TITLE: The Use of Gabapentin for Post-Operative Pain Control and Narcotic Reduction in Scrotal Surgery

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Statement of Compliance

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the WCMC Institutional Review Board (IRB) Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCMC.

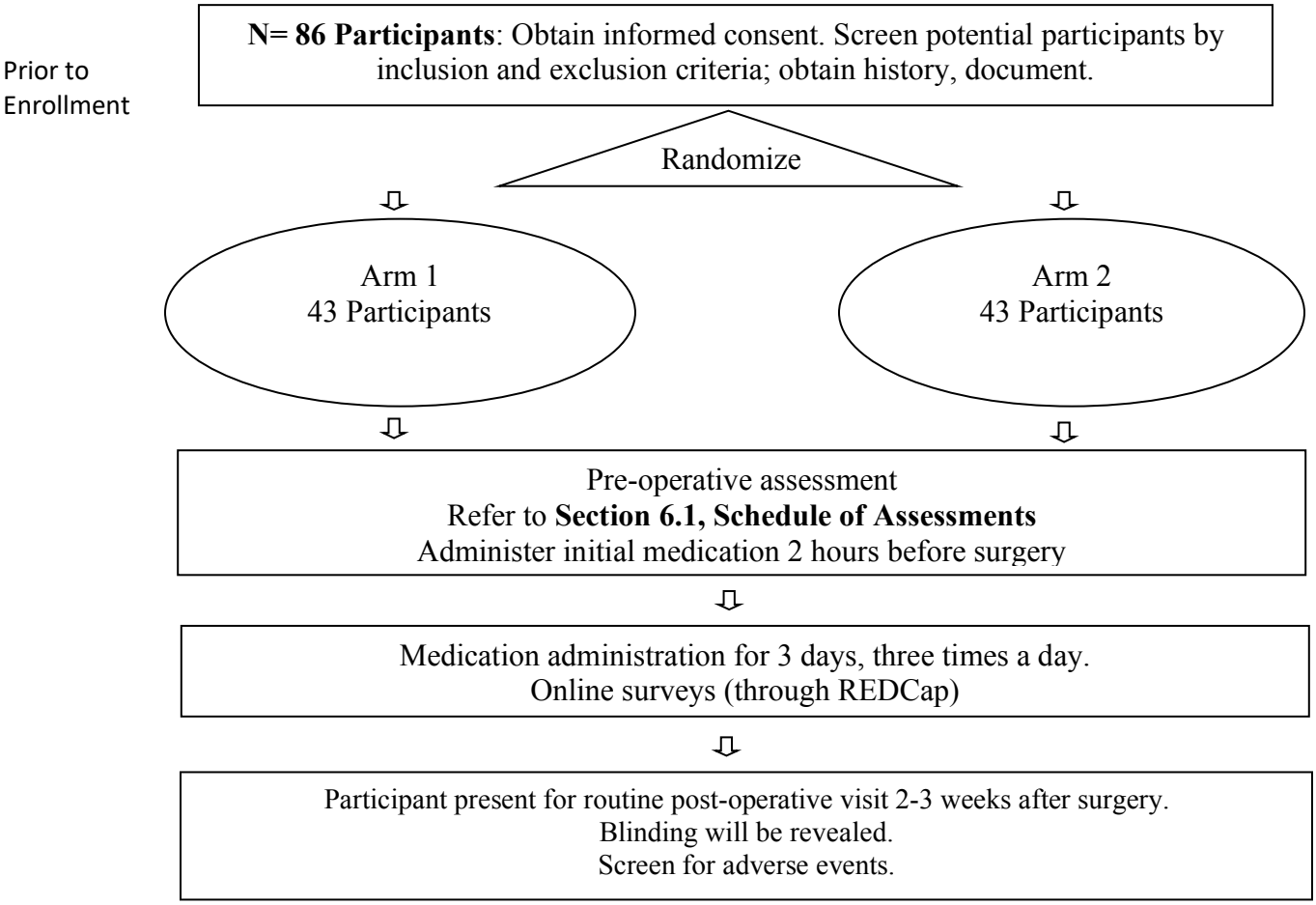
List of Abbreviations

AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
CTSC	Clinical Translational Science Center
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HUD	Humanitarian Use Device
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
NRS-11	Numerical Pain Score
PHI	Protected Health Information
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
UIRTSO	Unanticipated Problem Involving Risks to Subjects or Others
WCM	Weill Cornell Medicine

1. Protocol Summary

Full Title:	*Multi-modal Analgesia to Reduce Narcotics After Scrotal Surgery*
Short Title:	*Narcotic Reduction After Surgery*
Clinical Phase:	*III*
Principal Investigator:	*Jessica Marinaro*
Study Description:	*The use of non-narcotic multi-modal analgesia to be used in the pre-operative, peri-operative and post-operative period to reduce or potentially eliminate narcotic usage following scrotal surgery. We have shown that the use of anti-inflammatories in the peri-operative period reduce both pain and narcotic use. Our hypothesis is that adding another agent in the multi modal pathway will further reduce pain and potentially reduce narcotic usage.*
Sample Size:	*N=* 86 *(43 participants in each arm)*
Enrollment:	*This study will enroll 86 participants but will screen 114 participants accounting for an approximate 25% screening failure rate.*
Study Population:	*Participants undergoing microsurgical testicular sperm extraction for non-obstructive azoospermia.*
Enrollment Period:	*2 years.*
Study Design:	*Double-blind, placebo-controlled, randomized trial* *Two study arms (43 participants per arm)* *Addition of gabapentin pre- and post-operatively*
Description of Sites/ Facilities Enrolling Participants:	*This will be a single center study at Weill Cornell Medicine/New York Presbyterian Hospital.*
Study Duration:	*December 31, 2023*
Participant Duration:	*7 days.*
Study Agent/Device Name Intervention Description:	*Arm #1 – Gabapentin 600mg taken pre-operatively and 300mg taken three times a day for 3 days.* *Arm #2 – Placebo taken pre-operatively and three times a day for 3 days.*
Primary Objective:	*Pain scores*
Secondary Objectives:	*Narcotic consumption*
Exploratory Objectives:	*Symptom modification (ie. nausea)*
Endpoints:	*Numerical pain rating scale* *Narcotic prescription usage*

1.1 Schema


Prior to Enrollment
N= 86 Participants: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.
Randomize
Arm 1
43 Participants
Arm 2
43 Participants
Pre-operative assessment
Refer to Section 6.1, Schedule of Assessments
Administer initial medication 2 hours before surgery
Medication administration for 3 days, three times a day.
Online surveys (through REDCap)
Participant present for routine post-operative visit 2-3 weeks after surgery.
Blinding will be revealed.
Screen for adverse events.

1.2 Study Objectives

1.2.1 Primary Objectives

To compare participant reported pain between participants receiving gabapentin and those receiving placebo in addition to standard of care. This will be assessed using the 11-point numerical pain rating scales (NRS-11) from post-operative day 1 to 7.

1.2.2 Secondary Objectives

To assess narcotic use following surgery including the number of tablets taken, frequency and time when narcotic is initially utilized. Study participants satisfaction will be documented.

2. Background

2.1 Disease

Microdissection testicular sperm extraction (microTESE) is the gold standard for sperm retrieval in research study participants with non-obstructive azoospermia for in vitro fertilization.[1] Scrotal and testicular surgery can be associated with post-operative pain and improper narcotic utilization has become a significant societal problem.[2]

2.2 Investigational Agent/Device, or Research intervention

Multi-modal analgesia has been used as an alternative to reduce narcotic usage in the peri-operative and post-operative period following scrotal surgery. Our previous work has looked at the role of anti-inflammatories, specifically COX-2 inhibitors, for this purpose and has shown a reduction in both post-operative pain and narcotic usage.[3] The addition of other non-narcotic analgesics may reduce and potentially eliminate narcotic usage following scrotal surgery.

Gabapentin is a well-known anti-convulsant medication that is commonly used by pain specialists in their approach to multi-modal pain control.[4] It is most often used to treat neuropathic pain often characterized by a burning or itching cessation and may be related to diseases such as diabetes.[5]

Gabapentin is a ligand of the a2delta subunit of voltage gated calcium channels, but the mechanism of action by which gabapentin facilities pain reduction is unclear, various hypotheses exist including reduced hyperexcitability of neurons resulting in central desensitization, decreased calcium entry caused by binding to the dorsal horn neurons reducing neurotransmitter release or through other channels such as sodium or NMDA channels.[6] Gabapentin is water soluble and rapidly absorbed with dose-dependent bioavailability, with a half-life of approximately 5-7 hours.[7] For this reason it is commonly dosed up to three times per day. It is cleared renally, and not metabolized and has no

impact on hepatic enzymes.[8] The medication is generally well tolerated with the most common effects of somnolence and dizziness, and does not need to be taken with meals.[9]

Previous studies have examined the role of gabapentin for relief of acute pain in the peri-operative period. Studies in the plastic surgery literature, obstetrical literature, general surgery literature and orthopedic literature have examined its use with varying impacts.[10-12] Various doses and schematics for administration have been studied, including meta-analyses, which show conflicting results.[10] Doses have been reported from 300mg-1200mg in these studies, and given before surgery and for a short duration afterwards. Some studies have also studied the combination of celecoxib with gabapentin showing an improved benefit in both pain scores, as well as side effect reduction.[13] A lack of robust, large and well controlled trials have been completed.[11]

Overall gabapentin has been shown to have minimal drug interactions due to its pharmacokinetics. Studies that have been completed often show varied results.[14]

Gabapentin is a FDA approved medication prescribed for the treatment of partial or focal seizures in adults and children, and for the management of post-herpetic neuralgia. The use of gabapentin in this study is considered investigational (ie. it is used for an unapproved indication). Investigators seek an IND exemption as the study uses gabapentin to assess pain reduction and gabapentin consumption after scrotal surgery. This study does NOT intend to support a significant change in the advertising for a prescription product, FDA approval of a new indication or a significant change in the product labeling, or FDA approval of change in route of administration, dose, and/or patient population.

2.3 Rationale

Pain management is an ongoing issue for all surgeons, and with rising concerns regarding opioid addiction and consumption, multi-modal strategies and alternatives are necessary.[2] Given that we have previously shown the role of anti-inflammatory medications reducing narcotic usage in the peri-operative period in addition to acetaminophen, we believe addition of another agent may reduce narcotic use completely.[3] No literature to our knowledge is available regarding the use of gabapentin in urologic surgery, and given its potential benefit in other surgeries we believe this will further reduce pain and possibly eliminate narcotic usage post scrotal surgery.

2.4 Risk/Benefit Assessment

2.4.1 Known Potential Risks

As per the FDA, gabapentin side effects commonly include dizziness and drowsiness. Other reported adverse events include headache, lack of coordination, viral infection, nausea and vomiting, difficulty speaking, tremor, swelling, fever, jerky movements, difficulty with coordination, double vision and unusual eye movement.

2.4.2 Known Potential Benefits

The benefits of the medication include known research showing improved pain control in certain populations. This could potentially reduce narcotic consumption and reduce costs associated with narcotic dependence and addiction.

2.4.3 Assessment of Potential Risks and Benefits

The research intervention has numerous health benefits to the individuals who will be participating in the study. Improved health outcomes are expected due to the research intervention such as better pain control in scrotal and urologic surgery, and clinical practice pertaining to reduced prescription and consumption of narcotics amongst patients with non-obstructive azoospermia undergoing scrotal surgery.

2.5 Correlative Studies Background

Not applicable

3. Study Design

3.1 Overall Design

This will be assessed in a phase III randomized, double-blind control trial. All eligible subjects will be included and enrolled sequentially from the study start date. The study will include two arms (gabapentin or placebo) at a single site in patients undergoing microsurgical testicular sperm extraction.

3.2 Scientific Rationale for Study Design

This study will use two arms to study the efficacy of gabapentin. A placebo will be used in order to blind the participants to reduce bias. The study will be designed to test superiority compared to placebo. The potential problems relate to the side effects of the medications themselves, otherwise all participants will receive sufficient analgesia in order to control their post-operative pain.

3.3 Justification for Dose

The dose for gabapentin will be in keeping with data from the literature and routine clinical practice. Various studies have examined doses from 300mg-1200mg, and while some have shown increased effects at maximal doses this is also associated with more side effects.[15,16] Given the outpatient nature of this procedure and many scrotal surgeries, dosing on the lower end was more justified with 600mg given 2 hours before surgery, and 300mg three times a day for 3 days.

3.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last pain score assessment and record of narcotic consumption on post-

operative day #7 as shown in the Schedule of Assessments (SoA), Section 6.1. The end of the study is defined as return of the pain score and narcotic consumption at post-operative follow-up visit.

4. Subject Selection

4.1 Study Population

Subjects undergoing microsurgical sperm extraction who meet the inclusion and exclusion criteria will be offered participation in this study.

4.2 Inclusion Criteria

1. Participants undergoing microsurgical testicular sperm extraction
2. Participants over 18 years of age who can provide informed consent
3. Participants with no contraindication to the consumption gabapentin or documented allergy/intolerance
4. Participants not currently using opiates for another reason

4.3 Exclusion Criteria

1. Contraindication to the consumption of celecoxib or gabapentin
2. History of substance abuse (including prior opiate abuse)
3. Narcotic use within last 3 months
4. Any of the following comorbidities: renal failure, heart disease, peptic ulcer disease, cerebrovascular disease, significant liver disease, untreated depression, chronic pain disorder, or bleeding diatheses
5. Medical history or concurrent illness that the investigator considers sufficiently serious to interfere with the conduct, completion, or results of this trial, or constitutes an unacceptable risk to the subject

4.4 Lifestyle Considerations

Not applicable.

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of an inability to take either study drug may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

4.6 Strategies for Recruitment and Retention

Participants will be recruited sequentially as any patient undergoing microsurgical testicular sperm extraction at Weill Cornell/New York Presbyterian Hospital by Dr. Peter N. Schlegel. All participants over 18 years of age will be considered.

We anticipate an accrual rate of 80% from a single site. These study participants will be recruited in the clinic at the time of surgical consent.

Participants will be identified and approached by a member of the research team.

Participants will not receive any compensation for their participation in the study.

5. Registration Procedures

5.1 Subject Registration (WCM only)

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

6. Study Procedures

6.1 Schedule of Assessments

Table 1. Schedule of trial events

	Pre-Study	Day of Surgery	POD #1	POD #2	POD #3	POD #7	Off Study
Agent Administration		X	X	X	X		
Informed consent	X						
Demographics	X						
Medical history	X						
Concurrent meds	X						
Outcome Evaluation (Pain Scores)		X	X	X	X	X	
Outcome Evaluation (Narcotic Usage)		X	X	X	X	X	

6.1.1 Screening Visit (*-7 days before start of Research Intervention*)

- Informed consent
- Medical history
- Medication history

6.1.2 Intervention Phase (Phase III)

Eligible subjects will be randomly assigned to one of the arms using a computer-generated randomization scheme developed by the data manager.

6.1.2.1 Visit 1 (end of study)

Collection of pain score questionnaires and narcotic consumption.

6.1.3 Follow-up Phase

Participant recorded questionnaires and data will be obtained at the standard surgical follow-up visit.

7. Study Intervention

7.1 Study Intervention/Device Description

Gabapentin will be prepared in a capsule format. It will be shipped to the PI's address at Weill Cornell. The drug may be stored at room temperature which will be indicated on the product label.

The placebo will also be prepared in a capsule format. It will be shipped to the PI's address at Weill Cornell. The drug may be stored at room temperature which will be indicated on the product label.

The exact shipping address is below:

Research Pharmacy #PH#
NewYork-Presbyterian Hospital/Weill Cornell Medical Center
525 E. 68th St., Room F06
New York, NY 10065

7.2 Availability

The use of gabapentin in this study is considered investigational as it is used for an unapproved indication.
Gabapentin is an investigational agent supplied to investigators by Curis Pharmacy.

7.3 Acquisition and Accountability

Contact person:

Nicole @ Curis Pharmacy
1853 S Dixie Highway
Pompano Beach, FL
33060

Phone: 855 472 1894- Fax 800 419 2801.

Time necessary to fill order depends on quantity needed. Two day priority shipping is available.

Agent Inventory Records/Device Logs – The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of all agents/device received from *Sponsor* on a Drug Accountability Record Form (DARF) or Device Log.

7.4 Formulation, Appearance, Packaging, and Labeling

Both the gabapentin and placebo will be identical appearing capsules. The appearance will be blue Opaque capsules. The packing will vary based on quantity ordered (ie. larger quantities will be sent in unguator jars). Pills will be labelled generically to ensure blinding.

7.5 Product Storage and Stability

Product will be stored at room temperature.

7.6 Preparation

No preparation is needed, the capsules are ready for oral use.

7.7 Dosing and Administration

Each participant will receive the same dose of the drug.

Gabapentin will be administered as a single dose pre-operatively 600 mg and then 300mg three times a day for three post-operatively.

Placebo medication will be administered in the same fashion.

7.7.1 Dosing Delays/Dose Modifications

If a subject demonstrates side effects, the dose will be reduced to half. If there is a significant adverse event, the drug will no longer be administered.

7.8 General Concomitant Medication and Supportive Care Guidelines

All concomitant medications will be recorded and/or updated on subject medication log in keeping with routine clinical practice and saved in subject binder, if applicable.

7.9 Duration of Therapy and Criteria for Removal from Study

In the absence of delays in administration of the investigational drug due to adverse event(s), drug administration may continue in the post-operative period for three days addition to the pre-operative period. Other reasons may include:

- Intercurrent illness that prevents further administration of investigational drug,
- Unacceptable adverse event(s)
- Subject decides to withdraw from the study, or
- General or specific changes in the subject's condition render the subject unacceptable for further administration of drug in the judgment of the investigator

7.10 Duration of Follow Up

Subjects will be followed until their first post-operative visit, at which time they will be removed from the study, or until death, whichever occurs first. Subjects removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

7.11 Measures to Minimize Bias: Randomization and Blinding

Permuted blocked randomization will be performed. A series of randomized blocks with a defined block size will be generated with a 1:1 allocation ratio to allow for an equal number of participants in the study drug and placebo groups. A statistician from the Weill Cornell CTSC Biostatistics, Epidemiology and Research Design (BERD) Core will create the randomization list and will not be involved with the study statistician(s). The randomization list will also reside in the Research Pharmacy. Only the BERD statistician and the Research Pharmacy will have a copy of the blocked randomization list and will know the true meaning of the block assignments. If unbinding is necessary, the BERD statistician (or Research Pharmacy) can immediately determine whether or not the participant received the study drug or placebo.

7.12 Study Intervention/Follow-up Compliance

Study participant adherence will be completed in the form of a reminder phone call. Participants will be required to complete questionnaires for a visual analogue scale as well as daily narcotic usage.

Participants will be seen for their study materials at their usual post-operative follow-up visit. Two attempts will be made to contact the subject if they do not return for their follow-up visit or provide the necessary study documents, at which point the subject will be considered "lost to follow-up" and no longer participating in the study.

8. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

Participants may withdraw voluntarily from the study or the PI may discontinue a participant from the study at any time. The following adverse events would necessitate discontinue of the study intervention or participant discontinuation/withdrawal:

- Drug Reaction with Eosinophilia and Systemic Symptoms (Multiorgan hypersensitivity)
- Anaphylaxis and Angioedema
- Severe Somnolence/Sedation and Dizziness
- Suicidal Behavior and Ideation

Participants may discontinue the study intervention, but remain in the study for follow-up, especially for safety and efficacy study endpoints (if applicable).

8.1 Discontinuation of Study Intervention

Discontinuation from gabapentin administration does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Post-operative follow-up to ensure any adverse event resolution

8.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive the medication
- Participant lost to follow-up after several attempts to contact subject to schedule study visit.

Subjects will be medically monitored by clinicians in the research team for detection of any adverse events. The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

8.3 Lost to Follow Up

A participant will be considered lost to follow-up if he or she fails to return for 1 scheduled visits and is unable to be contacted by the study site staff following 2 attempts.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 4 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 2 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

10. Measurement of Effect

Effect of pain will be measured using the validated numerical rating scale.

Narcotic consumption will be recorded as a numerical value.

10.1 Response Criteria

The study participants will be prompted to complete online surveys administered through REDCap. The REDCap database allows for HIPAA compliant data gathering through this format. Each survey will include the following: a numerical rating scale (0 through 11) to rank current pain, number of narcotic tablets consumed since the prior survey, overall satisfaction of pain control (binary yes/no) as well documentation of other related symptoms (ie. nausea).

11. Data Reporting / Regulatory Considerations

11.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all research intervention procedures outlined in the protocol, toxicity, efficacy, and adverse event data for all enrolled study participants. To ensure maximum compliance, subjects will be prompted by email, phone, or with a text message to their mobile phone. To ensure HIPAA compliance, text messages will only read as "A new survey is due." Participants will be informed of this prompting protocol beforehand. No PHI, or any details of medical therapy, will be revealed in the text message or in the surveys administered through REDCap (please see the survey attachment to review how each survey will appear). Texts will be sent from a study dedicated phone controlled by the study staff. The study phone will be encrypted and managed by ITS per WCM regulation. Subjects will complete surveys at the following intervals: every 8 hours post-operative day 1 and 2, Every 12 hours post-operative day 3 through 7.

11.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

11.2 Regulatory Considerations

11.2.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the study participants, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IRB together with the approved ICF must be filed in the study files.

The Principal Investigator will report promptly to the IRB any new information that may adversely affect the safety of the study participants or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB as required. On completion of the study, the IRB will be notified that the study has ended.

All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill Cornell Medicine, updated documents will be provided to participating sites, as applicable. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.2.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

11.2.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-GCP and local regulations, as applicable, from each potential subject or each subject's legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB requirements, applicable laws and regulations.

11.2.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.2.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. In addition, all subjects' medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice. Research records will be kept for at six years after the end of the study.

12. Statistical Considerations

12.1 Study Design/Endpoints

The study will be a randomized double blind placebo controlled trial. We will randomize 86 study participants into two arms, with equal numbers in each arm.

Both the control arm and intervention arm will receive medication to be taken 2 hours before surgery as well as for three days three times a day after surgery. The team will be blinded to medication each study participant is receiving and will be recorded using a subject coded system.

Participants will receive reduced oxycodone prescriptions (quantity to be determined by clinical practice and prescribing surgeon) as needed, as well as celecoxib and acetaminophen to be taken as prescribed for the peri-operative period and up to 7 days post-operatively.

During the 7 subsequent post-op days participants in both the intervention and control arms will be asked to maintain a pain diary. The diary will be implemented online through the REDCap platform, which allows for secure online surveys. To ensure maximum compliance, subjects will be prompted by email, phone, or with a text message to their mobile phone. To ensure HIPAA compliance, text messages will only read as "A new survey is due." Participants will be informed of this prompting protocol beforehand. No PHI, or any details of medical therapy, will be revealed in the text message or in the surveys administered through REDCap (please see the survey attachment to review how each survey will appear). Texts will be sent from a study dedicated phone controlled by the study staff. The study phone will be encrypted and managed by ITS per WCM regulation. Subjects will complete surveys at the following intervals: every 8 hours post-operative day 1 and 2, Every 12 hours post-operative day 3 through 7.

Participants will be monitored for adverse events by the pre-operative nurses as well as the post-operative anesthesia care nurses who will be counselled on symptoms to examine for. Participants will have the opportunity to document any adverse events on their surveys.

Our primary endpoint will be to compare participant reported pain between participants receiving gabapentin and those receiving placebo in addition to standard of care. This will be assessed using the 11-point numerical pain rating scales (NRS-11) from post-operative day 1 to 7.

Our secondary endpoints include narcotic use following surgery including the number of tablets taken, frequency and time when narcotic is initially utilized. Participant satisfaction will be documented. Reduction in other symptoms such as nausea will also be recorded.

12.2 Statistical Analysis

The primary objective of this double-blind, placebo controlled randomized trial is to compare the participant-reported pain scores taken on an 11-point numerical rating scale (NRS-11) between subjects who received Gabapentin and controls who received placebo on day-7 post-scrotal surgery. The secondary objective is to determine whether the addition of gabapentin for post-operative pain control reduces narcotic intake. This study will also explore the effect gabapentin has on symptom modification.

Assuming a baseline NRS-11 score of 3.8 (from previous study) and a goal is to detect a two-point difference (reduction) in the day-7 pain score between the two groups, a sample size of 86 participants (43 per arm) will yield a power of 80% when using a two-sample t-test with a 0.05 two-

sided significance level. To account for potential loss to follow up and drop-out at a rate of 25%, each arm will require 43 study participants for a total recruitment of 86 study participants. This calculation assumes a standard deviation of 2.9, which is based on a previous study that looked at the effect of celecoxib in the same patient setting.[3]

Approximately 150 to 250 microTESE procedures are conducted at our site annually. As a result, we plan to accrue and complete the study in 29 months (i.e. ~9 study participants per month).

Descriptive statistics will be calculated to describe the cohort of study participants using N (%) and mean, median, range for categorical and continuous factors, respectively. A two-sample t-test or nonparametric Wilcoxon rank-sum test will be used, as appropriate, to compare the mean (median) participant-reported pain scores on day 7 post-scrotal surgery between the two arms. A chi-square test or Fisher's exact test will be used, as appropriate, to compare the proportion of narcotic use post-scrotal surgery between the two arms and to compare the proportion of adverse events experienced post-scrotal surgery between the two arms. Similar analyses will also be completed on the NRS-11 pain score, narcotic use, and reported adverse events on day-1 post-scrotal surgery. Generalized estimating equations (GEE) modeling will also be performed to compare NRS pains scores, assessed over all post-operative days 1 to 7, between the gabapentin and placebo groups. GEE allows for multiple observations per participant (i.e., pain scores for day 1 to day 7, per participant) and also allows for the incorporation of missing pain scores at some of the defined time points.

All p-values will be two-sided with statistical significance evaluated at the 0.05 alpha level. Ninety-five percent confidence intervals for all parameters of interest will be calculated to assess the precision of the obtained estimates. All analyses will be performed in R Version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). Note: The statistical considerations section was written in conjunction with Charlene Thomas, MS, in the Division of Biostatistics and Epidemiology, Department of Healthcare Policy & Research.

12.5 Interim Analysis

No interim analysis for efficacy will be performed.

12.6 Reporting and Exclusions

12.6.1 Evaluation of Toxicity

The frequency of subjects experiencing toxicities in each research study arm will be tabulated. Toxicities will be assessed and graded according to CTCAE v. 5.0 terminology. Exact 95% confidence intervals around the toxicity proportions will be calculated to assess the precision of the obtained estimates.

13. Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards,

contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

13.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

13.1.1 Investigational Agent or Device Risks (Expected Adverse Events)

Gabapentin is a medication known to treat seizures. It does have known adverse events especially when taken at high doses. As per the FDA in participants taking gabapentin for pain, side effects occurring >8% of the time compared to placebo include dizziness, somnolence, and peripheral edema. Other side effects were seen in less than 5% including asthenia, GI symptoms, weight gain, abnormal thinking, incoordination, ataxia, or ocular symptoms.

13.1.2 Adverse Event Characteristics and Related Attributions

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the research intervention.
  - Probable – The AE *is likely related* to the research intervention.
  - Possible – The AE *may be related* to the research intervention.
  - Unlikely – The AE *is doubtfully related* to the research intervention.
  - Unrelated – The AE *is clearly NOT related* to the research intervention.

13.1.3 Recording of Adverse Events

All adverse events will be recorded on a subject specific AE log. The AE log will be maintained by the research staff and kept in the subject's research chart.

13.1.4 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:
http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.2 Definition of SAE

SAEs include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

13.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.2.2 Reporting of SAE to FDA [For Protocols Where WCMC is the Sponsor-Investigator]

If an SAE occurs on this study, the event will be filed on a MedWatch form with the FDA. The investigator must notify the FDA of any SAE's as soon as possible but no later than 7 calendar days after the initial receipt of the information

CDER INDs:

Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

13.2.3 Reporting of SAE to *Curis Pharmacy*

Not applicable.

13.3 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the subject discontinues participation from the study.

13.4 Time Period and Frequency for Event Assessment and Follow Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The primary investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

14. Unanticipated Problems Involving Risks to Subjects or Others

14.1 Definition of Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- 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
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

14.1.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPIRTSOs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UPIRTSO report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UPIRTSO;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UPIRTSO.

To satisfy the requirement for prompt reporting, UPIRTSOs will be reported using the following timeline:

- UPIRTSOs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the event.
- Any other UPIRTSO will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), Food and Drug Administration (FDA), and the Office for Human Research Protections (OHRP) within <insert timeline in accordance with policy> of the IRB's receipt of the report of the problem from the investigator.

15. Data and Safety Monitoring Plan (DSMP)

- Adverse events will be recorded by the study nurse and clinical fellow during follow-up phone calls and clinic visits with each post-operative patient. Minor adverse events will be examined and reviewed for intervals of every 10 subjects during accrual. Any significant adverse events or grade 4 events possibly related to the study product will trigger a temporary cessation of the trial and full review by the principal investigator, as well as the WCM DSMB as to whether the study should continue.

- The WCM DSMB will be utilized in our investigator-initiated study, with evaluation of adverse events at specific intervals. This will occur at 6 month time periods.

- Data
    - Adverse event data
        - Major: Allergic reaction, suicidal behavior and ideation, driving impairment
        - Minor: dizziness, somnolence, peripheral edema, ataxia, fatigue, nystagmus, GI symptoms
    - Study-related data
        - Pain scores (NRS-11), Narcotic tablet tally, overall pain control satisfaction (Yes/No question)
    - Demographics

  - Age, male infertility diagnoses (i.e. presence of varicocele), prior surgical history, current medications, historical lab evaluation (FSH, LH, total testosterone, semen analyses, sperm DNA integrity tests such as tunel or SCSA assay, karyotype data, y-microdeletion status), pathology results of testis biopsy
- Data safety
  - Data will be kept in REDCap, which is licensed by WCMC and is HIPAA compliant. Only study personnel will have access to the database. Hard or software copies of the database will not be allowed. The database will only be accessed within the WCMC network utilizing WCMC tagged devices. Subject identifiers will be replaced by study identifiers as soon as data collection is complete.

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