TITLE: **Randomized Controlled Trial of Repeat vs. Single Quadratus Lumborum Block to Reduce Opioid Prescriptions After Open Resection of Retroperitoneal Sarcoma ("RESQU-SARC" Trial)**

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1.0 Objectives

Primary: To use a pragmatic **phase II randomized controlled trial** to compare two standardized bundles of usual care for postoperative pain management to reduce the initial discharge prescription opioid volume.

Secondary: To assess which pragmatic arm improves aspects of postoperative recovery including 30-day, 3-month, and 1-year opioid use, patient symptom inventory at those time points, hospital measures including length of stay and inpatient pain scores.

The **primary aim** of this proposal is to use a pragmatic **phase II randomized controlled trial** to compare two standardized bundles of usual care for postoperative pain management. One arm has the **intervention of an intraoperative plus second regional anesthetic block (QL block) versus a comparison/control** arm of a single intraoperative QL block, **both bundled** with a standardized non-opioid pain management protocol, to **decrease the initial discharge prescription opioid volume for retroperitoneal sarcoma survivors** after potentially curative surgery. The primary outcome measure will be the initial discharge opioid prescription (oral morphine equivalents, OME) of patients in each arm. **Both arms will include a standardized non-opioid bundle** for pain control supplementation during hospital stay and upon discharge and previously published enhanced surgical recovery protocols, based on clinically relevant preoperative strata.

PICO: In patients undergoing open retroperitoneal/intra-abdominal sarcoma resection using general anesthesia with regional pain block (QL block with 72-hr liposomal bupivacaine) [**Patients**], can the placement of a 2nd QL block on postoperative day 4 ("Rescue" block [**Intervention**] more effectively wean patients off postoperative opioids during the inpatient stay vs. usual care of QL block (both arms with low-dose IV-PCA plus non-opioid bundle) [**Comparison/Control**]. The primary outcome measure will be the initial discharge opioid prescription volume of patients in each arm [**Outcome**].

Outcome Measures:

Primary:

- **Initial discharge prescription OME [continuous variable]**

Secondary:

- **Hospital Measures**
  - Proportion of patients with discharge prescription OME = zero
  - Patient Reported Outcomes for gastrointestinal surgery– MD Anderson Symptom Inventory (MDASI-GI)
  - Daily inpatient pain scores
  - Total length of stay and cost

- **Discharge Measures**
  - 30-day total OME
  - Initial discharge Rx volume <200mg (Y/N)

- Number of postoperative days until zero opioid use
- Opioid use at 30 days, 3 months, and 12 months (Y/N, OME)
- MDASI-GI at 30 days, 3 months, and 12 months
- 3-mo and 1-yr follow-up – patients free of opioid use (Y/N)

2.0 Rationale

There is increasing evidence that an elective surgical event is often a patient's initial and greatest exposure to opioids.[1-3] In survivors of cancer surgery, persistent opioid use can be predicted by the dispensed volume of a patient's initial outpatient prescription at surgical discharge.[1,4,5] Furthermore, national prescribing pattern data have shown that the initial outpatient prescription of *oral morphine equivalents (OME)* can be predicted by opioid utilization during the last 24hrs in the hospital.[6,7] A tangible contribution from the surgical community would be the active implementation of a protocol to eliminate or reduce outpatient opioid dissemination in a greater proportion of cancer survivors after oncologic surgery. In this context, we have implemented regional anesthetic techniques including ultrasound-guided four-point *bilateral quadratus lumborum (QL) block using 72-hr liposomal bupivacaine.* Despite the hospital-wide emphasis on enhanced surgical recovery principles to reduce hospital length of stay, opioid reduction has not been a focused tenet of our enhanced surgical recovery goals until recently. In a recent analysis of five commonly performed Index operations from our Department of Surgical Oncology (including sarcoma resection), only 5% of our patients were discharged without opioids.

We thus see an opportunity to accelerate postoperative opioid weaning to reduce the total opioids used in the postoperative setting with the downstream effect of having less patients using opioids past the initial recovery period (characterized in literature as "persistent use"). We hypothesize that a second, repeat QL block on postoperative day 4 will bridge the gap between the initial intraoperative QL block and ambulatory status, reduce the total postoperative OME, and increase the proportion of sarcoma survivors free of opioids beyond the postoperative recovery period. **"Rescue blocks" are currently used on an as-needed basis** only when the first block is insufficient or if the clinical team decides that the opioid use is subjectively too much**.** Until recently with our **"RESQU-BLOCK" trial** (PA18-0859, NCT03745794), we had not been routinely using a 2nd block, because opioid-free discharge has never previously been a goal, even with enhanced surgical recovery protocols. However, with the successful implementation and enrollment of the RESQU-BLOCK trial (similar goals as this trial except in pancreatectomy, with first enrollment 3/1/2019)**,** our new long-term goal is to **reduce dissemination of opioids into the community and reduce the risk of persistent opioid use among survivors, their families, and their communities.**

"Enhanced recovery after surgery," or ERAS, is no longer a novel idea. However, its benefits are beginning to be seen beyond the early metrics of hospital stay and activities of daily living. Downstream benefits have included reduced complications, fewer readmissions (despite earlier discharges), less hospital resource consumption (cost), and improved postoperative quality of life. With the opioid epidemic increasingly discussed in both medical

and lay literature, we are seeking to modify our enhanced recovery program in abdominal cancer surgery to reduce opioid exposure in the hospital. Medical literature has shown that oftentimes the first exposure or greatest exposure to opioids comes from an elective surgical event. Persistent opioid use can be predicted by the size of a patient's initial outpatient prescription **oral morphine equivalents (OME)** and the **initial outpatient prescription OME can be predicted by the amount of opioids used in the last 24hrs of hospitalization,** which is often the result of how quickly the inpatient pain medications are weaned.

We recently analyzed opioid prescription patterns for patients who underwent major surgery in 5 major disease sites within Department of Surgical Oncology from March 2016 to April 2018, and one of these disease sites was sarcoma. A total of 192 patients underwent an operation for sarcoma with a median total inpatient OME of 171 mg (IQR 80-375 mg). Moreover, patients undergoing sarcoma surgery received a median of 300 mg OME (IQR 200-608 mg) at discharge, which was the 3rd highest of those analyzed. This revealed that **discharge prescription OME** after sarcoma surgery were paradoxically **higher than** their median **total inpatient OME** use after surgery. **They received more opioids at discharge than they used in the entire hospitalization.** Notably, across the entire surgical oncology patient cohort, 23% of patients used zero opioids during the last 24 hours of hospitalization, yet the majority of these patients (83%) were still prescribed discharge opioids (median 210 mg, IQR 150-326 mg).

We thus see an **opportunity to reduce opioid exposure** and **accelerate the weaning process** to decrease the **volume of opioids disseminated to patients and the community in the critical early days after discharge**. We plan to implement an enhanced surgical recovery bundle for sarcoma patients by using standardized non-narcotics and reducing initial IV-PCA settings. This trial will help answer which arm (both within "usual care" parameters) will be better at reducing postoperative opioid use.

HYPOTHESIS

- We hypothesize that a **second, repeat QL block on postoperative day 4** will bridge the gap between the initial intraoperative QL block and ambulatory status, facilitating a rapid opioid wean and **thus decrease the volume of opioids used by sarcoma surgery survivors after index hospitalization.** Ultimately, this should reduce dissemination of opioids into the community and reduce the risk of persistent opioid use in survivors and diversion to families and communities.

3.0 Eligibility of Subjects

Inclusion:

- Patients ≥ 18 years of age undergoing elective open sarcoma resection for potentially curative intent who would otherwise be treated with QL block + IV-PCA converted to oral pain meds [non-narcotic bundle + opioid pain pill].

Exclusion:

- Patients with current or past substance [drug or alcohol] abuse disorder
- Laparoscopic or minimally invasive surgery
- Cases in which *anticipated* discharge is on or before postoperative day 4

4.0 Research Plan and Methods

This is a **single-center pragmatic phase II open-label randomized controlled trial** to compare two standardized bundles of usual care for postoperative pain management. The single difference in intervention is an additional QL block on POD4 in patients undergoing sarcoma surgery with potentially curative intent. The **primary endpoint is the initial discharge prescription OME**. Patients will be randomized with 1:1 ratio to receive either QL in OR + non-opioid bundle +/- low-dose IV-PCA (control arm) or QL in OR and QL on POD4 AM + non-opioid bundle +/- low-dose IV-PCA (experimental arm). The **randomization will occur on postoperative day 3** so that usual care will be performed intraoperatively and for the first 3 days after surgery. On POD3, at the time of randomization, patients will be stratified based on preoperative use of long-term opioids (e.g. extended or continuous release) (yes vs. no) and preoperative average daily OME use (>7.5mg vs. ≤7.5mg OME, which allows 1 tramadol, 1 oxycodone, or 1 hydrocodone per day in the lower stratum) in the 7 days before surgery. Patients will further be stratified by whether they undergo nephrectomy (yes vs. no) as part of their operative procedure, or if they have a previous surgical history of nephrectomy, as this would impact their eligibility for some of our frequently used adjunct pain medications (e.g. Celebrex, Toradol). There will be no standardization of postoperative dietary advancement, fluid management, or postoperative care, other than standardization of the IV and oral non-opioid bundle and initial IV-PCA settings in the recovery room on POD0.

Method of Group Assignment and Randomization

- **Stratified Randomization**: REDCap will be used for 1:1 allocation and stratification for preoperative long-term (≥ 3 months) opioid use (yes vs. no), preoperative average daily OME use (>7.5mg vs. ≤7.5mg OME), and nephrectomy status (yes vs. no), as detailed above.

- **Implementation:** Acute pain team, surgeons, advanced practice providers, fellows, and nurses will perform interventions and assessments per usual care.

- **Blinding:** This is an open-label study since the intervention arm will receive a 2nd QL block which cannot be blinded from the patient or treating physician. The allocation will be unmasked immediately upon randomization on POD3 morning after clinician rounds.

Intervention Strategy:

On postoperative day 4 [at least 96hrs from initial QL on postoperative day “0”, which is the day of surgery, per FDA guidelines], patients will undergo a 2nd QL procedure in the regular

hospital room by the Acute Pain Service attending anesthesiologist using ultrasound guidance, which is usual routine method. The intent will be to do the 2nd QL. Patients or providers may choose to forego the option if patients are already opioid-free or nearly opioid-free or for any other reasons provided by the patient.

This will be a **4-point Type I QL + subcostal block,** which allows an anterior approach to the targeted fascial layers. Using sterile technique, the attending anesthesiologist will guide the needle through the appropriate skin, subcutaneous, and muscle layers to find the right fascial plane **using ultrasound localization**. The risk of complications is virtually nil, because most hospital subcutaneous and intramuscular shots which are done blindly or by "landmark," the QL block will be done by exact ultrasound guidance. **This block will only be done by Acute Pain Service certified faculty**. We are not studying this block's mechanism or the drug's mechanism – both of which are well documented in thousands of patients. **This pragmatic RCT focuses on the novel timing of using this regional block to measure its effectiveness in accelerating the opioid weaning process.**

Patients will not be randomized if anticipated to be discharged by 7am on POD4, or if they are already opioid-free on POD3 at time of randomization. The clinical team will be able to anticipate any early discharges (defined as discharge before POD4) and therefore exclude those patients from randomization.

(The **usual measures of non-opioid bundle** [including acetaminophen, NSAIDs, muscle relaxers] and conversion from IV pain meds to oral pains will be done to reduce total opioid exposure and use. Clinicians may choose to add additional non-opioids if clinically indicated. Non-opioids will be standardized for dosing, timing, and route, and will be given unless contraindicated (e.g. holding NSAIDs if nephrectomy performed for the sarcoma resection).

The 2nd block is a "Rescue Block" which we currently utilize on the floor for patients with pain control issues that are not making the anticipated progress, on postoperative day 4, and if we want to avoid opioids due to traditional concerns like ileus, somnolence, and nausea. Thus, in terms of hospital billing, this is well within the spectrum of usual care. **No component of this trial is experimental. All components are within usual care, except both arms are standardized to minimize variation for the clinical teams.**

There will be no sham procedure in the control/comparison arm. In other words, there will not be any subcutaneous injection of placebo drug in patients in the comparison arm, since this is a study of treatment sequencing rather than one focused on the drug itself. A sham procedure would be required if we were using an experimental drug in the intervention arm, but the analgesic effect of liposomal and regular bupivacaine is well-proven already. The "treatment" herein is the bundle of standardized non-opioids and the clinical care that is typically given for weaning pain medications through an inpatient stay. The only difference between the 2 arms is that the "intervention" arm has the option (patient may refuse if they are already off opioids) for the rescue block while the "comparison" arm has to use the (strictly bundled) usual measures to continue weaning opioids.

Pain measurement: Pain scores will be measured using usual care – visual analog scale by hospital inpatient nurses. They ask the patient every 4hrs on a scale 0-10, and this is documented in the EHR. Nurses then offer patients with symptomatic scores additional oral or IV pain meds as appropriate based on usual clinical care (IV if not eating or severe breakthrough pain) and oral if eating and pain is not urgent.

- **Liposomal bupivacaine – 72-hr action**
  - No repeat in 96 hrs per drug label
  - Rarely completely enough for pain control – often needs low-dose IV-PCA as well, but can reduce total opioid use if an opioid-sparing bundle is standardly used, which we will do (both arms get the same non-opioid bundle in hospital and upon discharge).
  - **Dosage instructions in Figure 3 below.** The Operating Room pharmacy has calculated the appropriate max dose of long-acting and short-acting bupivacaine, which can be safely mixed. There are laminated placards in every operating room as protective measures to prevent dosage miscalculations, and most nurses know the mixture. The Acute Pain Service attendings know as well since they have performed thousands of these injections in the past few years at our institution.
  - **Liposomal bupivacaine has become our standard of care for open surgery.** We use this in the majority of our open abdominal cancer surgery patients, while an ever-decreasing minority still get epidurals. There is extensive experience using liposomal bupivacaine for regional blocks. This RCT does not focus on the use of the block per se (since it is routine or usual care), but rather the timing of it.

Comparison Strategy:

The comparison arm patients will have usual care with just the single QL using ultrasound guidance placed in the OR. When the liposomal bupivicaine wears off, **there will be no second QL block**. The **usual measures of non-opioid bundle** [including acetaminophen, NSAIDs, muscle relaxers] and conversion from IV pain meds to oral pains will be done to reduce total opioid exposure and use.

Decision on Discharge Opioid Prescription

To avoid bias in one arm or the other, all discharge prescriptions will be standardized. Both arms will get standard non-narcotic bundles of acetaminophen 650mg q6hrs, celecoxib 100mg q12hrs, and methocarbamol 250-500mg q8hrs. Slight dose variations can be allowed here based on pharmacy availability (e.g. recent national shortage of methocarbamol 500mg pills). Patients who undergo nephrectomy will not receive celecoxib due to risk of renal insufficiency. To standardize the opioids, we will use a multiplier of 5x the last-24hrs OME count. This 24-hr count can be easily found in the electronic health record and will be taken from the time of final discharge prescription writing. If this is POD4, it will be calculated after the 2nd block, if one is administered. We chose 5x because the CDC recommends 7 days max prescription and less than 200mg OME. All patients have

clinic appointments within one week of discharge and have phone numbers to call if their multimodal pain management plan is insufficient. The chance of this is very low considering these patients are on the same plan on discharge as they have been in the last 24hrs in the hospital.

Interim Analyses:

One interim analysis will be performed when half of the patients (n=42) have been randomized. The trial will be stopped due to futility if the p-value is >0.732 for the primary endpoint.

- **Anticipated Results:**
  - **Participant Flow Diagram: see Figure 1**
  - **Recruitment**
    All patients meeting eligibility criteria above will be recruited from clinic either during the consultation meeting or during any of the follow-up or preoperative meetings. Information regarding the trial may be sent to patients outside of clinic in order to provide time for answering questions before consent. Prior to these meetings, the patients may be sent a letter through MyChart (Appendix E) requesting permission to seek financial clearance in advance to avoid delays should the patient agree to participate in the study. An informational flyer may also be distributed to potential participants (Appendix F).
  - **Generalizability**
    The chosen regional block is a well-documented procedure in the anesthesia literature. The drug used in the block is universally available for other types of block. The non-narcotic bundle consists of generic drugs with minimal costs and are all well within usual care guidelines. The postoperative care pathways are published and reproducible.

Potential Harms/Adverse Events:

- Because regional blocks with liposomal bupivacaine are usual care and have been performed in thousands of MD Anderson Cancer Center patients, there are almost no clinically relevant adverse events that we anticipate besides the "trouble" of collecting the equipment, gathering the Acute Pain Service, and asking the patient to lie flat in bed for 30min on POD4. This is an extra procedure at bedside on POD4.
- There could be pain and anticipatory anxiety for the bedside procedure.
- Hematoma from needle sticks are possible but almost never seen.
- There is the cost of the procedure which is a "rescue block," which we have used before for failed 1st time blocks. **We have typically not used it as a supplemental block to facilitate weaning patients down to zero opioids, because being completely opioid-free has never been a priority.** The reality is that it is "easier" to just order oral opioids on POD4 and beyond rather than going to the "trouble" of doing a bedside procedure on POD4 to potentially reduce opioid use.

- Unblinded providers may affect discharge OME in one arm over another. We will minimize this using 2 methods to protect patients:
  - Standardized IV-PCA settings will be used starting in the recovery room immediately out of the operating room. Unless there is an allergy, we will use our standard medication, dilaudid 0.1mg IV q 10min as needed, with no basal dose. This can be adjusted based on clinical needs. This will be weaned off when the patient starts solid food diet.
  - Patients' daily pain scores (checked by nurses q4hr) will be used to ensure that adequate pain control is prescribed before discharge. There is no "threshold" score that will be used since one patient's "4" is different than another patient's "4," but the trend will be useful to ensure patients are not being ignored. More importantly, all patients will be judged by their activities of daily living on the last 24hrs to ensure pain control is adequate.
  - **The number of opioid pills will be formulaic to avoid bias** by clinicians or patients in one arm or the other **- we will take the last 24hrs of inpatient OME used and multiply by a factor of 5x to make this number standardized between the 2 arms. This will be calculated at the time of discharge prescription writing and after the 2nd block for patients in the intervention arm if discharge date is POD4.**
  - Both arms get the same non-opioid pain management bundle for inpatient and discharge.

- **Prospective AE Records**
  - Inpatient advanced practice providers (nurse practitioner or physician assistant) will document complications daily, prospectively.
  - **Hospitalization, 30-day, and 90-day complications will be prospectively recorded** into a Sarcoma Surgery Quality Improvement Database.

- **Safety Review**
  - The study will be monitored by the MDACC Data and Safety Monitoring Board (DSMB).
    - At the time of interim futility analysis (N=42, randomized), we will also assess the length of stay for each arm. The trial will be terminated if the median LOS in the intervention arm is >/=25% longer than the median LOS in the comparison arm. We assume that the extended LOS was caused by higher complication rate, thus leading to deviation from the usual pathway and anticipated LOS.

Figure 1. Study schema

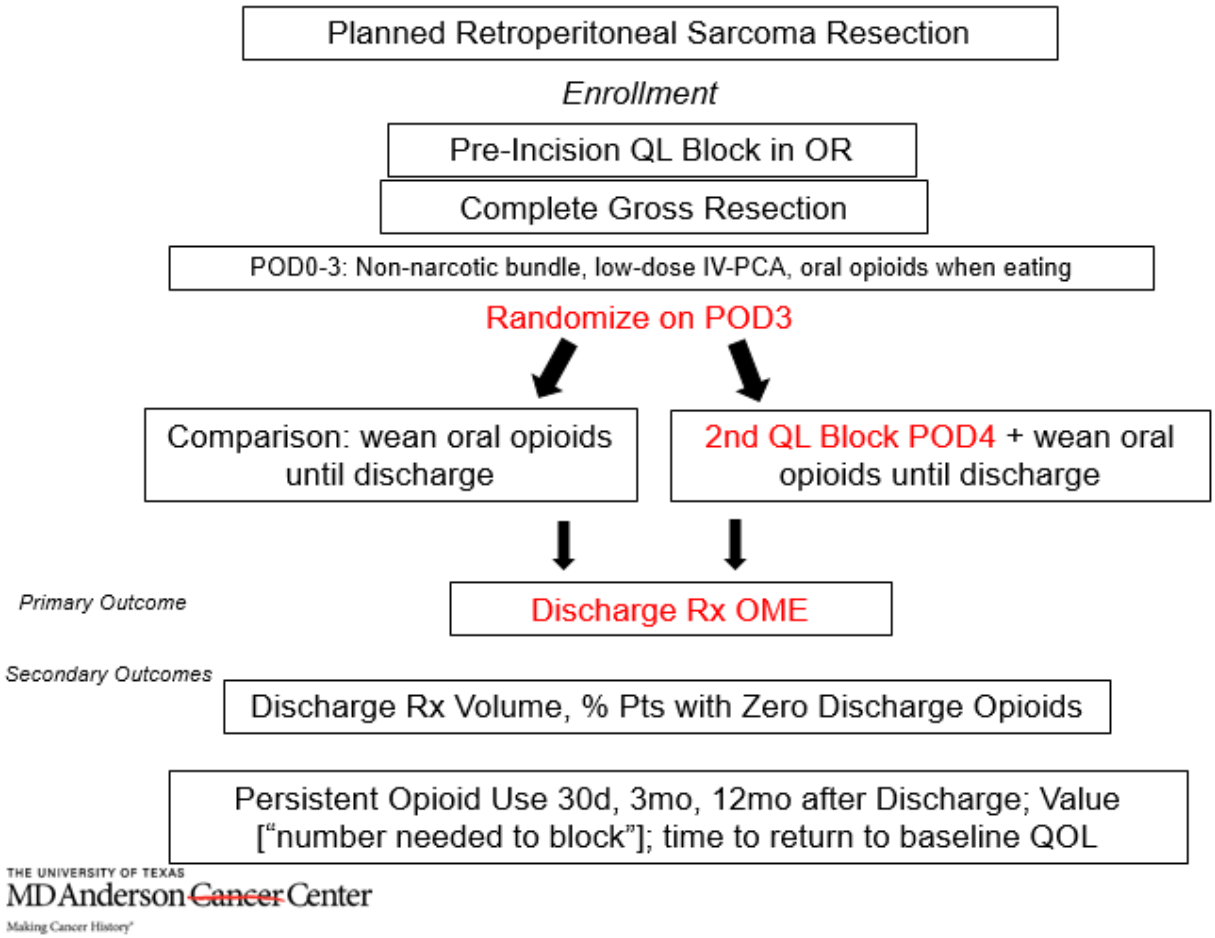


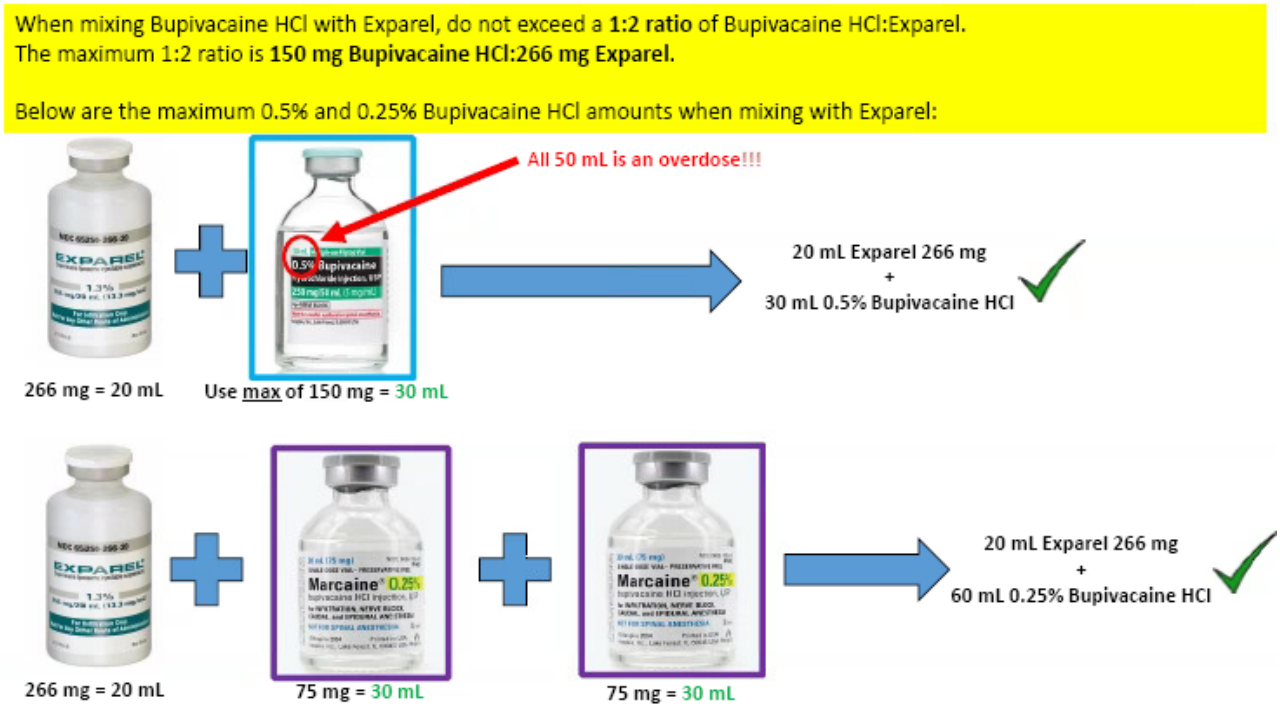
Figure 2. Study intervention timeline

	Pre-Op Days	Inpatient Postop Day										Outpatient Month [a, b]		
Time	-30 to 0	PACU "0"	1	2	3	4	5	6	7	8	DC	1	3	12
Oral Morphine Equivalents	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MDASI-GI	X					X					X [c]	X	X	X
Pain Score	X	X	X	X	X	X	X	X	X	X	X			
Hospital Cost											X			
Adjuvant Therapy [if needed]												X	X	X
Informed Consent	X													

Day of surgery is called postoperative day "0" and the 1st day after surgery is called postop day 1. This is different than medical terminology in which the "count" of hospital days starts at "1," not "0" as with surgery.

a. +/- 1 week for outpatient follow up.
b. During outpatient timepoints, survey may be administered via phone, email, or in clinic.
c. MDADI-GI on DC can be collected from DC to the first post-OP visit via phone, email, or in clinic.

Figure 3. Liposomal bupivacaine mixture recommendations from OR Pharmacy [approved 2 years ago]



5.0 Statistics and Justification of Sample Size

For the primary analysis, we will perform two-sample t-test to compare the mean doses of **discharge prescription OME** between the two groups. In addition, multiple linear regression analysis will be carried out to assess the difference between the two arms after adjusting for the stratification factors and other patient characteristics at baseline. Similar analyses will be performed for other continuous secondary outcomes such as total length of stay, 30-day total OME, initial discharge pain prescription dosage/size, number of postoperative days until zero opioid use, etc. Logistic regression analyses will be performed for binary secondary outcomes, such as discharge prescription OME = zero, discharge Rx dosage/size total OME <200mg (yes vs. no), opioids use at POD 30 (Y/N), etc. For repeated measures, linear mixed model will be used for continuous outcomes such as daily inpatient pain scores and GEE model will be fit for binary outcomes such as opioid use at various time points. Other statistical analyses may be performed as appropriate.

Based on historical data as of August 2019, the **mean discharge OME** for the comparison arm was about **200 mg (standard deviation 200mg)** and we anticipate that with a **second, repeat QL block,** the discharge OME for the intervention arm will reduce to **75 mg.**

Under this assumption and assuming a common SD of 200, the study will require 84 patients (42 in each arm) in order to have 81% power to detect the difference in discharge OME with a two-sided 5% significance level. East 6 was used for the sample size calculation. Assuming a liberal 20% dropout rate, a total of 106 patients will be enrolled from our single institution. Based on our historical operation volume of 120 patients per year, we anticipate the ability to complete enrollment within 1 year of opening the protocol. One interim analysis will be performed when half of the patients (N=42) have been randomized. The trial will be stopped due to futility if the p-value is >0.732.

- Power and significance: 81% power (β=0.19) and α=0.05 (two-sided)
- Baseline estimate of mean comparison/control arm: 200mg OME
- Estimate of mean experimental arm:75mg OME
- Sample size per arm: 42 pts
- Assume 20% dropout: 53 per arm
    - [1 year to complete enrollment]

6.0 Procedure to Obtain Informed Consent

The investigator must obtain documentation of consent from each potential subject prior to participating in a clinical trial.

The protocol and informed consent documentation for this study must conform to institutional regulations and local and national laws and regulations. As soon as a potential subject is considered for this study and prior to any other study procedures, each prospective subject will be given a full explanation of the purpose of the study, the procedures to be carried out and the potential hazards. Once this essential information is provided to the subject and once the Investigator believes that the subject understands the implications of participating in the study, the subjects will be asked to provide written informed consent and authorization to access medical records needed for study documentation. Subjects will be required to read, sign, and date a properly executed written Informed Consent Form prior to enrollment and will be assured that they may withdraw from the study at any time without jeopardizing their medical care. They will be given a copy of their Informed Consent Form.

7.0 Data Confidentiality

Data will only be available to the PI and people directly involved with the collection and analysis of data related to this project. IRB approval will be obtained for any exchange of data outside of MD Anderson.

Collection of Identifiers:
Identifiers (name, dates, phone number, email address and MRN) will be collected. Applicable identifiers will be replaced by study numbers in the analytic file. The key linking these numbers will be retained in a locked file by the investigator designated personnel. Dates will be retained as a limited data set. Data will not be shared with any party outside of MD Anderson and will not be retained or disseminated for other research without prior IRB approval.

Training of Personnel:
All MD Anderson personnel will be fully trained to maintain the patient health information confidentially. Training will be documented as required by institutional policy.

Data Storage:
The PI and research staff will attempt to minimize risk through only storing information containing subject identifiers in locked file storage, on password-protected computers, and in password-protected databases, on encrypted servers behind an institutional firewall and according to current institutional and federal data security requirements. In addition, access to patient identifiers will be limited to the minimum number of necessary research personnel, and only to those research personnel directly involved with obtaining patient information and assigning random study identifiers. Keys containing information linking study subjects to personal identifiers will be maintained in locked storage for paper records or behind institutionally approved firewall and electronic security measures for electronic keys, and available ONLY to the PI and research personnel directly involved in creating random study identifiers. Information containing subject personal identifiers will not be removed from MD Anderson Cancer Center and will not be shared in publications or reports concerning this research study.

Data Sharing:
Study data will not be shared with any individuals or entities that are not involved in the study without IRB approval. No identifying information will be shared with outside collaborating sites or outside collaborating research staff without prior IRB approval and a data use or material transfer agreement has been implemented. If approval is obtained, sharing of data would be done after approval of the PI and only by secure mechanisms, as approved by MD Anderson Information Security.

Final Disposition of Study Records:
These data will be used for this research study. Data that is in hard-copy form will be retained on site until the study is terminated, and may be stored indefinitely, per institutional standards, in long-term off-site storage with an MD Anderson approved, secured contract site. Electronic data will be retained indefinitely on MD Anderson servers behind the institutional firewall. Data will not be shared with any party outside of MD Anderson without IRB approval and will not be retained or disseminated for other research without prior IRB approval. Study data and paper records will not be destroyed but will be retained permanently.

8.0 References

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