IRB Minimal Risk Protocol Template

Note: If this study establishes a human specimen repository (biobank) for research purposes, do not use this template. Use the Mayo Clinic Human Specimen Repository Protocol Template found on the IRB home page under Forms and Procedures at http://intranet.mayo.edu/charlie/irb/

First-time Use: Use this template to describe your study for a new IRB submission.

1. Complete the questions that apply to your study.
2. Save an electronic copy of this protocol for future revisions.
3. When completing your IRBe application, you will be asked to upload this document to the protocol section.

Modification: To modify this document after your study has been approved:

1. Open your study in IRBe. Click on the study 'Documents' tab and select the most recent version of the protocol. Save it to your files.
2. Open the saved document and activate "Track Changes".
3. Revise the protocol template to reflect the modification points , save the template to your files
4. Create an IRBe Modification for the study and upload the revised protocol template.

General Study Information

Principal Investigator: Matthew Ziegelmann, MD

Study Title: A Randomized-Controlled trial comparing long-acting and short-acting local anesthetics at the time of penile prosthesis placement.

Protocol version number and date: Version 2; July 21, 2021

Research Question and Aims

Hypothesis:
Local anesthesia with liposomal bupivacaine administered at the time of penile prosthesis placement will reduce postoperative opioid use and decrease post-operative pain when compared with administration of ropivacaine.

Aims, purpose, or objectives:
This study aims to determine if using liposomal bupivacaine, when compared with ropivacaine, for postoperative pain control in patients undergoing surgical placement of a 3-piece inflatable penile prosthesis is associated with less overall opioid use and lower postoperative pain scores during the early postoperative period. Variables to be analyzed will include pre- and postoperative pain and anxiety scores, in-hospital (if-applicable) and home opioid use postoperatively, and adverse intraoperative, perioperative, and postoperative events.

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc.*):

The United States is in the midst of an opioid epidemic, with prescription-related drug deaths at an all time high over the last decade. Surgeons are responsible for a significant proportion of opioid prescribing for postoperative pain control, and it is estimated that 2-6% of patients who receive opioids postoperatively may go on to develop persistent use or dependence.[1,2] To this end, urology has been at the forefront in attempts to develop extended recovery after surgery (ERAS) protocols to optimize pain control while minimizing the need for opioid medications.

Penile prosthesis placement is considered the gold standard for the management of men with medication-refractory erectile dysfunction (ED). It is associated with high levels of patient and partner satisfaction and restores the ability for a patient to engage in satisfactory sexual activity.[3] Multiple innovations in device technology and operative approach have minimized adverse events such as device infection and mechanical malfunction, making this a highly effective and reproducible treatment for men with severe ED.[4] The procedure itself can be associated with significant perioperative and postoperative pain due to the high density of pain receptors located within the penis, scrotum, and inguinal regions. Historically, many prosthetic surgeons have compensated for this by prescribing large quantities of opioids to be used for breakthrough pain. However, in the era of increasing awareness regarding the negative effects of opioid medications, there has been renewed interest in alternative pain control regimens. For example, Lucas et al found that postoperative pain scores and opioid use were significantly lower in patients who underwent penile prosthesis placement with a multi-modal pain regimen that included acetaminophen, meloxicam or celecoxib, and gabapentin and intraoperative dorsal and pudendal nerve blocks with lidocaine/bupivacaine.[5] This and another novel approaches are appealing, but clinical experience has revealed short-comings with pain control regimens based on short-acting local anesthetics such as lidocaine/bupivacaine, wherein the local effects may wane within several hours. Neuroleptics including gabapentin are also suboptimal due to untoward side-effects including sedation and even adverse anesthesia events such as prolonged sedation requiring a longer stay in the postoperative recovery unit. For these reasons, a longer-activing local anesthetic is particularly appealing from both safety and efficacy perspectives.

Liposomal bupivacaine (LB) is a long-acting local anesthetic that has been shown to promote local pain control in the postoperative period for up to 72 hours, as compared to traditional local anesthetic agents with half-lives ranging from 1-6 hours. The prolonged pain control duration is the result of suspending the bupivacaine within a lipid vessel that creates slow release of the medication within tissues over time. Within the realm of urology very few studies have assessed outcomes in patients who receive perioperative LB. A study by Cotta et al from 2016 retrospectively explored their experience with LB (n=13) compared with those receiving local bupivacaine (n=24) for anesthesia during penile prosthesis placement.[6] The authors found that patients receiving LB used significantly fewer opioids postoperatively. Two additional studies by Alom et al and Ziegelmann et al described LB for use with office-based surgical procedures involving the penis and scrotum, although outcomes related to pain control were not specifically evaluated.[7,8] Finally, a recent study by Taniguchi and Mulhall showed that LB did not adversely impact systemic hemodynamics when administered within the corpora cavernosa of patients at the time of penile prosthesis placement, supporting the safety of this medication in the perioperative setting.[9]

It has been our experience that LB optimizes pain control in the postoperative setting when administered at the time of penile prosthesis placement. This has become a routine part of clinical practice. However, LB results in added expense, and to date there has never been an adequately powered prospective study comparing outcomes between LB and other shorter-acting local anesthestics to determine if this added expense is justified. Therefore, we intend to assess perioperative and postoperative outcomes including safety and pain control in patients who receive local anesthesia with LB versus ropivacaine at the time of penile prosthesis placement.

References:
1. Brummett CM, Waljee JF, Goesling J, et al. New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. *JAMA Surg.* 2017;152(6):e170504.
2. Welk B, McClure JA, Clarke C, et al. An opioid prescription for men undergoing minor urologic surgery is associated with an increased risk of new persistent opioid use. Eur Urol. 2020; 77(1):68-75.
3. Akapo W, Pineda MA, Burnett AL. Critical Analysis of Satisfction Assessmente After Penile Prosthesis Surgery. Sex Med Rev. 207 Apr;5(2):244-251.
4. Chung E. Penile prosthesis implant: scientific advances and technological innovations over the last four decades. Transl Androl Urol. 2017 Feb;691):37-45.
5. Lucas J, Gross M, Yafi F, et al. A multi-institutional assessment of multimodal analgesia in penile implant recipients demonstrates dramatic reduction in pain scores and narcotic usage. J Sex Med. 2020 mar;17(3):518-525.
6. Cotta BH, Welliver C, Brahmamdam A, et al. Long-acting liposomal bupivacaine decreases inpatient narcotic requirements in men undergoing penile prosthesis implantation. *Turk J Urol.* 2016;42(4):230-234.
7. Alom M, Ziegelmann M, Savage J, et al. Office-based andrology and male infertility procedures- a cost-effective alternative. Transl Androl Urol. 2017;6(4):761-772.
8. Ziegelmann M, Dodge N, Alom M, et al. Office-based, Minimal-Incision Modified Fenestration Technique for Symptomatic Hydroceles Under Local Anesthesia. *Urology.* 2020; 135:159-164.
9. Taniguchi H, Mulhall JP. Intraoperative intracavernosal liposomal buipvacaine (Exparel) injection does not affect systemic hemodynamics. J Sex Med 2020 Mar;17(3):526-530.

Study Design and Methods

Methods: *Describe in lay terms, completely detailing the research activities that will be conducted by Mayo Clinic staff under this protocol*.

A single-blind, randomized study will be conducted in those patients who are undergoing 3-piece inflatable penile prosthesis placement for medication refractory erectile dysfunction by three fellowship-trained urologic prosthetic surgeons at Mayo Clinic in Rochester, MN. Study and surgical informed consent will be obtained preoperatively from those patients who are interesting in participating in the study and meet inclusion/exclusion criteria.

Study participants will be randomized to one of two study arms. Arm 1 will receive 40 mL of ropivicaine to be used for local anesthetic infiltration. Arm 2 will receive 40 mL of Liposomal bupivacaine (20 mL Exparel + 10 mL 0.25% bupivacaine) to be used for local anesthetic infiltration. The patient will be blinded to which study arm he is randomized to, but the surgeon will be aware (i.e. single blind). The specific agent (determined by study randomization) will be ordered by the performing surgeon through the “prep for case” inflatable penile prosthesis order set within EPIC. Two standardized order sets will be shared amongst the three performing surgeons and will also include standardized perioperative medication administration per a previously published enhanced recovery protocol (see reference #5 – Lucas et al).

Local anesthetic will be administered via a standard protocol at the time of penile prosthesis surgery. The block itself will include pudendal, scrotal, dorsal penile, and inguinal nerve blocks. The remainder of the penile prosthesis surgery will be per standard practice, with all surgeons currently utilizing a similar penoscrotal

approach. Of note, patients who currently receive intraoperative LB routinely wear a disposable bracelet with information for medical professionals regarding the recent receipt of this medication. This is worn for 72-96 hours postoperatively. For the study protocol, we will work with the perioperative nursing team to apply a similar bracelet describing the research study and acknowledging that each patient may have received LB versus ropivacaine during the surgery.

If the study coordinator is unable to meet with the patient to review consent, they will be a digital consent via email. The patient will be contacted by telephone and read a script about study participation. Patients will then have the ability to sign the consent form with their personal device. These digital consent forms will be stored in Ptrax.

If patients decide to consent digitally, they will be asked to complete the baseline requirements over the phone. These documents are the baseline anxiety inventory and the pain catastrophizing scale which will be recorded by the study coordinator.

Preoperative patient data including pertinent demographics as well as a baseline anxiety inventory and pain catastrophizing scale will be collected. They will also receive a medication log to track their narcotic intake until post-operative day 14. The patients will be followed-up by phone call or through electronic correspondence (RedCap) on post-operative days 3, 7, and 14. Participants in the study will be allowed to completed the questionnaires through RedCap with a +/- 2 day allowance on completion to avoid any study deviation. This follow-up will be obtained by the performing surgeons and/or the research office coordinator. At these planned follow-up intervals, patients will be evaluated using the Visual Analog Pain Scale (daily maximum and minimum) and visual analogue anxiety scale (daily maximum and minimum). In addition their pain control regimen (quantities of Tylenol, anti-inflammatories, and opioid pain medication) will be analyzed. Patients will be instructed to maintain a log of minimum and maximum daily pain scores and daily medication use. They will also be instructed to bring their medication bottles to their 3 week follow-up. Patient satisfaction with overall postoperative pain control will be measured based on subjective response. Finally, the duration of local anesthetic effect will be measured based on patient report.

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 130 patients (65 patients in each treatment arm) – this accounts for the necessary statistical power plus an anticipated approximately 20% dropout rate.

Subject population (children, adults, groups): Patients with medication-refractory erectile dysfunction undergoing penile prosthesis placement at Mayo Clinic in Rochester by Drs. Ziegelmann, Helo, and Kohler.

Inclusion Criteria:

1. Men undergoing 3-piece inflatable penile prosthesis placement under general anesthesia at Mayo Clinic - Rochester
2. ≥ 18 years old

Exclusion Criteria:

1. History of opioid exposure within the preceding 90 days prior to surgery (based on patient-report, review of the electronic medical record, and NMP prescribing database review)
2. Current or prior history of alcohol or drug abuse (illicit or prescription)
3. History of chronic pain conditions (chronic musculoskeletal pain, fibromyalgia, central sensitization, chronic pelvic pain syndrome, etc.)
4. History of cardiac arrhythmia or untreated severe cardiovascular disease
5. Uncontrolled hypertension
6. Hepatic insufficiency
7. Renal insufficiency (CKD stage IIIa or greater)
8. Current anti-platelet or anti-coagulation therapy with plans to continue at the time of prosthesis placement
9. Poorly controlled diabetes mellitus (defined as HgbA1c > 8.5 within 30 days of surgery)
10. Concurrent adjunctive operative procedures planned at the time of penile prosthesis placement (examples: male urethral sling, Peyronie's disease straightening with penile plication or incision/grafting)
11. Concurrent non-prosthetic surgery planned at the time of penile prosthesis placement (examples: circumcision, hernia repair, hydrocelectomy, etc.)
12. Planned infrapubic or subcoronal incision at the time of penile prosthesis placement
13. Patients who will be undergoing prosthesis placement using local, monitored, or spinal anesthesia (i.e. non-general anesthesia)
14. Allergy or history of intolerance to any local anesthetic agents included in the protocol
15. History of prior penile prosthesis or artificial urinary sphincter surgery
16. Revision penile prosthesis surgery

Study Feasibility: At Mayo Clinic – Rochester, we perform approximately 200 penile prosthesis procedures per year amongst the three prosthetic surgeons, of which an estimated 90% are primary prosthesis placements. The majority of patients who are candidates for penile prosthesis placement will meet our inclusion criteria. Given that we will be comparing administration of two local anesthetics that are generally considered as standard of care, and the fact that our study protocol involves minimal additional time commitment on the part of the patient participants, we anticipate a high rate of patient willingness to participate in the trial. We anticipate study dropout to approach approximately 20%. Therefore, we estimate the study duration inclusive of patient accrual, data collection, and statistical analysis to be approximately 24 months.

Biospecimens

Not-applicable

Review of medical records, images, specimens

Check all that apply (data includes medical records, images, specimens).

☐ Only data that exists before the IRB submission date will be collected.

Date Range for Specimens and/or Review of Medical Records:
Examples: *01/01/1999 through 12/31/2015*, or all records through *mm/dd/yyyy*.

Note: The Date Range must include the period for collection of baseline data, as well as follow-up data, if applicable.

☒ The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

Data Analysis

Power analyses may not be appropriate if this is a feasibility or pilot study, but end-point analysis plans are always appropriate even if only exploratory. Provide all information requested below, or provide justification if not including all of the information.

Power Statement: A total sample size of 110 (55 per arm) provides 90% power to detect a clinically relevant difference in discharge prescription opioids of 37.5 OME, based on a two-sample, two-sided, equal-variance t-test with significance alpha level 0.05, and assuming a common standard deviation of 60 OME. With an anticipated drop-out rate of 18%, total sample size will be 130 (65 per arm).

Data Analysis Plan:

Patient data will be recorded and stored in a study-specific database through RedCap. This database will be created by the primary investigator. At the completion of the study, statistical analyst support will be used to perform the final data analysis.

Preoperative data collection:
-State-Trait Anxiety inventory (attachment 1)
-Pain Catastrophizing scale (attachment 2)

Postoperative days 3,7,14 data collection:
-Visual-analogue pain score (attachment 3)
-Visual-analogue anxiety score (attachment 4)
-Analgesic quantities (acetaminophen, meloxicam, ibuprofen, gabapentin, oxycodone, tramadol)

Endpoints
Primary:

1. Postoperative opioid pain medication use (number of oral morphine equivalents consumed per day and total number)

Secondary:

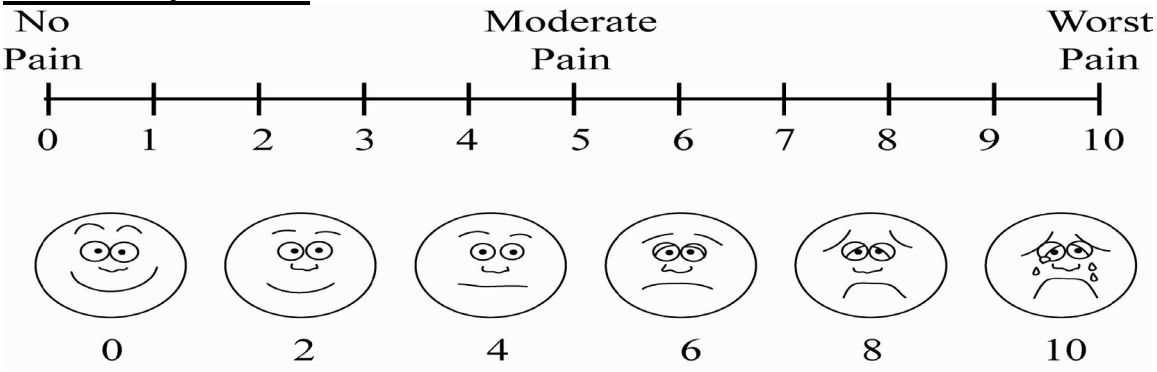
2. Postoperative pain scores (Maximum and minimum on visual analogue pain scale of 0-10) on postoperative days3, 7, 14
3. Postoperative non-narcotic pain medication use (non-steroidal anti-inflammatories, acetaminophen, gabapentin)
4. Postoperative anxiety scores (Maximum and minimum on visual analogue anxiety scale of 0-10) on postoperative days 0 – 7
5. Adverse perioperative events – cardiovascular parameter changes
6. Patient satisfaction (subjective, patient reported)
7. Duration of pain control from local anesthetic

Attachments:
-Visual-analog pain scale (attachment 1)
-Visual-analog anxiety scale (attachment 2)
-State-Trait Anxiety inventory (attachment 3)
-Pain catastrophizing scale (attachment 4)
-Perioperative analgesia protocol (attachment 5)
-Preoperative, perioperative, and postoperative clinical variables of interest (attachment 6)
-Proposed budget (attachment 7)

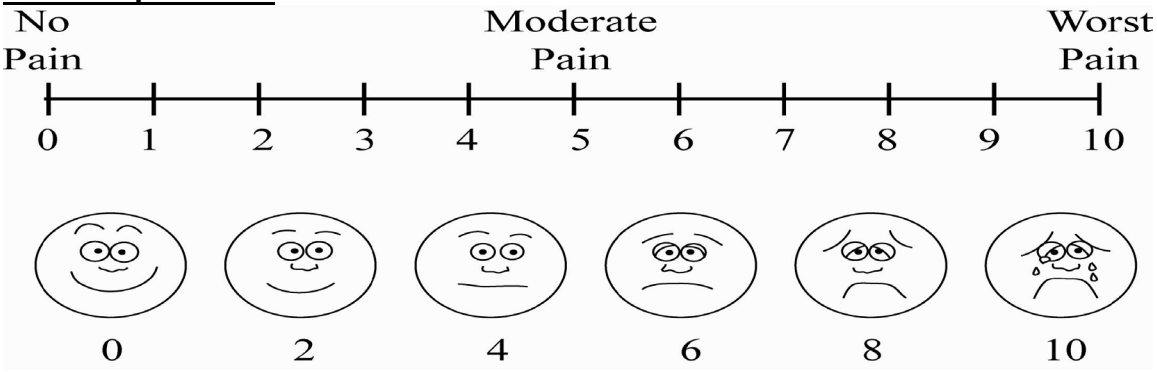
Attachment 1

Patient_____ DOB_____ MRN _____
Date of Procedure _____ Procedure performed _____
Pre-medication: Yes No If yes, what medication? _____

Prior to the procedure



After the procedure

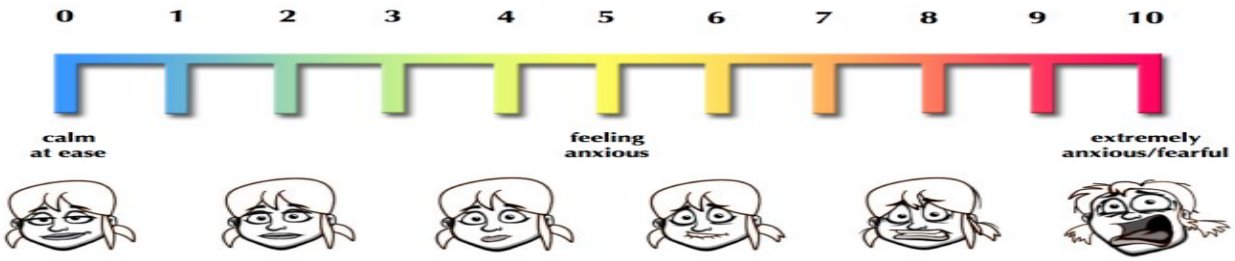


Attachment 2

Anxiety Scores

Prior to the procedure

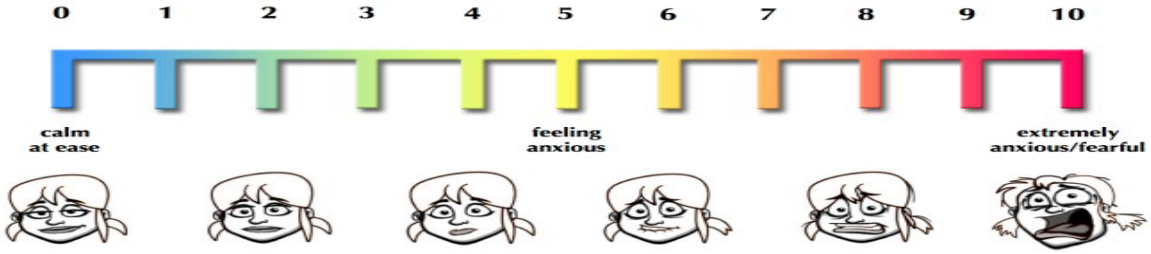
Mark (X) the point on the scale that best describes how you are feeling at the moment.
Use the Dowrick facial anxiety scale to assist you.



Edward Dowrick © 2016 Anxiety Level Self-assessment and facial anxiety scale female

After the procedure

Mark (X) the point on the scale that best describes how you are feeling at the moment.
Use the Dowrick facial anxiety scale to assist you.



Edward Dowrick © 2016 Anxiety Level Self-assessment and facial anxiety scale female

Attachment 3

State Trait Anxiety Inventory

How do you feel RIGHT NOW? Read each statement and select the number which most closely indicates how you feel right now. There are no right or wrong answers. Please give the answer which seems to describe your present feelings best.

	1	**2**	**3**	**4**
	Not at all	**A little**	**Somewhat**	**Very Much So**
1.	I feel calm	1	2	3	4
2.	I feel secure	1	2	3	4
3.	I feel tense	1	2	3	4
4.	I feel strained	1	2	3	4
5.	I feel at ease	1	2	3	4
6.	I feel upset	1	2	3	4
7.	I am presently worrying over possible misfortunes	1	2	3	4
8.	I feel satisfied	1	2	3	4
9.	I feel frightened	1	2	3	4
10.	I feel uncomfortable	1	2	3	4
11.	I feel self confident	1	2	3	4
12.	I feel nervous	1	2	3	4
13.	I feel jittery	1	2	3	4
14.	I feel indecisive	1	2	3	4
15.	I am relaxed	1	2	3	4
16.	I feel content	1	2	3	4
17.	I am worried	1	2	3	4
18.	I feel confused	1	2	3	4
19.	I feel steady	1	2	3	4
20.	I feel pleasant	1	2	3	4

Total: _____

Attachment 4

MAYO CLINIC

PCS

Client No.: _____ Age: _____ Sex: M(__) F(__) Date: _____

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0 – not at all **1** – to a slight degree **2** – to a moderate degree **3** – to a great degree **4** – all the time

When I'm in pain …

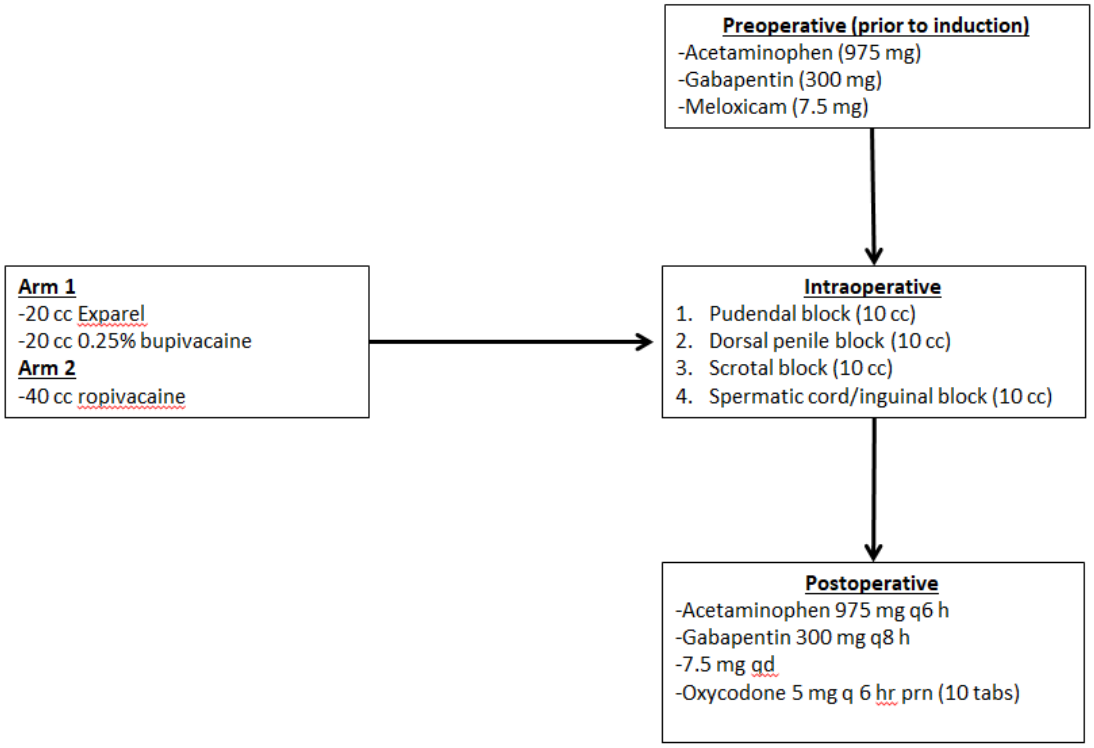
1. ☐ I worry all the time about whether the pain will end.
2. ☐ I feel I can't go on.
3. ☐ It's terrible and I think it's never going to get any better.
4. ☐ It's awful and I feel that it overwhelms me.
5. ☐ I feel I can't stand it anymore.
6. ☐ I become afraid that the pain will get worse.
7. ☐ I keep thinking of other painful events.
8. ☐ I anxiously want the pain to go away.
9. ☐ I can't seem to keep it out of my mind.
10. ☐ I keep thinking about how much it hurts.
11. ☐ I keep thinking about how badly I want the pain to stop.
12. ☐ There's nothing I can do to reduce the intensity of the pain.
13. ☐ I wonder whether something serious may happen.

… Total


MAYO
CLINIC

Attachment 5

Perioperative Analgesia Protocol



Attachment 6

	POD #1	POD #2	POD #3	POD #4	POD #5	POD #6	POD #7	POD #8	POD #9	POD #10	POD #11	POD #12	POD #13	POD #14
Minimum pain score (scale 0-10)														
Maximum pain score (scale 0-10)														
Acetaminophen (Tylenol), number of tablets used														
Gabapentin (Neurontin), number of tablets used														
Meloxicam (Mobic), number of tablets used														
Oxycodone, number of tablets used														
Other comments														

Attachment 7

Proposed Budget for Exparel IPP study

PERSONNEL (Period 1: 03/01/2021 - 03/01/2023)				
Name	**Role**			**Amount**
	Principal Investigator			
	Study Coordinator (12.5% x 2 years)			$7,875.00
	Subtotal Direct Cost - Personnel			**$7,875.00**
Internal Services (Period 1: MM/DD/YYYY - MM/DD/YYYY)				
	Entity			**Amount**
	Miscellaneous Costs – Men's Health Website			$500.00
	Statistical analyst support			$6,000.00
	Subtotal Direct Cost – Internal Service			**$6500.00**
Total Direct Cost			$14,375.00	
Indirect Rate			30.000%	
Total Indirect Cost			$4,312.50	
Total Cost (Period 1: MM/DD/YYYY - MM/DD/YYYY)			**$18,687.50**	