Wound infiltration with liposomal bupivacaine vs. standard wound infiltration with bupivacaine in patient's undergoing open gynecologic surgery on an Enhanced Recovery Pathway: a single-blinded, randomized, controlled study

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Study Site: MD Anderson Cancer Center

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Background:

Enhanced Recovery Pathways (ERP) has been shown to be safe for patients undergoing major gynecologic oncology operations. A successful ERP program has been associated with reduced length of hospital stay, increased patient satisfaction, and lower costs [1]. The multimodal ERP aims at a more evidence-based perioperative care pathway while challenging routine clinical practices [2]. One of the key elements of the Enhanced Recovery Pathways after Gynecologic Surgery Program at MD Anderson Cancer Center is preemptive analgesia and perioperative multi-modal opioid sparing strategies. This element is imperative as it reduces opioid related adverse events (ORADE) [3].

To achieve these goals, ERP programs focus primarily on reducing perioperative stress, achieving satisfactory pain control, resumption of normal gastrointestinal function, and early mobilization. Based on all of these key elements, we have implemented the ERP program shown in Tables 1-3 in the Department of Gynecologic Oncology & Reproductive Medicine at MD Anderson Cancer Center.

On the basis of current data, it appears that implementation of our ERP program may result in an overall improvement in postoperative outcomes. However, more studies are needed that include a consistent strategy with an evaluation of the key elements of care implemented in the perioperative period, and evaluating the outcomes based on the adherence to the key elements.

Recently, Nick et al. [4] conducted a study to evaluate the implementation of a multidisciplinary Enhanced Recovery Pathways (ERP) for all patients undergoing exploratory laparotomy for gynecologic indications in the Department of Gynecologic Oncology and Reproductive Medicine at MD Anderson Cancer Center. Consecutive patients managed under an ERP undergoing exploratory laparotomy between 11/3/2014 and 1/15/2015 were compared to historical controls (May-November 2014). Interventions included, but were not limited to, allowing oral intake of fluids up to 2 hours before induction of anesthesia; pre-, intra-, and post-operative euvolemia as well as opioid-sparing analgesia and anesthesia; wound infiltration with bupivacaine, early

ambulation and regular diet on the day of surgery. A total of 58 women in the enhanced recovery group were compared with women in the control group. Thus far, enhanced recovery has resulted in a 1-day reduction in hospital stay (median LOS pre-implementation: 4 days [2-27] vs. post-implementation: 3 days [1-11], p=0.001) with stable readmission rates (pre-ERP: 11.7% vs. post-ERP: 12%, p=1.00). No differences were observed in rates of pre-operative and post-operative complications (GI: pre-ERP 24% vs. post-ERP 15%, p=0.26; GU: pre-ERP 6% vs. post-ERP 13%, p=0.22; Neuro: pre-ERP 0.01% vs. post-ERP 0.02%, p=1.0; Hematologic: pre-ERP 6% vs. post-ERP 14%, p=0.13). Among those with advanced recurrent ovarian cancer (pre-ERP 57%; post-ERP 45%), median length of return to intended oncologic therapy (RIOT) was 30 days (range 15-52) pre-ERP compared to 22 days (range 20-41) post-ERP (p=0.08). The investigators concluded that implementation of an ERP at a tertiary cancer center is feasible with noted benefits to patient outcomes.

Moving forward, successful health care organizations will be patient-centered, multidisciplinary, process oriented and outcome-based. To that end, patient reported outcome measures (PROs) will influence the way we deliver medical care in the future of health care reform. PROs have long represented the gold standard for quality of life and patient satisfaction. Recently, they have also become an area of increasing focus in comparative effectiveness research, health care quality assessments, and as endpoints in clinical trials. [5-8] The Center for Medical Technology Policy (CMTP) recommends that prospective clinical comparative effectiveness research (CER) capture the subjective patient experience. [5]

We propose implementing the use of liposomal bupivacaine (Exparel) in our ERP for longer duration of analgesia and further reduction in opioid administration. We will be looking at the percentage of patients that are opioid free at 48 hours following surgery in the proposed study arms as a primary outcome.

Currently, there is a ***gap in knowledge*** in that there is no concrete evidence to support whether the infusion of liposomal bupivacaine directly into the wound after laparotomy

provides the most effective analgesia when compared to standard bupivacaine. The implementation of liposomal bupivacaine with its prolonged analgesic effects in an enhanced recovery pathway has the potential to improve pain management and decrease opioid administration. Given such gap in knowledge and the fact that there is considerable cost difference between liposomal bupivacaine and standard bupivacaine, our goal is to investigate whether in fact there is an added benefit to liposomal bupivacaine in our ERP patients undergoing gynecologic surgery. We aim to answer this very important question through our proposed study.

Official Title:

Wound infiltration with liposomal bupivacaine vs. standard wound infiltration with bupivacaine in patient's undergoing open gynecologic surgery on an Enhanced Recovery Pathway: a single-blinded, randomized, controlled study

Our hypothesis is that we will see an absolute increase of 20% in the proportion of patients opioid-free at 48 hours after end of surgery in the liposomal bupivacaine arm compared with the bupivacaine arm, regardless of the proportion of patients opioid-free in the bupivacaine arm.

Objective:

To compare the analgesic efficacy and functional recovery of local wound infiltration using liposomal bupivacaine compared with wound infiltration with bupivacaine in patients undergoing open gynecological surgery (laparotomy) on an enhanced recovery pathway.

Study Arms and Assigned Interventions:

This will be a randomized study with patients randomized equally to the following 2 arms:

Arm 1: Local wound **infiltration with 0.25% bupivacaine** immediately prior to wound closure (Control)

Arm 2: Local wound **infiltration with liposomal bupivacaine and 0.25% bupivacaine** admixed immediately prior to wound closure

Study Arms and Procedures:

At the completion of surgery and prior to incision closure, a total of 60 mL of 0.25% bupivacaine without epinephrine (Arm 1) or a volume specific to incision size of liposomal bupivacaine [0.25% bupivacaine and liposomal bupivacaine] (Arm 2) will be infiltrated into the wound as described below in the **Detailed Dosing Description (Page 9)**.

Study Type:

This will be a randomized, controlled single blind (patient) interventional study.

The benefit of a randomized trial in this setting lies in the fact that our group has achieved excellent results in our Enhanced Surgical Recovery Program in gynecologic oncology using standard bupivacaine. However, we aim to investigate whether liposomal bupivacaine will provide additional benefit to our patients as it pertains to pain management and impact on opioid consumption.

Study Design:

Endpoint Classification: Analgesic efficacy and functional recovery
Intervention Model: Double intervention
Masking: Single blinded (patient)
Primary Purpose: Treatment

Primary Outcome Measure:

1) Proportion of patients opioid-free at 48 hours after surgery.

Secondary Outcome Measures:

1) Number of opioid-free days (POD0, POD1, POD2, POD3)

2) Morphine Equivalent Daily Dose (MEDD): This will be calculated based on the total daily consumption of opioids. We will record the MEDD on POD1, POD2, and POD3 and MEDD will be calculated as the area under the dose-time curve (AUC).
3) Patient Reported Outcomes (PROs) with MD Anderson Symptom Inventory (MDASI) at baseline, daily while inpatient, day 3 (+/- 1 day) and 7 (+/- 1 day) after discharge and then weekly (+/- 3 days) to complete 8 weeks (+/- 3 days) from the date of surgery. Failure to complete any questionnaires will not be considered a deviation requiring reporting. While the patient is admitted, research personnel may assist the patient to complete the MDASI with verbal responses from the patient (Appendix A).
4) Assessment of pain will be performed daily after surgery every 4 +/- 2 hours while the patient is awake, up to 96 hours while in-hospital using the 0-10 Numeric Pain Rating Scale **(Appendix B).** If patient is discharged before 96 hours, pain will be assessed once a day via Interactive Voice Response (IVR) system, phone call or electronic survey until completion of 96 hours post-surgery [9]. If the participant is contacted by phone or if the assessment is administered in person, the information will be directly entered into REDCap. In the circumstance that the system is down, the patient refuses to respond electronically or there is no access to an electronic device, the use of paper forms will be permitted. Pain will be measured as the area under the pain-time curve (AUC).
5) Pain goals stated by the patient will be collected daily while in-hospital as routinely performed by nursing staff.
6) Time to first post-operative opioid administration after end of anesthesia.
7) Perioperative opioid administration (opioid type and dose)
8) Days to “discharge ready”. This will be the number of days from surgery to when the patient is considered ready for discharge to home. **(Appendix C).**
9) Postoperative complications: We will only collect postoperative complications that are felt to be related to either study drug at 30-days post-surgery and may include the following:

a) Central Nervous System Complication
    - Anxiety
    - Delirium (Acute altered and fluctuating mental status with features of inattention and an altered level of consciousness.)
    - CVA
    - Numbness and/ or weakness (extremities)
    - Other
b) Respiratory Complication
    - Dyspnea
    - Hypoxia
    - Pneumonia
    - Pulmonary embolism
    - Reintubation
    - Pulmonary edema
    - Pneumothorax
    - Other
c) Cardiovascular Complication
    - Arrhythmia
    - CHF
    - Myocardial Infarction
    - Arrest/CPR
    - Hypertension
    - Hypotension
    - Tachycardia
    - Syncope
    - Other
d) Gastrointestinal Complication
    - Ileus

- Diarrhea
- Constipation
- Obstruction
- Anastomotic Leak
- Nausea and vomiting
- Hematemesis
- Coffee ground emesis
- Small bowel perforation
- Large bowel perforation
- Enterocutaneous fistula
- Recto-vaginal fistula
- Other

e) Liver and Pancreas Complication

- Biliary obstruction
- Pancreatic leak
- Pancreatitis
- Other

f) Renal/GU Complication

- Acute renal risk: 1.5 fold increase in the serum creatinine or GFR decrease by 25% or urine output <0.5 mL/kg per hour for 6 hours.
- Acute renal injury: Twofold increase in serum creatinine, or GFR decrease by 50% or urine output <0.5 mL/kg per hour for 12 hours.
- Acute renal failure: Threefold increase in serum creatinine, or GFR decrease by 75%, or urine output of <0.3 mL/kg per hour for 24 hours or anuria for 12 hours.
- Urinary tract infection
- Urinary retention
- Urinary leak

- Urinoma
- Other

g) Endocrine Complication
    - Hyperglycemia
    - Other

h) Metabolic Complication
    - Electrolyte Imbalance
    - TPN
    - Other

i) Wound Complication
    - Surgical site infection
    - Dehiscence (Note: includes fascia separation)
    - Other site infection
    - Pelvic Abscess
    - Skin separation
    - Wound seroma
    - Other

j) Sepsis Complication
    - Sepsis
    - Septic shock

k) Hematologic Complication
    - Deep vein thrombosis
    - Anemia/transfusion
    - Thrombocytopenia
    - Neutropenia
    - Other

l) Other Complication

Data on complications will be collected per occurrence while in-patient, during patient visits, or at 30 day (+/- 3 days) follow up through telephone communication, by review of electronic medical records, and from pharmacy reports.

10) Complication grade will be determined using the Clavien-Dindo Surgical Complication Grading System **(Appendix D).**

Detailed Dosing Description:

This is a prospective, randomized, single-blinded study evaluating the analgesic efficacy of liposomal bupivacaine (EXPAREL) in conjunction with 0.25% bupivacaine used for local wound infiltration versus local wound infiltration with 0.25% bupivacaine undergoing open gynecological procedures (laparotomy) on an Enhanced Recovery Pathway. In Arm 1, patients will receive 150 mg of bupivacaine alone as this is the highest dose that can be given to patients that is below the level of potential toxicity. Hence, it allows the surgeons to have more volume of infiltration to cover more receptors along the surgical incision. In Arm 2, patients will receive 266 mg of liposomal bupivacaine + 150 mg of bupivacaine. The liposomal bupivacaine will release more slowly over 48 hours and the bupivacaine will provide immediate coverage. We are always concerned about patient safety so the dose of plain bupivacaine in any arm cannot be higher than 150 mg and we have adjusted for this in Arm 2 in order to ensure patient safety due to potential risk of neurologic and cardiac toxicity. In addition to this we are following the new updated prescribing information, which states bupivacaine HCl administered together with EXPAREL may impact the pharmacokinetic and/or physicochemical properties of EXPAREL, and this effect is concentration dependent. Therefore, bupivacaine HCl and EXPAREL may be administered simultaneously in the same syringe, and bupivacaine HCl may be injected immediately before EXPAREL as long as the ratio of the milligram dose of bupivacaine HCl solution to EXPAREL does not exceed 1:2. In our study we are administering them simultaneously. We are maintaining a 1:2 ratio as follows: The bupivacaine contained in EXPAREL® is free-base bupivacaine. This differs from other frequently used amide-type, bupivacaine-

based local anesthetics which contain the salt form of bupivacaine, bupivacaine HCl. Therefore, 266 mg of bupivacaine free base is chemically equivalent to 300 mg of bupivacaine HCl. After discussions with the FDA, it was recommended that the dosing of EXPAREL be expressed in terms of free-base bupivacaine (266 mg) rather than in bupivacaine HCl (300 mg) equivalents. Hence, for our study the bupivacaine HCl contents of Exparel are 300 mg, simultaneously injected with 150 mg of bupivacaine HCl we are at the 1:2 ratio aforementioned.

Arm 2 Summary Table:

Summary 3.5 inch needle	Large Incision	Medium Incision	Small Incision
Incision length (cm)	>31	25-30	<24
Total Volume (mL)	275	220	165
Subdermal (cc)	55	40	35
Above Fascia (cc)	220	180	130
Exparel Volume (mL)	20	20	20
Bupivacaine volume (mL) 0.25%	60	60	60
Additional saline * (mL)	195 +/- 10	140 +/- 10	85 +/- 10

*If the volume of normal saline changes within the allowed parameters, the total volume will be equally modified and reflected in a greater/lower volume injected either subdermal or above fascia

Arm 1:

On the bupivacaine arm 0.25% bupivacaine will be injected in an even volume of 60 mL (150 mg total dose) as follows:

- 20 mL fascial injection on each side of the wound in a fan-like fashion,
- 10 mL skin injection on each side of the wound.

Arm 2:

For the arm with local infiltration with 0.25% bupivacaine and liposomal bupivacaine administered simultaneously, the 266 mg (20 mL, 1.3% of undiluted drug) will be diluted in a volume of 60 mL 0.25% bupivacaine (150 mg) in addition to normal saline. The addition of saline will be dependent on the size of the incision as outlined in the summary table above (Page 11). This admixture will be injected as follows:

- Above fascial injection on each side of the wound in a fan-like fashion
- Subdermal injection on each side of the wound in a fan-like fashion.

The total amount to be injected at each injection site is determined by the incision length and the detailed dosing is provided in the summary table (Page 11).

Eligibility:

Inclusion Criteria:

- Undergoing an exploratory laparotomy for suspected gynecologic cancer, which includes metastatic disease from neoplasia originating in other organs
- Planned participation in the Gynecologic Enhanced Recovery Pathway
- Female 18 years of age or older.
- Patient must be able to read and speak English
- Consents to being part of a randomized, single-blinded study
- Patient has physical and mental capabilities to take part in study
- Bilirubin less than or equal to 1.5 × ULN; SGOT and SGPT ≤2.5 x ULN
- If the patient is of childbearing potential, the patient must have a negative blood or urine pregnancy test within 14 days of surgical treatment on study.

Exclusion Criteria:

- Sensitivity to amide-type local anesthetics
- Patients on long-acting opioid medications, or scheduled (four or more times a day for seven or more days) short-acting opioid medications within the last 30 days
- Emergency surgery of any type that does not allow for proper time for protocol review by the patient
- Surgery that involves known/anticipated resection of anterior abdominal wall with plastic surgery reconstruction
- Patients undergoing pelvic exenteration
- Patients undergoing known/anticipated anterior abdominal wall hernia repairs
- Patients weighing <50 kg

Pharmacokinetics of Liposomal Bupivacaine:

Absorption

Following its release from the liposomal bupivacaine particles, the rate of systemic absorption of bupivacaine is dependent upon the total dose of drug administered, the route of administration, and the vascularity of the administration site.

Distribution

After bupivacaine has been released from liposomal bupivacaine and is absorbed systemically, bupivacaine distribution is expected to be the same as for any bupivacaine HCl solution formulation. To some extent, local anesthetics are distributed to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain.

The rate and degree of diffusion are governed by:

- The degree of plasma protein binding
- The degree of ionization

- The degree of lipid solubility

Metabolism

Amide-type local anesthetics such as bupivacaine HCl are metabolized primarily in the liver via conjugation with glucuronic acid. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics. Pipecolylxylidine (PPX) is the (largely inactive) major metabolite of bupivacaine HCl: approximately 5% of bupivacaine HCl is converted to PPX.

Excretion

After bupivacaine has been released from liposomal bupivacaine and is absorbed systemically, bupivacaine excretion is expected to be the same as for other bupivacaine formulations.

Various pharmacokinetic parameters can be significantly altered by:

- The presence of hepatic or renal disease
- Factors affecting urinary pH
- Renal blood flow

The kidney is the main excretory organ for bupivacaine and its metabolite; only 6% of bupivacaine is excreted unchanged in the urine.

Hepatic Impairment

The effects of decreased hepatic function on bupivacaine pharmacokinetics following administration of liposomal bupivacaine were studied in patients with moderate hepatic impairment. Consistent with the hepatic impairment of bupivacaine, mean plasma concentrations were higher in patients with moderate hepatic impairment than in the healthy control volunteers.

Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, these drugs should be used cautiously in patients with hepatic disease. Patients

with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations.

Renal Impairment

Bupivacaine is primarily excreted by the kidneys, and the risk of toxic reactions to liposomal bupivacaine may be greater in patients with impaired renal function.

Storage

Liposomal bupivacaine vials should be stored refrigerated between 2°C to 8°C (36°F to 46°F).

Liposomal bupivacaine may be held at a controlled room temperature of 20°C to 25°C (68°F to 77°F) for up to 30 days in sealed, intact (unopened) vials. Vials should not be re-refrigerated. As a convenience to the pharmacist, each vial label includes space to record the date when the vial has been removed from refrigeration.

Liposomal bupivacaine should not be frozen or exposed to high temperatures (greater than 40°C or 104°F) for an extended period. Liposomal bupivacaine should not be administered if it is suspected of having been frozen or exposed to high temperatures.

Risks

Risks associated with bupivacaine may include: bleeding/oozing from the puncture site, bruising at wound site, death, edema, hematoma, and/or infection.

Benefits

The benefits of liposomal bupivacaine when compared to standard bupivacaine, is that it may provide superior results in reducing the incidence of pain, severity of pain, use of analgesics, and a reduced hospital stay.

Study Procedures

Patient Selection and Screening

Patients will be screened for study entry in the Gynecologic Oncology Center by a Research Data Coordinator (RDC) or Research Nurse. Patients will be screened according to the aforementioned Inclusion/Exclusion Criteria. Patients will be provided with study information and will be allowed ample time to read such information with sufficient time for the RDC, Research Nurse, or Principal Investigator to answer all questions pertaining to the study protocol or all associated inquiries as deemed necessary by patient. Once consent is provided by the patient, the RDC or Research Nurse will be allowed to enroll the patient on study.

Written Informed Consent

Written Informed Consent/Assent must be obtained for all patients who are potential study candidates before any study-specific tests or procedures are performed.

Patients who meet general entry criteria will be asked to sign the study-specific, Institutional Review Board (IRB) approved Informed Consent form before any study-specific tests or procedures are performed. Study personnel should explain that even if a patient agrees to participate in the study and signs an informed consent form, the surgeon may elect to withdraw that patient from the study for patient safety considerations.

Enrollment

Once a subject has been consented, she will be registered in CORE and considered enrolled into the study.

Pre-Operative

Prior to the patient's scheduled procedure, record the patient's demographic information (race, ethnicity, and date of birth), baseline information (height, weight, systolic/diastolic blood pressure, body mass index), incidence and severity of pain using the pain assessment tool (Appendix B), current pain medication use, comorbidities, previous surgeries, and administration of the MDASI questionnaire.

Within 30 days prior to the planned procedure date, obtain serum blood tests per

standard of care. These will typically include:

- SGOT, SGPT, and bilirubin
- Creatinine
- Platelet and white blood cells count
- Hemoglobin and hematocrit
- Serum or Urine Pregnancy test to be collected within 14 days of planned procedure date for women of child-bearing potential only

Preoperative Randomization

Once it has been determined that the patient meets all eligibility criteria, the patient is eligible for randomization. There will be a 1:1 randomization ratio as follows: local wound **infiltration with bupivacaine** immediately prior to wound closure (Arm 1), local wound **infiltration with liposomal bupivacaine and 0.25% bupivacaine** immediately prior to wound closure (Arm 2).

All randomization will be carried out using REDCap stratified by surgeon. We expect that approximately 10 surgeons will participate.

Methods and Procedure

This study will be conducted at one center. Following informed consent, patients will be prepared for surgery per standard institutional policy and practice.

Standard operative procedures will be followed regardless of randomization assignment or participation in the study. Data collection methods are described below.

Postoperative data will be collected regarding incidence and severity of pain, medication use, and length of recovery and hospital stay.

Discharge Procedure

All patients will be evaluated on a daily basis by nursing staff to determine readiness for discharge.

All patients will be discharged with the same analgesic opioid regimen (**oxycodone 1-2**

tabs (5 mg) PO Q4 hours PRN: pain) unless medically contraindicated, in which case an alternative breakthrough medication will be prescribed.

If patient is discharged before 96 hours post op, she will be contacted via IVR system or an electronic survey (via REDCap) will be sent by email or text message daily up to 96 hours post op to record incidence and severity of pain. If the patient does not complete the questionnaire through the IVR system or REDCap, the study staff will contact the patient by phone and enter the information directly into REDCap. In the circumstance that the system is down, the patient refuses to respond electronically or there is no access to an electronic device, the use of paper forms will be permitted. Patients will be asked the following questions regarding their pain and opioid consumption:

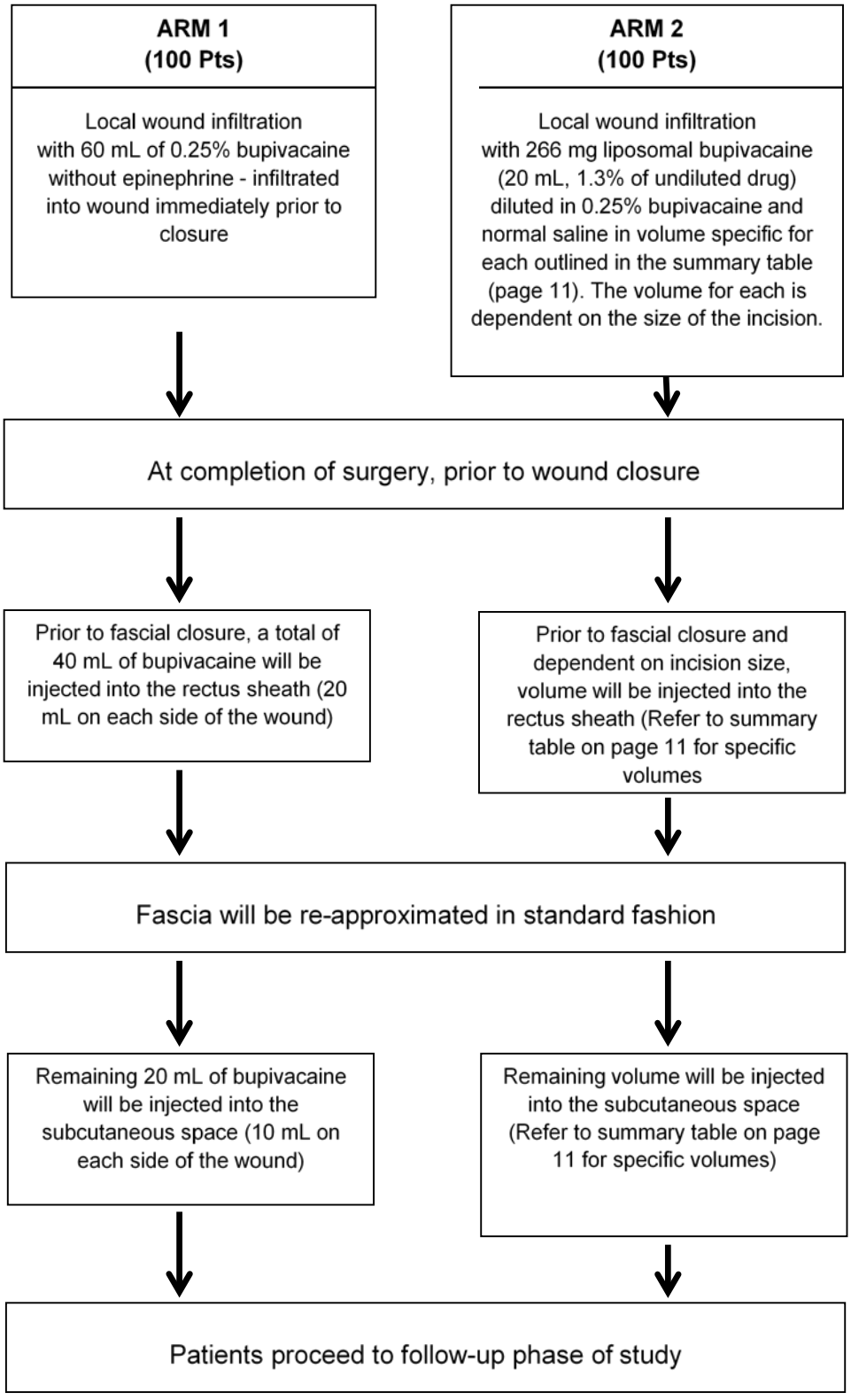
- Did you require any of your breakthrough pain medication yesterday? YES or NO
- If YES how many tablets total did you take?
- What was your highest level of pain yesterday on a scale from 0-10 (0 being no pain and 10 being the worst pain)?

Patient Study Schedule

				Follow-Up Phase			
			In-patient	After Discharge			
	Baseline[a]	Surgery	Daily	Week 1 Day 3	Week 1 Day 7	Weekly (weeks 2-8)	30-day(+/-3 days)[h]
Informed Consent	X						
CBC and Chemistry Panel[b]	X						
Pregnancy Test (Serum or Urine)[c]	X						
Randomization	X						
Administration of Analgesic Agent[d]		X					
MDASI Questionnaire[e]	X		X	X	X	X	
Opioid use[f]	X	X	X				
Pain Assessment[g]	X	X	X				
Adverse Events		X	X				X
Complications		X	X				X

a. Baseline assessments to be collected within 30 days unless otherwise specified
b. Serum blood tests to be performed per standard of care and may include: SGOT, SGPT, alkaline phosphatase, bilirubin, creatinine, platelets, white blood cell count, hemoglobin and hematocrit
c. Serum or Urine pregnancy test to be obtained within 14 days of planned procedure date for women of child-bearing potential only.
d. Analgesic agent and administration to be determined by randomization arm.
e. The MDASI Questionnaire may be administered via paper copy, sent by email or text message via REDCap, by interactive voice response (IVR) or phone calls depending on the patient location and preference. If the patient is contacted by phone or if the questionnaire is administered in person, the information will be directly entered into REDCap. In the circumstance that the system is down, the patient refuses to respond electronically or there is no access to an electronic device, the use of paper forms will be permitted.
f. Opioid use will be assessed daily while in-patient. If patient leaves before 96 hours after surgery, opioid use will be assessed via IVR, phone calls or by email or text message via REDCap upon patient preference. If the patient is contacted by phone or the questionnaire is administered in person, the information will be directly entered into REDCap. In the circumstance that the system is down, the patient refuses to respond electronically or there is no access to an electronic device, the use of paper forms will be permitted.
g. Pain will be assessed every 4 +/- 2 hours while patient is awake, up to 96 hours following surgery while in hospital. If patient is discharged before 96 hours post op, pain will be assessed once a day for up to 96 hours via IVR phone calls or by email or text message via REDCap. If the patient does not complete the pain assessment through the IVR system or REDCap, the study staff will contact the patient by phone and enter the information directly into REDCap. In the circumstance the system is down, the patient refuses to respond electronically or there is no access to an electronic device, the use of paper forms will be permitted.
h. Post-operative complications and adverse events will be assessed within 30 days (+/- 3 days) of surgery by telephone, and electronic chart review. If the patient is contacted by phone or if the questionnaire is administered in person, the information will be directly entered into REDCap. In the circumstance that there is no access to an electronic device, the use of paper forms will be permitted.

Trial Schema



Duration of Patient Participation

Patients enrolled in the study will participate until the Patient Reported Outcomes, using the MD Anderson Symptom Inventory (MDASI), have been collected at the eighth postoperative week. If patients have been consented to BS99-094, then PRO and associated clinical and demographic data from 2015-1119 (PACIRA) will be shared with BS99-094.

Statistical Considerations

A sample size of 100 patients per arm will yield at least 80% power to detect an absolute increase of 20% in the proportion of patients opioid-free at 48 hours after end of surgery in the liposomal bupivacaine plus 0.25% bupivacaine arm (Arm 2) compared with the bupivacaine arm (Arm 1), regardless of the proportion of patients opioid-free in the 0.25% bupivacaine arm, with a 2-sided significance level of 0.05. Therefore, we will enroll a total sample size of 200 patients. Sample size calculations were performed using East 5.4 (Copyright © 2010, Cytel Inc., Cambridge, MA).

Interim Analysis

We will use the methods of Lan and DeMets [10] to **perform an interim analysis for efficacy and futility once half the patients have been enrolled and evaluated at 48 hours after the end of surgery**. The interim analysis for futility will employ an O'Brien-Fleming [11] stopping boundary with a nominal significance level of 0.7221, while the interim analysis of efficacy will employ an O'Brien-Fleming stopping boundary with a nominal significance level of 0.0031. The nominal significance level for the final analysis is 0.049.

Final Analysis

We will use descriptive statistics to summarize the demographic and clinical characteristics of patients overall and by treatment arm. All patients will be followed for 8 weeks and will be considered off-study at 8 weeks from surgery. A final analysis will be performed once the last patient has been followed for 8 weeks.

Primary Outcome

We will compare the treatment arms with respect to the proportion of patients opioid-free at 48 hours using the Cochran-Mantel-Haenszel test stratified by surgeon.

Secondary Outcomes

We will tabulate the number of opioid-free days by treatment arm, and we will use the Cochran-Mantel-Haenszel test stratified by surgeon to compare treatment arms with respect to the number of opioid-free days.

We use descriptive statistics to summarize MEDD by treatment arm, and we will compare treatment arms with respect to mean MEDD using a 2-sample t-test. We will compare treatment arms with respect to median MEDD using the Wilcoxon rank sum test. We will similarly analyze the number of opioid doses per 24 hours.

We will use descriptive statistics and graphical methods to summarize MDASI scores at each assessment time by treatment arm. We will also use repeated measures ANOVA to assess differences between treatment arms over time.

We will calculate the area under the curve (AUC) for pain scores over time, and we will analyze pain scores using the same methods we use to analyze MEDD.

We will use the Kaplan-Meier [12] product limit estimator to estimate the time to first post-operative opioid administration stratified by treatment arm, and we will compare treatment arms with the log-rank test. We will similarly analyze time to “discharge ready”.

We will tabulate intraoperative opioid administration (opioid type and dose) by treatment arm, and we will use Fisher’s exact test to compare treatment arms with respect to the use of intraoperative opioids.

We will tabulate complications by using the Clavien-Dindo Classification of Surgical Complications (**Appendix D**) by treatment arm. We will use Fisher’s exact test to compare treatment arms with respect to incidence of complications by grade.

We will compare patients stated pain goal for the day between arm #1 and arm #2 during the length of inpatient stay.

Inclusion of Women and Minorities

We will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients in this protocol and therefore address the study objectives in a patient population representative of the entire population treated by this institution.

Adverse Events

All adverse events (AE) and serious adverse events (SAE) will be monitored from the time of randomization through the hospital discharge.

This trial will be comparing the efficacy of two FDA-approved drugs for this application (surgery) and uses the FDA-approved doses. The toxicity profile of each are well-described in the package insert.

Therefore, we will only collect AEs that meet the following criteria: grades 3 & 4 and deemed by the investigator as at least possibly related to either of the study drugs. The surgery itself is not a study procedure, however, we will collect complications as outlined under the secondary outcomes section.

All Serious Adverse Events will be reported per institutional guidelines and processes and will include surgical complications should they meet the reporting requirements. An AE is defined as any undesirable clinical occurrence in a patient whether or not it is considered to be drug related. In addition, the definition of AE applies to any event with an onset post study procedure or to any underlying diseases, present at baseline that exacerbate in severity post study procedure. Therefore, an underlying disease that was present at the time of enrollment is not reported as an AE, but any increase in the severity of the underlying disease is to be reported as an AE. All reported AEs must be recorded in the REDCap database. A description of the event, including the start date, resolution date, action taken, and the outcome should be provided, along with the Investigator's assessment of the relationship between the AE, the study treatment and the study procedure. Severity will be defined using CTCAE version 4.0.

A serious adverse event (SAE) is defined as an event that leads to:

- Death due to any cause
- Life-threatening condition
- Results in persistent or significant disability/incapacity
- Requires in-patient hospitalization or prolonged hospitalization
- Necessitates an intervention to prevent a permanent impairment of a body function or permanent damage to a body structure
- Results in congenital abnormality

All SAE's will be reported per standard institution guidelines and requirements.

Drug-Related Adverse Event: an adverse event is considered to be drug-related when, in the judgment of the Investigator, the clinical event has a reasonable time sequence associated with use of the drug and is unlikely to be attributed to concurrent disease or other procedures or medications. It is reasonable to believe that the drug directly caused or contributed to the adverse event.

Procedure-Related Adverse Event: an adverse event is considered to be procedure-related when, in the judgment of the Investigator; it is reasonable to believe that the event is associated with the assigned study procedure and is not specific to the drug used. Other products, surgical techniques, or medications required specifically for the procedure are likely to have contributed to the occurrence of the event.

Study Exit

Once the patient has completed all Patient Reported Outcomes (PROs) (8 weeks postop) or has withdrawn, she should be exited from the study provided she does not have any conditions that require continued follow-up. The date of exit and patient status should be recorded.

Withdrawal of Subjects

While study withdrawal is discouraged, patients may withdraw from the study at any time, with or without reason and without prejudice to further treatment. In all cases of withdrawal, the reason(s) for withdrawal (if given) will be recorded upon study termination.

In addition, the investigator may withdraw the subject due to any of the following situations:

- adverse event
- Any other reason determined by the investigator to be in the best interest of the subject.

Subjects withdrawn due to an adverse event should be followed until the event has been resolved or is stable, if at all possible.

Data Confidentiality Plan

Study data will be collected and managed using REDCap [13]
(Research Electronic Data Capture) electronic data capture tools hosted at MD Anderson. REDCap (www.project-redcap.org) is a secure, web-based application with controlled access designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless downloads to common statistical packages; and 4) procedures for importing data from external sources. In the case of multi-center studies REDCap uses Data Access Groups (DAGs) to ensure that personnel at each institution are blinded to the data from other institutions. REDCap (https://redcap.mdanderson.org) is hosted on a secure server by MD Anderson Cancer Center's Department of Research Information Systems & Technology Services. REDCap has undergone a Governance Risk & Compliance Assessment (05/14/14) by MD Anderson's Information Security Office and found to be compliant with HIPAA, Texas Administrative Codes 202-203, University of Texas Policy

165, federal regulations outlined in 21CFR Part 11, and UTMDACC Institutional Policy #ADM0335. Those having access to the data file include the study PI and research team personnel. Users are authenticated against MDACC's Active Directory system. External collaborators are given access to projects once approved by the project sponsor. The application is accessed through Secure Socket Layer (SSL). All protected health information (PHI) will be removed from the data when it is exported from REDCap for analysis. All dates for a given patient will be shifted by a randomly generated number between 0 and 364, thus preserving the distance between dates. Dates for each patient will be shifted by a different randomly generated number. Following publication study data will be archived in REDCap.

Data Elements to be collected may include the following:

Electronic CRFs will be also be used to collect the following data:

Pre-Operative

- Demographic information
- Pre-operative vitals
- Pre-operative labs
- Pain incidence and severity
- Current pain medication taken by patient
- Pre-operative pain medication

Intraoperative

- Date of surgery
- Blood loss
- Procedure time (initial incision to closure)
- Urine output
- Blood transfusions

- Intraoperative opioid administration

Post-Operative

- Tumor pathology: Malignant or benign.

Recovery room

- Severity and incidence of pain every 4 +/- 2 hours on day of surgery.
- SAEs and AEs will be recorded per occurrence on day of surgery.
- Any postoperative complications

In-patient Floor

- Incidence and severity of pain every 4 +/- 2 hours every day.
- SAEs and AEs will be recorded per occurrence.
- Any complications will be recorded per occurrence.
- Patient Reported Outcomes with MDASI daily while admitted.
- Pain goals daily while admitted.

Discharge

- Post op pain incidence and severity if patient is discharged before 96 hours post-surgery.
- Opioid use if patient is discharged before 96 hours post-surgery.
- Length of stay
- Patient Reported Outcomes with MDASI will be collected on day 3 and day 7 after discharge, and then weekly to complete 8 weeks from the date of surgery. For safety purposes, a notification to the primary surgical team will be given within 24 hours for any patient that reports pain, sadness or shortness of breath in the severe range (>=7)
- Any postoperative complications prior to discharge
- “Ready for discharge” date will be recorded

Follow-up

- Patients will be contacted within 30 days (+/- 3 days) of surgery by telephone, electronic correspondence, or clinic visit, depending on patient access to the hospital. SAEs, AEs, and postoperative complications will be assessed at follow up.

Study Conduct & the Declaration of Helsinki

The Physician Preference Study will be performed in accordance with the relevant parts of Title 21 CFR Parts 812, 50, 54, 56 and ISO 14155-1 / 14155-2.1; the ICH Guidelines for Good Clinical Practices (E6), the Declaration of Helsinki, and any regional and/or national regulations.

Data Safety Monitoring Board (DSMB)

The monitoring of this trial will be provided by MD Anderson Cancer Center DSMB.

Amending the Protocol

An Investigator may consider making changes to the protocol. All changes must be submitted and subsequently approved by the MD Anderson IRB. The investigative site (MD Anderson) must send PACIRA a copy of the IRB approval letter for the protocol amendment.

Emergency Actions

PACIRA accepts the right of the Investigator to deviate from the protocol in an emergency when necessary to safeguard the life or the physical well being of a study patient. The Investigator must give notice of any emergency deviations and justification for the deviation to PACIRA and the IRB as quickly as possible after the episode, in any event no later than 24 hours after the emergency.

Protocol Deviations

For purposes related to this study, a protocol deviation is defined as an event where the Clinical Investigator or site personnel did not conduct the study according to the protocol but does not affect the safety of the patient or the integrity of the data.

Investigators shall be required to obtain prior approval from PACIRA clinical study management before initiating significant deviations from the protocol, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval shall be documented in writing and maintained in clinical study management and Investigator files on the REDCap database. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, (e.g. subject was not available for scheduled follow-up office visit, blood sample lost by laboratory, etc.); however, the event is still considered a deviation and will be reported via the appropriate CRF.

Significant deviations must be reported to PACIRA regardless of whether medically justifiable, pre-approved by PACIRA or taken to protect the subject in an emergency. Subject specific deviations will be reported on the Protocol Deviation case report form. Investigators will also adhere to procedures for reporting study deviations to their IRB in accordance with their specific IRB reporting policies and procedures.

Regulations require that Investigators maintain accurate, complete and current records, including documents showing the dates of and reasons for each deviation from the protocol. Minor Deviations that continue to occur at an investigational site may be re-classified as violations if corrective action is not taken to secure future compliance to the protocol.

Violations will be reported per institution guidelines and requirements.

Coverage of Expenses

The treated subjects will not be reimbursed or compensated for participating in the Study.

Confidentiality

Confidentiality of subjects will be maintained throughout the Study. A unique identification code will be assigned to each subject participating in this Study. Any data that may be published in abstracts, scientific journals, or presented at medical meetings

may reference a unique subject code and will not reveal the subject's identity. The CRO representative will make every reasonable effort to protect the confidentiality of the subjects participating in the Study.

Institutional Review Board/Ethics Committee

A copy of the protocol, proposed Informed Consent form, other written patient information and any proposed advertising material must be submitted to the IRB for written approval. A copy of the written IRB approval of the protocol and Informed Consent form must be received by PACIRA before recruitment of patients into the study.

The Investigator must submit and, where necessary, obtain approval from the IRB for all subsequent significant protocol amendments and significant changes to the Informed Consent form. The Investigator should notify the IRB of deviations from the protocol or SAEs occurring at the site and other SAE reports received from PACIRA in accordance with local procedures.

The Investigator will be responsible for obtaining annual IRB approval and/or renewal throughout the duration of the study. Copies of the Investigator's reports and the IRB continuance of approval must be sent to PACIRA.

Source Documentation

The Principal Investigator must maintain detailed source documents on all Study patients who are enrolled in the Study or who undergo screening. Source documents include patient medical records, hospital charts, clinic charts, Investigator's Study files, as well as the results of diagnostic tests (e.g., laboratory tests).

The following minimum information should be recorded in the patient's medical records:

- The date the patient entered the Study and the patient number
- The Study protocol number
- The date that informed consent was obtained

- Evidence that the patient meets Study eligibility requirements (e.g., medical history, Study procedures and/or evaluations)
- Evidence that required procedures and/or evaluations were completed
- Opioid use
- All lab reports taken for this study
- Occurrence and status of any Adverse Events
- The date the patient exited the Study, and a notation as to whether the patient completed the Study or was discontinued, including the reason for discontinuation.

Record Retention

The Investigator will maintain all essential study documents and source documentation, in original format that support the data collected on the study patients in compliance with the ICH/GCP guidelines. Study data will be archived in REDCap.

Investigator Responsibilities

- Agree to sign and adhere to the Investigator Agreement
- Agree to participate in Investigator meetings as scheduled by PACIRA.
- Be willing to provide required assessments for analysis
- Be willing to perform and be capable of performing treatment procedures as outlined in this protocol
- Comply with all required elements of this protocol (e.g., perform testing and follow-up as specified, especially during personnel transitions) and supply material suitable for quantitative analysis
- Agree to obtain written Informed Consent before any study specific procedures are performed
- Complete all CRFs prior to scheduled monitoring visits

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Abbreviations

ERP	Enhanced Recovery Pathway
MDASI	MD Anderson Symptom Inventory
MEDD	Morphine Equivalent Daily Dose
POD	Post-Operative Day
PROs	Patient Reported Outcomes

Appendix A: MD Anderson Symptom Inventory – GYN Cancer (MDASI-GYN)

Date : ☐☐ / ☐☐ / ☐☐ (month) (day) (year)

Participant Initials: ☐☐☐

Study Participant #: ☐☐☐☐

Wound infiltration with liposomal bupivacaine vs. standard wound infiltration with bupivacaine in patient's undergoing open gynecologic surgery on an Enhanced Recovery Pathway: a single-blinded, randomized, controlled study

Protocol #: 2015-1119

PI: Pedro Ramirez, MD

TimePoint: ☐☐☐

M. D. Anderson Symptom Inventory - GYN Cancer (MDASI-GYN)

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours.*** Please select a number from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your **pain in the abdomen** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Draft

Date : (month) / (day) / (year)

Participant Initials:

Study Participant #:

Wound infiltration with liposomal bupivacaine vs. standard wound infiltration with bupivacaine in patient's undergoing open gynecologic surgery on an Enhanced Recovery Pathway: a single-blinded, randomized, controlled study

Protocol #: 2015-1119

PI: Pedro Ramirez, MD

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
15. Your **feeling bloated** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your **constipation** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
17. Your **problem with paying attention (concentrating)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your **urinary urgency** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your **pain or burning with urination** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your **back pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your **leg cramps** or **leg muscle pain** at their WORST?	○	○	○	○	○	○	○	○	○	○	○
22. Your **diarrhea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
23. Your **indigestion (heartburn)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms **interfered** with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items ***in the last 24 hours***:

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
24. **General activity**?	○	○	○	○	○	○	○	○	○	○	○
25. **Mood**?	○	○	○	○	○	○	○	○	○	○	○
26. **Work** (including work around the house)?	○	○	○	○	○	○	○	○	○	○	○
27. **Relations** with other people?	○	○	○	○	○	○	○	○	○	○	○
28. **Walking**?	○	○	○	○	○	○	○	○	○	○	○
29. **Enjoyment** of life?	○	○	○	○	○	○	○	○	○	○	○

Signature: _____

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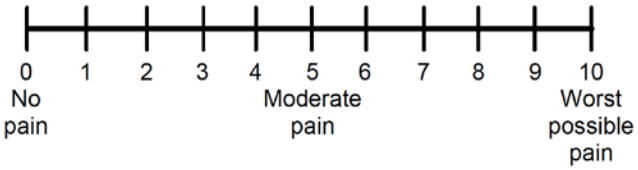
Appendix B: Pain Assessment Tool

0–10 Numeric Pain Rating Scale



Appendix C: Discharge Ready Criteria

- Ambulates 4 times per day
    - Date that patient accomplished ambulation criteria
- Eats all meals sitting up in a chair
    - Date that patient ate all meals sitting up in a chair
- Tolerates 3 regular meals per day
    - Date that patient tolerated a regular diet
- Voiding independently (if Foley catheter is due to be removed on POD1)
    - Date that patient voided independently
- Reports adequate pain control with oral medications
    - Date that patient reported adequate pain control with oral medications
- Criteria for discharge met
    - Date criteria for discharge was met

Appendix D: The Clavien-Dindo Classification of Surgical Complications

Grade I: Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.

Grade II: Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.

Grade III:
Requiring surgical, endoscopic or radiological intervention

Grade IIIa: intervention not under general anesthesia

Grade IIIb: intervention under general anesthesia

Grade IV: Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management

Grade IVa: single organ dysfunction (including dialysis)

Grade IVb: Multi-organ dysfunction

Grade V: Death of a patient. If the patients suffers from a complication at the time of discharge, the suffix “d” (for ‘disability’) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

‡ brain hemorrhage, ischemic stroke, subarrachnoidal bleeding,but excluding transient ischemic attacks (TIA);IC: Intermediate care; ICU: Intensive care unit.