.

3. McQuay HJ, Poppleton P, Carroll D, Summerfield RJ, Bullingham RE, Moore RA. Ketorolac and acetaminophen for orthopedic postoperative pain. *Clin Pharmacol Ther.* 1986;39(1):89-93.

4. Tashjian RZ, Deloach J, Porucznik CA, Powell AP. Minimal clinically important differences (MCID) and patient acceptable symptomatic state (PASS) for visual analog scales (VAS) measuring pain in patients treated for rotator cuff disease. *J Shoulder Elbow Surg.* 2009;18(6):927-932.

5. Uquillas CA, Capogna BM, Rossy WH, Mahure SA, Rokito AS. Postoperative pain control after arthroscopic rotator cuff repair. *J Shoulder Elbow Surg.* 2016;25(7):1204-1213.

6. White PF, Joshi GP, Carpenter RL, Fragen RJ. A comparison of oral ketorolac and hydrocodone-acetaminophen for analgesia after ambulatory surgery: arthroscopy versus laparoscopic tubal ligation. *Anesth Analg.* 1997;85(1):37-43.

Please reference the Investigator Manual for local institutional requirements.