Placing Numbing Medication Over Diaphragm to Reduce Shoulder Pain After Gynecologic Surgery: A Randomized Control Trial

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Instillation of bupivacaine with epinephrine over diaphragm to reduce postoperative shoulder pain following benign gynecologic laparoscopic surgery: A randomized control trial

Short Title: Bupivacaine with epinephrine over diaphragm in laparoscopy

Protocol Number: 00003947

Principal Investigator: Kelly Wright, MD

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Summary of Changes from Previous Version:

V	Affected Section(s)	Summary of Revisions Made	Rationale
2.0	1.2 Schema	-sample size updated to 94	-IRB biostatistics recommended sample size of 47 per group
3.0	1.2 Schema 6.3 Measures to minimize bias 6.5 Concomitant therapy General	-sample size updated to 100 Addressed research coordinators role in study randomization Addressed that patients with history of chronic pain or regular pain medication use will not be eligible for the study -inconsistencies in study drug have been corrected -study drug measurement has been clarified -addressed “off-label” use of study drug and updated language from “sprayed” to “instilled” to improve clarity -preoperative and postoperative drug regimen addressed	-IRB recommended sample size of 100 to account for study drop out

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9.3 STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

Clinical trial site staff who are responsible for the conduct, management, or oversight of clinical trials have completed Human Subjects Protection Training.

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

1 PROTOCOL SUMMARY

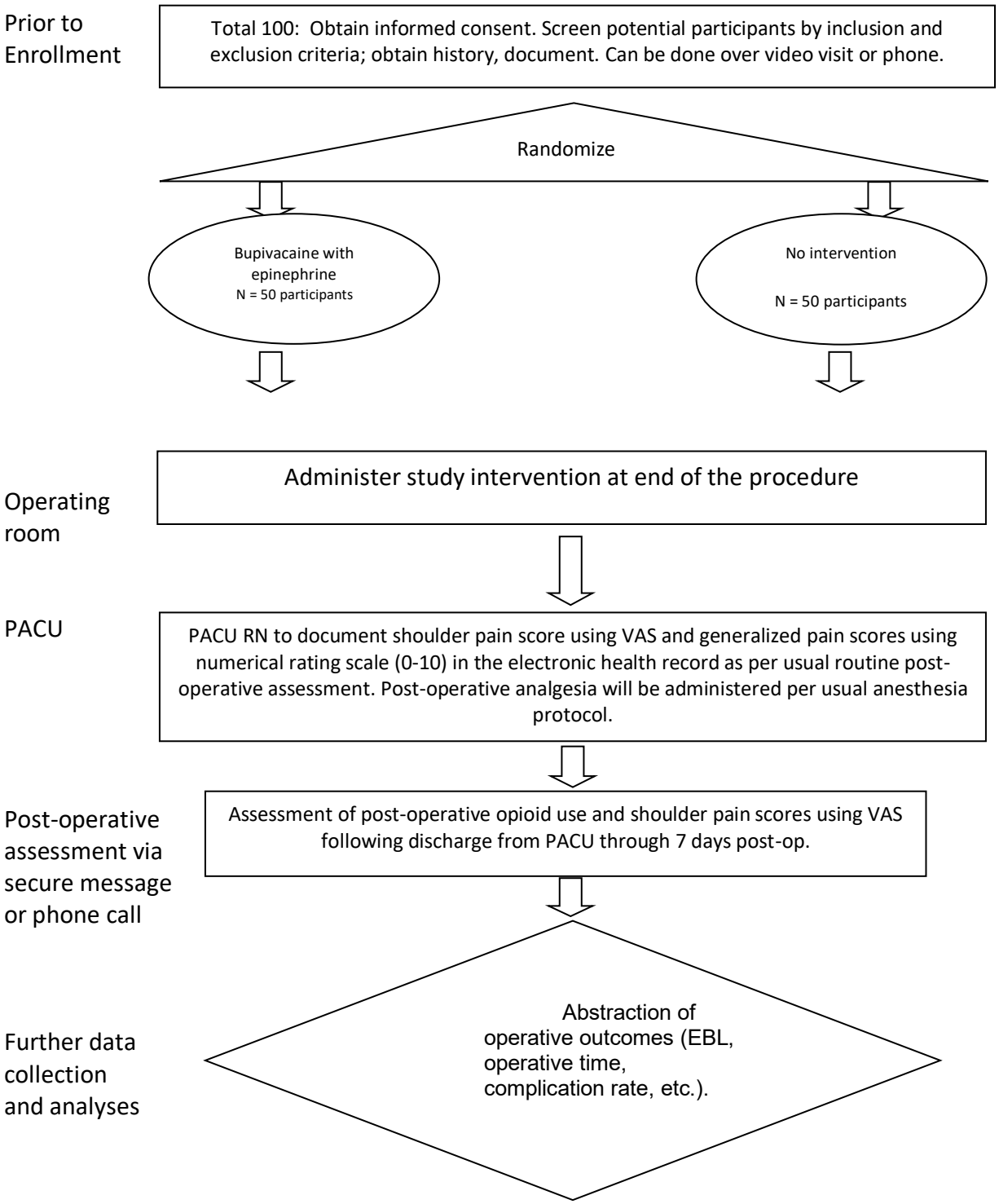
1.1 SYNOPSIS

Title:	Instillation of bupivacaine with epinephrine over diaphragm to reduce postoperative shoulder pain following benign gynecologic laparoscopic surgery: A randomized control trial
Study Description:	Postoperative pain is a significant area of interest in laparoscopic gynecologic surgery. Postoperative shoulder pain is often reported to be particularly bothersome after laparoscopy. The benefits of local anesthetic applied to subcutaneous tissue for postoperative pain management after surgery is well established. However, there have been no studies on instillation of bupivacaine with epinephrine over the diaphragm to reduce shoulder pain in laparoscopic surgery. We hypothesize that instilling infra-diaphragmatic bupivacaine with epinephrine compared to no intervention will improve postoperative shoulder pain in benign laparoscopic gynecologic surgery.
Objectives:	**Primary Objective**: To evaluate the impact of instilled infra-diaphragmatic bupivacaine with epinephrine on post-operative pain scores for shoulder pain. **Secondary Objectives:** To evaluate the impact of instilling infra-diaphragmatic bupivacaine with epinephrine on postoperative overall pain, opioid use, length of stay in PACU, and surgical outcomes.

Endpoints:	**Primary Endpoint:** ● Reported shoulder pain score using visual analog score (VAS) on postoperative day 1 (POD1) **Secondary Endpoints:** ● Maximum reported shoulder pain in PACU using VAS ● Daily reported shoulder pain using VAS for 5 days postoperatively ● First reported generalized pain score in PACU using the numerical rating scale (0-10). ● Last reported generalized pain score in PACU prior to discharge using the numerical rating scale (0-10). ● Total analgesic requirements in PACU (opioids to be reported in morphine milligram equivalents) ● Total opioid requirements in the 1 week following discharge ● Operative time ● Estimated blood loss ● Intraoperative complications ● Conversion to laparotomy ● Length of stay (from arrival to PACU to discharge home)
Study Population:	Individuals 18 years and older undergoing conventional laparoscopic or robotic-assisted laparoscopic surgery within the Minimally Invasive Gynecologic Surgery Division at Cedars-Sinai Medical Center. We anticipate 50 patients will be included in each arm.
Phase:	Phase 4
Description of Sites/Facilities Enrolling Participants:	Enrollment will occur at one site at Cedars-Sinai Medical Center
Description of Study Intervention:	30 ml of 0.25% bupivacaine with epinephrine (1:200,000) instilled over the diaphragm at the conclusion of the surgery
Study Duration:	12 months
Participant Duration:	2 weeks (from randomization to study completion)

1.2 SCHEMA

Flow diagram



1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening Day -30 to -1	Enrollment/Day of Surgery	Final Study Visit Post-operative day 7-14 (secure message or phone call)
Informed consent	X		
Demographics	X		
Medical history	X		
Randomization	X		
Administer study intervention		X	
Height		X	
Weight		X	
Adverse event review and evaluation		X	X
Pain assessment in PACU		X	
Assessment of post-operative oral opioid use			X

2 INTRODUCTION

2.1 STUDY RATIONALE

To investigate the effect of infra-diaphragmatic instilled bupivacaine with epinephrine over diaphragm on postoperative pain of patients undergoing laparoscopic gynecologic surgery.

2.2 BACKGROUND

Laparoscopy as the route of major gynecologic surgery has been increasing over the last decade (1-3). The laparoscopic approach to gynecologic surgery is preferred over other approaches due to less postoperative complications, less associated pain, less blood loss, and rapid recovery (4). However, postoperative pain remains a significant area of interest. In particular, patients often report pain in the shoulder after laparoscopy. Acute postoperative pain in laparoscopic surgery is thought to be caused by local injury, traction and tension of the peritoneum and diaphragm, increased intra-abdominal pressure, intraperitoneal inflammatory reactions, and traumatic and/or neuropathic pains (5-6). Lack of pain control can lead to issues, such as longer hospital stays, chronic pain, and opioid dependence (7-8). Although opioids are effective in providing analgesia, extensive use can lead to increased side effects including dependence, respiratory depression, urinary retention, nausea, vomiting, etc. (9). Therefore, it is important to obtain both safe and effective postoperative analgesia while reducing opioid use.

There are other nonopioid alternatives utilized in gynecologic laparoscopy to reduce pain and opioid use (10). Anesthetics, such as bupivacaine delivered via superior hypogastric plexus block has not been shown to reduce postoperative pain after laparoscopic hysterectomy while intraperitoneal infusion of bupivacaine has been demonstrated to improve quality of recovery in patients undergoing laparoscopic hysterectomy (11,12). Similar intraperitoneal use of lidocaine was found to improve pain management after cesarean delivery and reduced the number of opioids received in the postpartum period (13).

Instilling local anesthetics intraperitoneally under laparoscopy has been shown to be an effective method for post-operative pain control (14-16). Increased intraabdominal pressure from laparoscopic

surgery has been known to cause referred shoulder pain postoperatively. Both bupivacaine and ropivacaine are safe methods for abdominal instillation following surgery and are long-acting compared to their local counterparts. There have been multiple randomized control trials that investigate use of intraperitoneal local anesthesia with differing outcomes (14-16). For example, in a randomized control trial, Cho et al demonstrated that intraperitoneal bupivacaine significantly reduced shoulder pain following up to 24 hours following gynecologic laparoscopy (14). On the other hand, Sutchritpongsa et al found that subdiaphragmatic instillation of bupivacaine with morphine had no effect on reducing postoperative shoulder pain up to 24 hours after gynecologic laparoscopy (15). Majority of these studies do not specify location of bupivacaine administration, include other medications, or do not longitudinally follow patients postoperatively.

In this study, we hypothesize that infradiaphragmatic instillation of bupivacaine with epinephrine compared to no intervention will improve postoperative pain, specifically shoulder pain following laparoscopic gynecologic surgery.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

The risks are minimal in our study given the low dosage and amount of bupivacaine with epinephrine we plan on utilizing. The risks of use often are associated with the dose used and overall, extremely rare. Risks include potential interactions between ergot medications, blood thinners, antidepressants, or monoamine oxidase inhibitors. There are exceedingly rare immunologic reactions. Allergic reactions to amide-type local anesthetics are also rare and not often reported but are possible. There is also a risk of methemoglobinemia described in rare case reports. Other extremely rare adverse effects include nausea, vomiting, chills, shivering, headache, back pain, dizziness, tremors, coma, and cardiovascular collapse.

2.3.2 Known Potential Benefits

Bupivacaine with epinephrine is a commonly used drug for local or regional anesthesia or analgesia for surgeries. It is approved by the Food and Drug Administration for local infiltration (20). It is commonly used before, during and after surgery to aid in postoperative pain management. The onset of action is rapid while the anesthesia is long lasting. It is also known to be safe depending on proper dosage, correct technique, adequate precautions, and readiness for emergencies.

2.3.3 Assessment of Potential Risks and Benefits

Our study utilizes a lower dose of bupivacaine with epinephrine, thus the aforementioned risks are extremely rare. Multiple studies have demonstrated safety and efficacy of use for both local infiltration and abdominal instillation following laparoscopic surgery (18-19). Administration of local anesthesia before, during or after laparoscopic surgery is also quite common. Typically, opioids are used for analgesia postoperatively and given they are dose dependent, extensive use can cause unnecessary side effects, including respiratory depression, excessive sedation, nausea, vomiting, etc. Bupivacaine has nearly none of those side effects and provides a safe alternative to help reduce the amount of postoperative opioids required.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To assess the effectiveness of instilled bupivacaine with epinephrine under the diaphragm on pain in the immediate postoperative period	The primary endpoint is reported shoulder pain score using visual analog score (VAS) on POD1	Decreases in immediate post-operative pain scores may increase patient satisfaction, decrease postoperative opioid use, and shorten hospital stay. We chose the reported shoulder pain score in PACU as our primary endpoint as we believe this to be the most clinically relevant data point for this medication intervention in the immediate postoperative period for laparoscopic surgery.
Secondary/Exploratory		
To evaluate the impact of instilled bupivacaine with epinephrine under the diaphragm on pain scores at other time points in PACU and in the first week of recovery, post-operative opioid use, length of stay in PACU, and surgical outcomes.	● Maximum reported shoulder pain in PACU using VAS ● Daily reported shoulder pain score using VAS for 5 days postoperatively ● First-reported pain score in PACU using numerical rating score (NRS) ● Last reported pain score in PACU using NRS ● Total analgesic requirements in PACU (in morphine equivalents) ● Total opioid requirements in the 7 weeks following discharge ● Surgical safety outcomes (operative time, estimated blood loss, complications, conversions to laparotomy) ● Length of stay in PACU	We chose to examine pain scores at additional points in the PACU and at home to assess how our intervention may impact pain scores over time. Post-operative opioid use (in PACU and at home) will be examined both as a proxy for post-operative pain at various time points, and to examine the potential for our intervention to decrease opioid use and prevent dependency. The remaining secondary endpoints were chosen as a means of evaluating the safety and acceptability of our intervention.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This will be a single-center, single-blinded randomized controlled trial evaluating the impact of instilled infradiaphragmatic bupivacaine with epinephrine on post-operative pain and surgical field visualization among patients undergoing laparoscopic gynecologic surgery. We hypothesize that instilled bupivacaine with epinephrine on the diaphragm will decrease postoperative pain, specifically shoulder pain in the immediate postoperative period. The study will include 2 groups: patients receiving bupivacaine with epinephrine instilled over the diaphragm at the end of the procedure and patients who do not receive the intervention.

To minimize bias, the following measures will be taken to standardize pain management:

- Preoperative acetaminophen and celecoxib (or equivalent) per standard of care with Enhanced Recovery After Surgery (ERAS) protocol.
- Local subcutaneous infiltration of all port sites with 0.25% bupivacaine with epinephrine (1:200,000) will be performed prior to each incision. Remaining local anesthetic will be administered into the incision sites prior to the conclusion of the case (30cc total). This volume was selected as the bupivacaine that is typically used for surgery at our institution comes in 30 cc vial, and it is common practice to give the entire vial's worth. The maximum dosage in 24 hours is 400 mg; we use well below the maximum dosage.
- To evacuate residual carbon dioxide at the conclusion of the procedure, three positive pressure breaths will be administered with simultaneous compression of the abdomen prior to trocar removal.
- General anesthesia and post-operative analgesia will be administered per the standard of care at our hospital and not altered in any manner given participation in the study.
- In the post-anesthesia care unit, intravenous opioids (morphine, fentanyl or hydromorphone) will be administered at the discretion of the nursing and anesthesia teams as per routine care.
- Patients will be instructed to take extra strength acetaminophen and ibuprofen in a scheduled manner, with oxycodone as needed, following discharge as per current and routine post operative care. All patients will be prescribed a total of 10 pills of oxycodone 5mg to be taken every 6 hours as needed in the immediate postoperative period, which is the standard amount that our practice prescribes for patients after laparoscopic surgery. Additional pills may be prescribed during their postoperative course at the discretion of the surgical team if the patient is having greater than expected pain and runs out of the prescribed pain medication, per the standard of care and current practice of our division.

Study participants will be blinded to the study intervention. The surgical team and the post-operative care unit nurses will not be blinded to the intervention.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is a superiority trial with respect to the primary outcome (pain scores).

4.3 JUSTIFICATION FOR DOSE

The planned maximum dosage is 30mL of 0.25% bupivacaine with epinephrine 1:200,000, which is already approved for use for local infiltration and therefore is routinely used for infiltration at incision

sites during laparoscopic cases. Our study utilizes a very low dose as typically, the maximum dose is up to 400 mg in 24 hours. We plan to provide only one dose at 75 mg.

4.4 End of Study Definition

A participant is considered to have completed the study once all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3, are complete.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. 18 years of age or older
4. Undergoing laparoscopic surgery at Cedars-Sinai Medical Center with a surgeon in the Minimally Invasive Gynecologic Surgery division

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Pregnancy
2. Urgent/non-scheduled surgery
3. Scheduled for planned or possible concomitant non-gynecologic surgery (e.g., urologic or colorectal procedure)
4. Baseline shoulder pain
5. Baseline opioid use
6. Baseline of chronic pain syndrome
7. Conversion to open surgery
8. Allergy or intolerance to bupivacaine, lidocaine (or amide class of anesthetics), oxycodone, acetaminophen, or ibuprofen
9. Planned post-operative admission

5.3 Lifestyle Considerations

Not applicable

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to

respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

We do not anticipate any modifiable factors that would initially exclude participation in the trial but later allow a patient to become eligible for participation (allowing for re-screening).

5.5 Strategies for Recruitment and Retention

- Patients who are scheduled for laparoscopic gynecologic surgery at Cedars-Sinai Medical Center with a surgeon in the minimally invasive gynecologic surgery division will be identified.
- We anticipate needing to screen approximately 200 patients for eligibility to achieve our sample size.
- Anticipated accrual rate = 8 people per month
- Anticipated number of sites = 1 (Cedars-Sinai Medical Center)
- Potential participants will be identified in the outpatient setting prior to surgery. Eligible participants will be notified about the study at their preoperative visit or via secure message by their surgeon or study team member prior to their surgery (see recruitment template)
- Given the nature of our specialty, all patients in our study population were assigned female sex at birth and most identify as women. Our patient population is racially and ethnically diverse, thus we will be actively recruiting historically under-represented populations.

6 STUDY INTERVENTION

6.1 Study Intervention(s) Administration

6.1.1 Study Intervention Description

i. Dosing and Administration

The study intervention includes **30 ml of 0.25% bupivacaine with epinephrine** instilled over the diaphragm at the conclusion of the surgery. Prior to desufflation of the abdomen during the procedure, the surgeon will instill the drug laparoscopically aiming to cover the diaphragm with liquid. Our study utilizes a very low dose as typically; the maximum dose is up to 400 mg and can be repeated once every three hours. We plan to provide only one dose at 75 mg.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and accountability

Per standard care. 0.25% bupivacaine with epinephrine is already approved for use for local infiltration and therefore is routinely used for infiltration at incision sites during laparoscopic cases. Thus, the study intervention will be readily available for use at bedside.

6.2.2 Formulation, Appearance, Packaging, and Labeling

Per standard care.

The following description was obtained from the package insert:
"Sensorcaine ® (bupivacaine HCl) injections are sterile isotonic solutions that contain a local anesthetic agent with and without epinephrine (as bitartrate) 1:200,000 and are administered parenterally by injection.
Sensorcaine-MPF with Epinephrine 1:200,000 (as bitartrate) is a sterile isotonic solution containing sodium chloride. Each mL contains bupivacaine hydrochloride and 0.005 mg epinephrine, with 0.5 mg sodium metabisulfite as an antioxidant and 0.2 mg citric acid (anhydrous) as stabilizer."

6.2.3 Product Storage and Stability

Per standard care. Bupivacaine with epinephrine is to be stored at 20 to 25°C (68 to 77°F); excursions permitted between 15° to 30°C (59° to 86°F).

6.2.4 Preparation

Per standard care. Preparation required is minimal. Operating room staff are well-versed in drawing up bupivacaine with epinephrine with a syringe.

6.3 Measures to Minimize Bias: Randomization and Blinding

Participants will be 1:1 allocated to the bupivacaine with epinephrine and no intervention groups (parallel design) by block randomization and assigned a serial study identification number. Randomization groups will be allocated to each study identification number using an online tool and concealed until the time of enrollment. Once the patient is consented and enrolled, the surgeon will be informed which group the patient is randomized to by the research coordinator.

Only patients will be blinded to the intervention group. The surgeons, OR nurses performing the procedure, and post-op nurses will not be blinded to the study group and thus can intervene if needed.

Since we do not anticipate plausible serious adverse events related to using bupivacaine with epinephrine, there will not be a reason to unblind the intervention group to the patient. Any unintentional breaking of the blind will be reported to the principal investigator of the study.

6.4 Study Intervention Compliance

The entire surgical team will be notified of the assigned group. Completion of the provider survey and patient reporting of postoperative opioid use will be tracked by the study coordinator.

6.5 Concomitant Therapy

Not applicable. Patients who routinely take pain medications or have chronic pelvic or shoulder pain are not eligible for the study. This screening will occur prior to enrollment.

6.5.1 Rescue Medicine

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Indications for discontinuing the study intervention (i.e., refraining from additional use of bupivacaine (with epinephrine) are the same as indications for refraining from additional use of bupivacaine with epinephrine during any laparoscopic surgery (i.e., local anesthetic toxicity including seizures, cardiac arrhythmias, and hypotension). These indications are incredibly rare. Bupivacaine with epinephrine will already be utilized per protocol at the beginning of the procedure and therefore, if there is a reaction at that time, the patient will be withdrawn from the study.

7.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Patient randomized but did not receive assigned intervention at any point (e.g., failed to remember to distribute medication at the end of the case)
- Procedure aborted, e.g., due to physiologic intolerance of bupivacaine with epinephrine
- Conversion to laparotomy (will included in all intra-operative variable analyses but omitted from all postoperative analyses)
- Patients with unplanned admission post-operatively (will be omitted only from postoperative opioid analysis)
- Patients unable to report pain scores post-operatively (i.e., unplanned transfer to intensive care unit while still intubated)
- If any clinical adverse event (AE) other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Following enrollment, participant does not undergo scheduled surgery

The reason for participant discontinuation or withdrawal from the study will be recorded on the REDCap data collection form. Subjects who sign the informed consent form and are randomized

but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, will not be replaced.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if the participant fails to return for the post-operative visit and is unable to be contacted by the study site staff to report postoperative opioid use.

The following actions must be taken if a participant fails to attend their postoperative visit:

- The site will attempt to contact the participant and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, a secure patient message, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Efficacy Assessments

The following data points will be obtained through review of data in the electronic medical record, as this information is collected and documented in the electronic medical record as part of regular standard of clinical care.

Baseline/Operative Data:

- Medical Record Number
- Age at time of surgery
- Body mass index at time of surgery
- Race
- Ethnicity
- Prior abdominal surgeries
- American Society of Anesthesiology class
- Procedure type (endometriosis resection, adnexal surgery, hysterectomy, myomectomy, other)
- Specimen weight
- Number of port sites
- Size of all ports

Safety data:

- Operative time
- Estimated blood loss
- Intraoperative complications

Efficacy data:

- Postoperative pain scores on numerical rating score (documented by nursing team per routine protocol)
- Daily reported shoulder pain using visual analog score for 7 days postoperatively

- Quantity of analgesics administered in the PACU (opioids reported in morphine milligram equivalents)
- PACU length of stay

The remaining study data will be obtained via questionnaires as follows:

Efficacy Data:

- The study staff will ask patients about the quantity of postoperative opioids taken via secure message using the patient portal or via a telephone call. An instrument will not be used for collecting pain medication usage information, as the study staff will just ask the patients how many pain pills they took.
- Postoperative pain scores (shoulder specific and generalized) will be collected in a similar fashion by nurses via secure message or phone call.

8.2 Safety and Other Assessments

Safety outcomes will be gathered from the electronic medical record and via questionnaires as indicated above (section 8.1).

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization (other than for routine post-operative care) or prolongation of existing hospitalization, or a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. Important medical events that may not result in death, be life-threatening, or require prolonged hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 Classification of an Adverse Event

1.1.1.1 Severity of Event

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate –** Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious."

1.1.1.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study intervention must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

OR

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

1.1.1.3 EXPECTEDNESS

The principal investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel at the time of surgery, in the immediate postoperative period, or at the patient's 2-week post-operative visit.

All AEs will be documented on the patient data collection tool in REDCap. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

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

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

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

8.3.5 Adverse Event Reporting

The investigator will record any adverse events on the REDCap data collection tool and if indicated, will report them to the IRB.

8.3.6 Serious Adverse Event Reporting

The study clinician will immediately report any serious adverse event to the IRB if indicated (i.e., the adverse event is unexpected and there is a reasonable possibility that is related to participation in the study).

8.3.7 Reporting Events to Participants

Any AEs or SAEs that occur during surgery will be promptly disclosed to the patient, as would be the case with any complication that could occur during surgery.

8.3.8 Events of Special Interest

Not applicable.

8.3.9 Reporting of Pregnancy

Not applicable

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

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

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied.
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

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

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

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

- UPs that are serious adverse events (SAEs) will be reported to the Cedars-Sinai IRB within 30 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 10 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 10 days of the IRB's receipt of the report of the problem from the investigator.

ii.8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable.

10. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):
  - **Post-operative shoulder pain scores (superiority):** Null hypothesis = pain scores will not differ among the bupivacaine with epinephrine vs no intervention group; Alternative hypothesis= pain scores will be lower among the bupivacaine with epinephrine group

- Secondary Efficacy Endpoint(s):
  - **Post-operative shoulder pain scores at home (superiority):** Null hypothesis = pain scores will not differ among the bupivacaine with epinephrine vs no intervention group; Alternative hypothesis= pain scores will be lower among the bupivacaine with epinephrine group
  - **Post-operative generalized pain scores (superiority):** Null hypothesis = pain scores will not differ among the bupivacaine with epinephrine vs no intervention group; Alternative hypothesis= pain scores will be lower among the bupivacaine with epinephrine group
  - **Post-operative opioid use (superiority):** Null hypothesis = post-op opioid use will not differ among the bupivacaine with epinephrine vs no intervention group; Alternative hypothesis= post-op opioid use will be lower among the bupivacaine with epinephrine group
  - **Surgical outcomes (EBL, operative time):** Null hypothesis = each of these outcomes will not differ between groups; Alternative hypothesis = each of these outcomes will be improved in bupivacaine with epinephrine group
  - **Length of stay in PACU (superiority):** Null hypothesis = PACU length of stay will not differ among the bupivacaine with epinephrine vs no intervention group; Alternative hypothesis= PACU length of stay will be shorter in the bupivacaine with epinephrine groups

9.2 SAMPLE SIZE DETERMINATION

Prior studies have cited a clinically significant reduction in pain on the numerical rating scale to be 1.3-1.5 [14,15]. We estimated the standard deviation on the numerical rating scale to be 2.5 for post-operative shoulder pain following minimally invasive gynecologic surgery, based on a prior similar study [9]. To detect a difference of at least 1.5 between groups on the 11-point VAS with 80% power and a significance level of .05, a total of 50 participants per group (100 total) would be required. To account for protocol deviations, we added approximately 10% to the number of participants, resulting in a sample size of 100 (50 per group). We anticipate needing to recruit and screen approximately 200 patients to reach this sample size. Sample size calculation was performed using G*Power version 3.1.9.7 (Heinrich-Heine-Universität, Düsseldorf, Germany).

The above sample size calculation was powered specifically for the primary outcome (reported shoulder pain score 24 hours postoperatively). The sample size was not powered for the secondary endpoints of daily shoulder pain scores at home, maximum, first, and last reported pain scores in PACU, post-operative opioid use, PACU length of stay, and surgical outcomes.

10.3 Populations for Analyses

An intention-to-treat analysis of all randomized participants will be conducted.

9.4 Statistical Analyses

i. 9.4.1 General Approach

- Descriptive statistics will be presented with standard descriptive summaries (mean/standard deviation for normal data, median/range for non-normal data, and frequency/percentage for categorical variables.
- Checks of normality will be performed, and non-parametric tests will be used to analyze non-normal data.
- Chi-square and Fisher's exact test will be used for categorical variables as appropriate. Continuous variables will be analyzed using analysis of variance for variables with normally distributed data and the Kruskal Wallis test for variables with non-normally distributed data.
- A 2-sided p-value of <.05 will be considered statistically significant.

ii. 9.4.2 Analysis of the Primary Efficacy Endpoint(s)

Primary endpoint: Reported right shoulder pain score using visual analog score (VAS) 24 hours postoperatively.

- Assessed using the validated 100-mm scale with a range of 0-10 (11-point numerical rating scale), an ordinal scale.
- Analyzed using the Kruskall Wallis test (as the data from the scale is typically not normally distributed); pairwise analyses will then be conducted using the Dunn post-hoc test if statistically significant.
- Assuming non-normality, data will be presented as median (range).
- Patients without any postoperative documentation of pain scores will be withdrawn from the study and thus excluded from the analysis.

iii. 9.4.3 Analysis of the Secondary Endpoint(s)

Secondary outcomes

- **Maximum reported shoulder pain in PACU using VAS**
- **Daily reported shoulder pain score using visual analog scale for 5 days postoperatively**
  - Assessed using the validated 100-mm scale with a range of 0-10 (11-point numerical rating scale), an ordinal scale.
  - Analyzed using the Kruskall Wallis test (as the data from the scale is typically not normally distributed); pairwise analyses will then be conducted using the Dunn post-hoc test if statistically significant.
  - Assuming non-normality, data will be presented as median (range).
  - Patients without any postoperative documentation of pain scores will be withdrawn from the study and thus excluded from the analysis.
- **First and last reported generalized pain score in PACU using numerical rating score**

- Assessed using the validated 11-point numerical rating scale (0-10), an ordinal scale.
- Analyzed using the Kruskall Wallis test (as the data from the scale is typically not normally distributed); pairwise analyses will then be conducted using the Dunn post-hoc test if statistically significant.
- Assuming non-normality, data will be presented as median (range).
- Patients without any postoperative documentation of pain scores will be withdrawn from the study and thus excluded from the analysis.

- **Total analgesic requirements in PACU (in morphine equivalents)**
  - Calculated in morphine milligram equivalents (continuous data)
  - Analyzed using the Kruskall-Wallis test (assuming non-normal data)
  - Data will be presented as median (range)
- **Total opioid requirements in the 1 week following discharge**
  - Number of pills used reported by patient (interval data)
  - Analyzed using the Kruskall-Wallis test
  - Data will be presented as median (range)
- **Surgical safety outcomes**
  - Continuous variables: operative time, estimated blood loss
    - Analyzed using ANOVA if normally distributed, Kruskall-Wallis test if not normally distributed
  - Binary data: Surgical complications, conversions to laparotomy
    - Analyzed using chi-square test
- **Length of stay in PACU**
  - Documented in minutes (continuous data)
  - Analyzed using ANOVA if normally distributed, Kruskall-Wallis test if not normally distributed

iv. 9.4.4 Safety Analyses

Surgical safety outcomes will be analyzed as above (section 9.4.3.)

v. 9.4.5 Baseline Descriptive Statistics

The following baseline characteristics will be collected, with the corresponding descriptive statistics reported:

- Age (mean/SD or median/range depending on normality)
- Body Mass Index (mean/SD or median/range depending on normality)
- Race/ethnicity (n, %)
- Prior abdominal surgery (median, range)
- American Society of Anesthesiology Class (n, %)

Additionally, the following operative variables will be collected (in addition to secondary endpoints as above), with the corresponding statistics reported:

- Surgery type (endometriosis resection, adnexal surgery, hysterectomy, myomectomy, other) (n, %)

- Specimen weight (median, range)
- Number of port sites (median, range)
- Size of all ports (median, range)

vi. 9.4.6 Planned Interim Analyses

Not applicable.

vii. 9.4.7 Subgroup Analyses

There is no indication to perform subgroup analyses for the primary or secondary outcomes based on demographic characteristics. We have no reason to suspect that the study intervention will differentially impact patients of different age, race, or ethnicity.

viii. 9.4.8 Tabulation of Individual Participant Data

Individual participant data will not be tabulated.

ix. 9.4.9 Exploratory Analyses

Not applicable.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

x. 10.1.1 Informed Consent Process

1.1.1.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol:

- Consent Form (HRP 610-A) – to be uploaded onto REDCap (plan for electronic informed consent per IRB protocol)

1.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will be encouraged to discuss the study with their family or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Given that most pre-operative patient visits conducted in our division are virtual, the verbal explanation of the study and potential risks will be discussed virtually or by phone. Consent forms will be made available to the patient and signed via REDCap as part of the electronic informed consent process.

xi.10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the study participants and investigator. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance with protocol requirements
- Data that is not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

xii.10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will all be maintained securely within REDCap electronic data capture tools and on Box, HIPAA-compliant secure storage systems within the Cedars-Sinai network with access restricted to approved members of the research team. Patient identifiers (i.e., medical record number) will be linked to participant data in order to allow for data abstraction from the electronic medical record. At the end of the study, all study databases will be de-identified.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be stored on REDCap electronic data capture tools and on Box. Study data will not be used for further analyses following completion of the study.

xiii.10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	Medical Monitor
Kelly Wright, MD	*N/A*
Cedars-Sinai Medical Center	*N/A*
444 S San Vicente Blvd #1003 Los Angeles, CA	*N/A*
310-423-9268	*N/A*
Kelly.Wright@cshs.org	*N/A*

The principal investigator will be responsible for the oversight of the trial, including safety monitoring and handling of unforeseen adverse events.

xiv. 10.1.6 Safety Oversight

Safety oversight will be under the direction of the principal investigator.

xv. 10.1.7 Clinical Monitoring

All study participants will be monitored clinically by the surgical team as part of their routine perioperative care.

xvi. 10.1.8 Quality Assurance and Quality Control

The principal investigator will be responsible for ensuring that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigation site will provide direct access to all source data/documents, and reports for the purpose of monitoring and inspection by local and regulatory authorities.

xvii. 10.1.9 Data Handling and Record Keeping

1.1.1.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All study data will be documented electronically using REDCap electronic data capture tools, a HIPAA-compliant secure storage system within the Cedars-Sinai network with access restricted to approved members of the research team.

Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including surgical complications, adverse events (AEs) and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system hosted at Cedars-Sinai Medical Center. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appears inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

1.1.1.2 Study Records Retention

Records will be retained for a minimum of 3 years following completion of the study.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or the International Conference on Harmonisation Good Clinical Practice (ICH GCP). The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 30 working days of identification of the protocol deviation, or within 30 working days of the scheduled protocol-required activity. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

This study will comply with the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 3 years after the completion of the primary endpoint by contacting the investigator or co-investigator.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest among people who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, people who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with Cedars-Sinai Medical Center has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

None

10.3 ABBREVIATIONS

AE	**Adverse Event**
ANOVA	Analysis of Variance
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
CONSORT	Consolidated Standards of Reporting Trials
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	Intention-To-Treat
MOP	Manual of Procedures
MME	Morphine milligram equivalent
OHRP	Office for Human Research Protections
PACU	Post-anesthesia recovery unit
PI	Principal Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

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