DEPARTMENT OF THE ARMY
WALTER REED NATIONAL MILITARY MEDICAL CENTER
BETHESDA, MD 20889

MCAT-TCW

15NOV2021

COVER LETTER

1. OFFICAL TITLE OF STUDY: Local Anesthetics on Postsurgical Analgesia Following Posterior Colporrhaphy
2. NCT NUMBER: NCT04032327
3. DATE OF LAST APPROVAL: MARCH 10, 2020

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LTC, MC
CHIEF, UROGYN DIVISION
DEPT OB/GYN, WRNMMC

EIRB Protocol Template (Version 1.4)

1.0 General Information

***Please enter the full title of your study:**

Efficacy of Injectable Local Anesthetics on Postsurgical Analgesia Following Posterior Colporrhaphy: A Prospective, Randomized, Double-Blinded Trial

***Please enter the Protocol Number you would like to use to reference the protocol:**

11111
* This field allows you to enter an abbreviated version of the Protocol Title to quickly identify this protocol.

Is this a multi-site study (i.e. Each site has their own Principal Investigator)?

No

Does this protocol involve the use of animals?

○ Yes ◉ No

2.0 Add Site(s)

2.1 List sites associated with this study:

Primary Dept?	Department Name
◉	**P and R** - Walter Reed National Military Medical Center (WRNMMC)

3.0 Assign project personnel access to the project

3.1 *Please add a Principal Investigator for the study:

Dengler, Katherine Laura, MD MAJ

Select if applicable

☐ Student
☐ Resident
☐ Site Chair
☑ Fellow

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

CRAIG, Eric Robert, MD LT
Associate Investigator
Gonzalez, Hector

Associate Investigator
Gruber, Daniel D, MS, MD
Associate Investigator
Stone, George William, MAJ
Associate Investigator

B) Research Support Staff

Hill, Micah Joseph, DO
Monitor
Shelton, Taneshia Knight, Ph.D.
Research Coordinator

3.3 *Please add a Protocol Contact:

Dengler, Katherine Laura, MD MAJ
Shelton, Taneshia Knight, Ph.D.

The Protocol Contact(s) will receive all important system notifications along with the Principal Investigator. (i.e. The protocol contact(s) are typically either the Protocol Coordinator or the Principal Investigator themselves).

3.4 If applicable, please select the Designated Site Approval(s):

Csokmay, John Michael, LTC
Department Chair

Add the name of the individual authorized to approve and sign off on this protocol from your Site (e.g. the Site Chair).

4.0 Project Information

4.1 Is this a research study?

(•) Yes ( ) No

4.2 What type of research is this?

- [x] Biomedical Research
- [ ] Clinical trial (FDA regulated)
- [ ] Behavioral Research
- [ ] Educational Research
- [ ] Psychosocial Research
- [ ] Oral History
- [ ] Other

4.4 Is this human subjects research (Activities that include both a systematic investigation designed to develop or contribute to generalizable knowledge AND involve a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or identifiable private information. Activities covered by 32 CFR 219.101(a) (including exempt research involving human subjects) and DoDI 3216.02)?

◉ Yes ○ No

4.5 Do you believe this human subjects research is exempt from IRB review?

○ Yes ◉ No

5.0 Personnel Details

5.1 Will you have a Research Monitor for this study?

◉ Yes
○ No
○ N/A

Research Monitor Role:

1. Promptly reporting any observations and findings to the Institutional Review Board (IRB), the Human Protections Administrator (HPA), or the Institutional Official;
2. Stop the research study in the presence of safety concerns for the human subjects involved in the protocol. The RM may remove human subjects from the study and take any others actions necessary to protect the subjects of the study. The RM may discuss the protocol with the investigators, interview human subjects, and consult with others outside the protocol about the research;
3. Review the study monitoring plans, review Adverse Events and determine their relatedness to the protocol, review Unanticipated Problems Involving Risks to Subjects of Others, make recommendations on changes to the informed consent process based on the review of study events, and review and sign the continuing review report and other substantial submissions to the IRB.
4. Observe recruitment, enrollment, consent procedures and oversee study interventions.

If applicable, you may nominate an individual to serve as the Research Monitor:

Selected Users
Micah Joseph Hill, DO

6.0 Data/Specimens

6.1 Does the study involve the use of existing data or specimens only (no interaction with human subjects)?

○ Yes ◉ No

7.0 Funding and Disclosures

7.1 Source of Funding:

Funding Source	Funding Type	Amount
: Other		

Department of Research Programs - WRNMMC	: Other	13568

Total amount of funding:

13568

7.2 Do you or any other Investigator(s) have a disclosure of a personal interest or financial nature significant with sponsor(s), product(s), instrument(s) and/or company(ies) involved in this study?

○ Yes ◉ No

8.0 Study Locations

8.1 List any Research Team members without EIRB access that are not previously entered in the protocol:

No records have been added

8.2 Has another IRB reviewed this study?

○ Yes ◉ No

IRB Name	Review Date	Determination
No records have been added		

8.3 Is this a collaborative or multi-site study? (e.g., are there any other institutions involved?)

○ Yes ◉ No

8.4 Study Facilities and Locations:

Institution	Site Name	Site Role	FWA or DoD Assurance Number	Assurance Expiration Date	Is there an agreement?	IRB Reviewing for Site
No records have been added						

Other:

Other Institution Site	Site Role	FWA or DoD Assurance Number	FWA or DoD Expiration Date	Is there an agreement?	IRB Reviewing for Site
No records have been added					

8.5 Are there international sites?

Attach international approval documents, if applicable, when prompted. Note: Ensure local research context has been considered

○ Yes ◉ No

8.6 Is this an OCONUS (Outside Continental United States) study?

○ Yes ◉ No

Select the area of responsibility:

Have you obtained permission from that area of responsibility? (This is a requirement prior to study approval)

○ Yes ◉ No

9.0 Study Details

9.1 Abstract/ Summary:

Summarize the proposed study in 500 words or less, to include the purpose, the subject population, the study's design type, and procedures

Effective post-surgical pain management is a crucial component of a patient's postoperative course following posterior colporrhaphy. Narcotics are the cornerstone for postoperative analgesia with a frequent re-dosing requirement, a lengthy list of side effects and adverse reaction risks[5]. The colorectal, orthopedic and general surgery literatures have reported on an extended-release bupivacaine liposomal injection, Exparel®, which remarkably reduces acute post-operative pain; however, literature regarding this medication specific to Urogynecology and Gynecology is limited. [6,7,8,9,10,14]

We propose a prospective, randomized, double blind, trial with 120 subjects recruited from the WRNMMC Urogynecology Clinic to study postsurgical pain control after posterior repair. There will be two arms in the study; one arm with bupivacaine alone and a second arm with bupivacaine mixed with Exparel®(extended-release, liposomal bupivacaine) injected vaginally in patients undergoing posterior colporrhaphy. Subjects will be randomized to receive either 20mL of plain bupivacaine or 20mL (10ml+10ml) mixture of bupivacaine plus Exparel®.

The primary objective of the trial will be to evaluate the postsurgical vaginal pain using a visual analog pain scale[19] at days 1, 2, 3 post-procedure. All subjects will have acetaminophen, a non-steroidal anti-inflammatory drug and narcotic pain medication available for pain control regardless of assignment, which is the usual postoperative pain control regimen. We hypothesize a 30% difference in post-operative pain measurements between the two groups.

Additional objectives of this study are to evaluate total medication usage on days 1, 2 and 3 and any post-operative voiding and defecatory dysfunction, comparing the two groups.

9.2 Key Words:

Provide up to 5 key words that identify the broad topic(s) of your study

Posterior colporrhaphy
Posterior repair
Exparel
Postoperative pain
Buplvicaine

9.3 Background and Significance:

Include a literature review that describes in detail the rationale for conducting the study. Include descriptions of any preliminary studies and findings that led to the development of the protocol. The background section should clearly support the choice of study variables and explain the basis for the research questions and/or study hypotheses. This section establishes the relevance of the study and explains the applicability of its findings

Background:

An integral part of every patient's postsurgical recovery is adequate and appropriate pain management. Uncontrolled postsurgical pain can affect both the physical and mental recovery period, extend hospital stays and increase the potential for serious adverse reactions with pain medications. Additional outcomes of ineffective post-operative pain management include deep vein thrombosis, pulmonary embolism, coronary ischemia, myocardial infarction, pneumonia, poor wound healing, insomnia and demoralization[1]. This issue has become such an important topic The Joint Commission (TJC) has issued advisories regarding the need for better pain management and heightened awareness of potential adverse reactions with opioid use.[2] The Federal Drug Administration (FDA) has restricting the amount of acetaminophen pharmacies are allowed to combine with opioids in hopes of decreasing the number of incidental overdoses seen every year in the emergency rooms.[3] To complicate the issue even further, third-party payers have begun reimbursing hospitals based on patient satisfaction, with adequate pain management being a large component of this satisfaction.[4] The need for a safe, effective, long-acting medication to treat post-operative pain has reached a critical point in the current health care climate.

Intra-operative pain analgesia can be beneficial in reducing both immediate and long-term post-operative pain. Intra-operative analgesia during posterior colporrhaphy and other urogynecologic surgeries may include such modalities and intra-operative IV acetaminophen, IV ketorolac, and local anesthetic such as lidocaine or bupivacaine. Amides such as lidocaine and bupivacaine, especially with epinephrine also function for local hemostasis and contribute minimally to post-operative pain control because of their relatively short duration. Lidocaine provides pain control for 1.5 to 3 hours and bupivacaine (Marcaine®) is only slightly longer at seven hours, neither of which provides a long-acting result. In the recovery room, patients will receive additional intravenous medications for acute pain and are then transitioned over to oral tablets as soon as possible. Oral analgesia regiments for Urogynecology patients include a combination of non-steroidal anti-inflammatory medications (ibuprofen, naprosyn, celecoxib), acetaminophen (Tylenol) and an opioid (oxycodone IR, hydromorphone, tramadol, dilaudid, morphine). The timing of medication doses, both opioid and non-opioid, can be complex to ensure not only adequate analgesia but to avoid overdosing and serious adverse effects. Wheeler et al performed a comprehensive review of case reports, observational studies and randomized controlled trials and concluded that in over 40, 000 surgical patients, 1.8% experienced an opioid related adverse drug event such as nausea/vomiting, itching/rash, mental status changes, respiratory depression or failure, hypoxia, urinary retention, hypotension, fever and bradycardia.[5] These potential adverse events can deter from receiving adequate pain relief, resulting in continued postsurgical pain.

General surgery, colorectal and orthopedic literature have published studies on an FDA-approved, long-acting bupivacaine liposomal injection. [6,7,8,9,10] This new formulation of bupivacaine was shown to provide up to 96 hours of post-operative analgesia with minimal adverse side effects. In a multi-center, randomized, double blind, parallel-group, placebo-controlled phase three study, 189 patients underwent a hemorrhoidectomy procedure and were randomized to either the long-acting bupivacaine or a placebo. Pain intensity scores were significantly lower in the bupivacaine extended-release group in comparison with the placebo group. More patients in the bupivacaine extended-release group remained opioid free from 12 hours to 72 and the more patients were satisfied in the study group with their postsurgical analgesia than in the placebo group.[11] Similar results were reported in the Journal of Pain Research with an overall decrease in pain levels and reduced opioid consumption during the first 72 hours following surgery in several surgical models (total knee arthroscopy, breast augmentation, hernia repair, hemorrhoidectomy, and bunionectomy).[12] Since then, there has been limited research published studying the use of Exparel® in urogynecologic procedures. A study published in January 2018, compared the efficacy of Exparel® versus normal saline when injected directly into both abdominal and vaginal incisions during robotic sacrocolpopexy combined with posterior colporrhaphy.[13] There was no statistically significant difference in pain scores between arms and no serious adverse effects were report. An IRB approved study #399635 was completed at WRNNMC in AUG2017 comparing the efficacy of Exparel® vs normal saline injected in the perineum after urogynecologic surgery for postoperative pain control. This study revealed lower pain scores with the placebo arm (normal saline) with no serious side effects noted with use of Exparel®. We suspect these outcomes were due to location and timing of the injection and how the Exparel® was distributed in the tissues.

Significance:

The FDA indication for Exparel®, a long-acting, liposomal bupivacaine injection is postsurgical analgesia for soft-tissue surgical procedures.[14] A Medline and Pub-Med search revealed limited research in the fields of Urogynecology or Gynecological utilizing this new medication for post-operative analgesia. Urogynecology patients typically have surgical incisions involving the perineum and posterior vagina (soft tissue) and experience post-operative pain shortly after

leaving the operating room. Pain for these patients involves a multi-modal approach, utilizing medications such as intravenous acetaminophen, ketorolac and opioid medications. Many patients are admitted overnight in the hospital to ensure adequate pain control is achieved. Patients are discharged home with a combination of NSAIDs, Tylenol and an opioid for home pain management.

The ability to provide long-acting post-operative analgesia could potentially shorten the hospital stay for these patients, remarkably decrease the number of analgesia tablets consumed, thereby decrease cost to the military system. The Department of Defense price per 20mL vial of Exparel® is approximately $250. Decreasing the potential for adverse effects by minimizing the amount of opioid intake can maximize patient safety. Finally, by providing a single dose injection in the operating room for post-operative analgesia for up to 96 hours, patient satisfaction can be optimized and facilitate a healthy recovery period. Performing a prospective, randomized, double-blinded study evaluating the effectiveness of bupivacaine alone versus bupivacaine plus Exparel® on postsurgical analgesia following Urogynecology surgeries could provide a much-needed alternative for many patients. This information could be utilized throughout the specialty of Gynecology and its surgical sub-specialties.

Literature Review

The FDA indication for Exparel®, a long-acting, liposomal bupivacaine injection is postsurgical analgesia for soft-tissue surgical procedures.[14] A Medline and pub-med search completed on 28FEB2018 revealed limited research in the fields of Urogynecology and Gynecology studying the effectiveness of Exparel® in management of postoperative pain. One study published in January 2018, utilized long-acting, liposomal bupivacaine injection for post-operative analgesia in patient's undergoing mid-urethral sling (anterior vaginal wall). This study by Mazloomdoost, et al. showed decreased postoperative pain in the Exparel® group versus placebo when injecting 30ml total of medication down trocar tracts and directly into the vaginal wall anteriorly as well as decreased narcotic use on postop day two without serious adverse side effects. [15] There was a single case report published in 2016 that reported reversible fecal incontinence after single injection of 20mL Exparel® in the left anterior quadrant of the left anterior transsphincteric perianal fistula. On postoperative day one the patient had numbness in the perianal region and fecal incontinence which then resolved on postoperative day five. [16] Since this procedure operates on the anal sphincter it is difficult to determine if this is known postoperative complication of the surgery itself versus due to the injection of Exparel®. A study by Yeung, et al. published in January 2018, compared the efficacy of Exparel® versus normal saline when injected directly into both abdominal and vaginal incisions during robotic sacrocolpopexy combined with posterior colporrhaphy.[13] They found no difference in pain scores or narcotic use across the two groups with the injectable anesthetic utilized in both abdominal and vaginal incision sites. We suspect these outcomes were due to location and timing of the injection and how the Exparel® was distributed in the tissues.

The general surgery, colorectal, plastics and orthopedic literature have recently published several studies on the Exparel® with up to 96 hours of post-operative analgesia and minimal adverse side effects. [6,7,8,9,10] In a multicenter, randomized, double blind, parallel -group, placebo-controlled phase three study, 189 patients underwent a hemorrhoidectomy procedure and were randomized to either the long-acting bupivacaine or a placebo. Pain intensity scores were significantly lower in the bupivacaine extended-release group in comparison with the group-receiving placebo (141.8 vs 202.5, $p < 0.0001$). More patients in the bupivacaine extended-release group remained opioid free from 12 hours (59%) to 72 hours (28%) after surgery compared with patients receiving placebo (14% and 10%; $p < 0.0008$ through 72 h). The mean total amount of opioids consumed through 72 hours was 22.3 mg and 29.1 mg in the bupivacaine extended-release and placebo groups ($p< 0.0006$). The median time to first opioid use was 14.3 hours in the bupivacaine extended- release group vs 1.2 hours in the placebo group ($p<0.0001$). A greater proportion of patients in the bupivacaine extended-release group were satisfied with their postsurgical analgesia (95% vs 73%, $p <0.0007$) than in the placebo group.[11] Similar results were reported in the Journal of Pain Research with an overall decrease in pain levels and reduced opioid consumption during the first 72 hours following surgery in several surgical models (total knee arthroscopy, breast augmentation, hernia repair, hemorrhoidectomy, and bunionectomy).[12] Baxter et al, A plastic surgery research group published their retrospective review of 10 clinical trials on the effects of Exparel® on wound healing and demonstrated that liposome bupivacaine (Exparel®) given locally at the surgical wound site appeared to have no clinically evident impact on wound or bone healing at doses up to 532 mg across different surgical models. The wound-healing profile of liposome bupivacaine was similar to that of bupivacaine HCl.[17]

The third aim of our study is to evaluate post-operative voiding function and compare the two study groups. In a retrospective paper published in 2012, the investigators noted an increase in the rate of postoperative transient urinary retention following posterior colporrhaphy, 32.4%.[18] T

his rate was compared with another commonly performed Urogynecology procedure, suburethral sling placement (a procedure performed on the anterior vaginal wall). The authors surmised that post-operative pain maybe contributing to transient voiding dysfunction. This has been the only study found to assess voiding function after posterior colporrhaphy. The comparison of these two groups will lend more knowledge to the transient post-operative voiding dysfunction which occurs in some patients and provide information regarding adequate pain control.

Human Subjects Justification

Exparel® is already FDA approved for soft-tissue post-operative analgesia and is currently available at WRNMMC for this indication. In order to evaluate the efficacy of bupivacaine alone versus buplvacaine plus Exparel® for postsurgical pain control in subjects undergoing posterior colporrhaphy, a prospective study is the next most appropriate step.

9.4 Objectives/Specific Aims/Research Questions:

Describe the purpose and objective(s) of the study, specific aims, and/or research questions /hypotheses

Primary objective: Compare the effectiveness of bupivacaine alone versus bupivacaine plus Exparel® in providing adequate pain control following posterior colporrhaphy days one, two and three post-operatively. We hypothesize the group receiving the combined Exparel® and bupivacaine will experience 30% less vaginal pain post-operatively during the first three days following surgery.

Secondary aim: Assess whether the study medication decreases the need for pain medication, specifically opioids, during the post-operative period. We hypothesize the group that receives the combined bupivacaine plus Exparel® will use 30% less rescue pain medication during the first three days following surgery.

Third aim: Evaluate post-operative voiding and defecatory function after posterior colporrhaphy, comparing the bupivacaine plus Exparel® group versus the buplvacaine alone group. We hypothesize there will be no difference in voiding function and defecatory function between the two groups.

Fourth aim: Evaluate the impact pain has on quality of life comparing the bupivacaine plus Exparel® group and the bupivacaine alone group. Quality of life impact will be evaluated by visual analog supplemental question scale. We hypothesize the combined group will have a better quality of life score (lower score) compared with the bupivacaine alone group.

9.5 Study Design:

Describe study design in one to two sentences (e.g., prospective, use of existing records/data /specimens, observational, cross-sectional, interventional, randomized, placebo-controlled, cohort, etc.). Specify the phase – Phase I, II, III, or IV – for FDA-regulated investigational drug research

The study is designed as a prospective, randomized, double-blinded trial.

9.6 Target Population:

Describe the population to whom the study findings will be generalized

Females with vaginal prolapse that will be undergoing urogynecologic surgery (specifically posterior colporrhaphy) to help with post-operative pain control after surgery.

9.7 Benefit to the DoD:

State how this study will impact or be of benefit to the Department of Defense

The ability to provide long-acting post-operative analgesia could potentially shorten the hospital stay for these patients, remarkably decrease the number of analgesia tablets consumed, thereby decrease cost to the military system. The Department of Defense price per 20mL vial of Exparel® is approximately $250. Decreasing the potential for adverse effects by minimizing the amount of opioid intake can maximize patient safety. Finally, by providing a single dose injection in the operating room for post-operative analgesia for up to 96 hours, patient satisfaction can be optimized and facilitate a healthy recovery period. Performing a prospective, randomized, double-blinded study evaluating the effectiveness of bupivacaine alone versus bupivacaine plus Exparel® on postsurgical analgesia following Urogynecology surgeries could provide a much-needed alternative for many patients. This information could be utilized throughout the specialty of Gynecology and its surgical sub-specialties.

10.0 Study Procedures and Data management

10.1 Study Procedures:

Describe step-by-step how the study will be conducted from beginning to end

All female subjects age 18 or older eligible to receive care at WRNMMC and who are scheduled to undergo surgery with the Urogynecology Service with posterior colporrhaphy will be screened for potential recruitment in our postsurgical pain management trial prior to their pre-operative appointment. This will be done by the PI or AI s by reviewing the Urogynecology Service surgical calendar for any upcoming surgeries that involve a posterior colporrhaphy under general anesthesia. The Walter Reed S3 operating room scheduling system will be reviewed to confirm the planned procedures. Those subjects who meet inclusion criteria for the study will be recruited at the time of their pre-operative visit.
** Only the PI and AIs who are also health care providers in this Clinic will have access to the surgical calendar. Also only study team members who are also health care providers will access prospective research participants EMR prior to obtaining HIPAA authorization under HIPAA's Preparatory to Research provision.**

This discussion of the study will occur after the surgical consent form for the scheduled surgery has been signed and when discussion of post-operative pain management is addressed. There is no monetary payment for joining the study and subjects may choose to leave the study at any point during the study without consequence. Regardless of the decision to participate in the study or which treatment group assignment, all subjects will have the same options for post-operative pain medications. They will still receive the same high standard of care from our Service. Study participants will review the study consent form in detail with a surgeon--also an Associate Investigator or part of the surgical team in the study (delegated authority). The subject will be given a copy of the signed consent and a copy will remain on file in a locked cabinet in the Urogynecology Clinic.

During the consenting process, potential study subjects will be informed that the purpose of the study is compare the efficacy of 0.25% plain bupivacaine alone versus 0.25% plain bupivacaine plus 1.3% long-acting liposomal bupivacaine (Exparel®) on post-operative vaginal pain following Urogynecology surgical procedure involving the posterior vaginal wall. These medications are FDA (Food and Drug Administration) approved and are currently being used in our hospital by other surgical sub-specialties as part of a multi-modal approach to post-operative pain control. There will be no additional time spent under anesthesia as a participant in our study.

They will be informed that the study is designed as a double blind, randomized study. This means neither the surgeon nor the subject will know which group a subject is assigned to until completion of the study. Randomization will occur using a computer-generated randomization program carried out in the Investigational Pharmacy with block randomization. If a potential subject chooses to participate, she will be randomized by the pharmacy to one of two groups, either an 20mL injection of 0.25% plain bupivacaine or an 20mL injection of bupivacaine (10ml) plus 1.3% long-acting liposomal bupivacaine (10mL) that will be injected in the subject's vagina at the level of the ischial spines at the beginning of the case (prior to incision) while she is under general anesthesia in the operating room.

The primary goal of the study is to assess how effective the study medications are in providing adequate pain control for the vaginal area following surgery; therefore, the subjects' post-operative pain will be assessed at various intervals following their procedure. On post-operative day one, approximately 24 hours post-operative, subjects will be asked questions regarding their pain level on their abdomen and in their vaginal area utilizing an 11 point visual pain scale. Both

vaginal and abdominal pain will be assessed as some patients will be undergoing concurrent surgeries in the pelvis (for example but not limited to hysterectomies, suspension procedures, etc). Subjects will also be asked about their bowel movements and any associated pain, again, using the same pain rating scale. Subjects will also be asked to the impact the pain has on 4 quality of life measures using an 11-point visual pain scale. Subjects will also be called or contacted via email thru Relay Health on post-op day two and on post-op day three to assess pain on those days. Part of the study's goal is to assess whether the study medication provides pain control for longer than the acute (24 hour) period. Subjects will be given the visual pain scales to go home with so that they can reference it during their post-operative phone or email follow-ups. Additionally, subjects will be asked to gather their pain medication bottles in order to count out the remaining pills in each bottle. This will allow us to determine the amount of oral pain medication used since surgery. Subjects will be asked on the final day, post-operative day 3 which medication they think they received.

Following review of the study and obtaining of a consent form, the pain scale on the visual analog scales will be reviewed with the subject. Subjects must be willing to speak with a member of the Urogynecology Service on post-operative day one, two, and three regarding their post-operative pain, medications and bowel movements. For the majority of subjects admitted for inpatient care following surgery, completion of day one data will occur in the hospital approximately 24 hours post-operatively, prior to hospital discharge. The subject will be asked to indicate whether they prefer contact via phone or by email, using the Relay Health Network for day two and three. A maximum of three attempts will be made to contact the subject on their designated follow up date, between the hours of 0800 and 2000. We will attempt to collect the data during midday for all patients. Time of inquiry and number of hours postop will be annotated. At the conclusion of the pre-operative visit, the subject will be reassured that if they desire removal from the study at any time, there will be no change in their customary post-operative care. Subjects will pick up their discharge post-operative pain medications prior to their surgery date (as is customary in our clinic).

The data sheet with subject identification will be the only identifying information on the sheet. The subject's pre-operative demographic data (gravida/parity, age, BMI, past medical history, past surgical history, allergies, current medications, history of significant drug or alcohol dependence) will be annotated on this data sheet along with the post-operative pain medications she receives. The data sheets will be kept in a locked cabinet within the Urogynecology Clinic, in a room locked during off-hours. A master list of subjects' full names and the subjects or their sponsor's last four of the social security number will be kept on a computer in the Urogynecology office that is password protected. The dates of enrollment surgery will be annotated on the master list as well. Follow-up phone call dates/email replies will be collected as well. Subjects will be re-assured that her participation in the study will be completely confidential and her identifying information will be double-locked when not being reviewed. Subjects may choose to have their allocated study arm disclosed at the completion of entire study.

On the day of surgery, the operating surgeon and team will meet with subject prior to the administration of anesthesia, review the operating plan and her consent for enrollment in our study. We will review our requirement to contact her on day one, two, and three. Any last minute questions can be answered and the subject may withdraw from the study at this time if desired.

The Investigational Pharmacy will randomize each subject to either bupivacaine alone group or bupivacaine plus Exparel® group and blind four 5mL syringes containing a total of 20ml of either 0.25% plain bupivacaine or 10ml of 0.25% bupivacaine plus 10ml of 1.3% liposomal bupivacaine (total of 4 injection sites). Syringe barrels will be covered with solid white labels to mask syringe contents. The Investigational Pharmacy will also print out a label to accompany the syringes to the Operating Room on the day of surgery stating:

"This subject is enrolled in study protocol #_____ and is to receive no additional bupivacaine post-operatively for 96 hours. "

This label will be placed in the subject's paper chart on the day of surgery. All subjects will have the same pharmacy label placed in their chart. It will assure that those subjects who receive liposomal bupivacaine will not receive additional injectable anesthetic but will still maintain blinding of all involved in the protocol.

During TEAM STEPPS, the surgeon will notify the anesthesiologist of the protocol and provide the anesthesiologist with a copy of the FDA handout on the 1.3% liposomal bupivacaine. We will answer any questions the operating team may have.

Once the patient is brought back to the OR and once general anesthesia is adequate, the circulating room nurse will remove the study syringes from the bag, verify the subject's name and date of birth and hand the four 5mL blinded syringes to the surgical assistant, who will

attach a 20 gauge injection needle to the first of the syringes. The assistant will then hand the first syringe to the operating surgeon. The surgeon will notify anesthesia prior to injecting study medication. The surgeon will identify the bilateral ischial spines. The first 5ml syringe will be injected. The syringe and needle will be handed back and the surgical tech will reload the needle on the next syringe (this will be repeated for all 4 blinded syringes). These 4 injections (5ml of medication at each injection site) will be placed on both the left and right sidewall of the vagina at the level of the ischial spines. After the injections have been performed, the operating team will perform the planned surgeries, using standard technique. At the completion of the surgery, the team will resume normal post-procedure care. The operating surgeon will verify the study protocol identification sticker has been placed in the subject's paper chart. Surgeon will annotate at this time which medication they feel they injected to evaluate blinding method.

Post-operatively, the subject will recover in the PACU per WRNMMC protocol and be transferred to either the floor or discharged home as per routine post-operative criteria. Post-operative pain control will be managed in the PACU as per routine protocol. Inpatient and home pain control will be managed by the Urogynecology team. Further injections of pain medications will not be given in the vagina outside of the operating room.

On post-operative day one, for inpatient subjects, any vaginal packing that has been placed will be removed and a voiding trial will be attempted. The presence or absence of vaginal packing along with the pass/fail of the voiding trial will be annotated on the data sheet. Once the subject has met discharge criteria (can ambulate her on own, tolerate a regular diet, pain is well controlled on oral pain meds, and a voiding trial has been attempted), the discharge order will be placed. A member of the surgical team will visit the subject prior to final discharge in order to obtain a pain rating from the patient referencing The Defense and Veteran's Pain Rating Scale (a visual analog pain scale) and impact on quality of life rating (0-10) asking about how pain is affecting activity, sleep, mood, and stress on the DOD/VA Pain Supplemental Questions (validation of the DVPRS Scale, see attachments and reference #19). These two forms will be further referenced as visual analog pain scales for the rest of this document. This will be documented as day one data. Subjects will be sent home with a minimum of 2 copies of the pain scale (one from their pre-operative visit and a 2nd copy provided with the hospital post-operative discharge paperwork). Post-operative care instructions will be reviewed and the subject will be reminded to expect a follow-up phone call or email via Relay Health on day two and three. The time the discharge order is placed will be recorded as well.

During each post-operative encounter, subjects will be asked to refer to their visual analog scale and their pain medication bottles. On post-operative day one (for subjects that were not admitted), two, and three, the subject will be contacted by one of the study Associate Investigators or member of the surgical team and asked the following questions.

- Would you please locate your visual analog pain scale and the bottles of medication given to you at discharge?
- Looking at the pain scale, how would you please rate your pain in your vagina from 0-10?
- Ms. _____, have you had a bowel movement since surgery?
- Did you experience pain during your bowel movement?
- If yes, what was the pain associated with this, using the same scale?
- How has the pain interfered with your usually activity from 0-10?
- Please rate how your pain interefers with your ability to sleep using the same scale?
- How has the pain affected your mood from 0-10?
- How has the pain contributed to your stess from 0-10?
- I would now like you to look at each of your pill bottles and tell me the names of the medications.
- Please count for me the number of pills remaining in that bottle.

All data sheets will be collected at the completion of each surgical day and placed in the locked cabinet. Surgical team members will have access to sheets to record data as it is collected. The data sheets will be held for a minimum of three years and then shredded and disposed in a HIPAA compliant recepticale per WRNMMC protocol. All consents and HIPAA authorizations will be maintined for six years after the study is closed. The Principal Investigator, will be available for debriefing of any subject after the study is completed if the subject desires.

10.2 Data Collection:

Describe all the data variables, information to be collected, the source of the data, how the data will be operationally measured, and approvals needed for use of information from DoD databases

For this research study, the research team will collect information regarding the subject's pain level after her surgery, ratings on 4 quality of life questions (activity, sleep, mood, and stress), a nd any pain medications the subject took to treat her pain. The research team will be collecting this information for three days after subject's surgery. Additionally, the research team will be collecting basic data like age, weight and height calculation (BMI or Body Mass Index), date of surgery, type of surgery, and any difficulty subject had emptying her bladder after subject's surgery.

The following PHI data elements will be collected:

- Names
- Dates including all elements (except year) directly related to an individual, including birth date, admission date, discharge date, and date of death
- Ages over 89 and all elements of dates (including year) indicative of such age, unless you will only request a single category of "age 90 or older"
- Telephone numbers
- Social Security numbers (SSNs)
- Medical record numbers
- DoD ID Number "

10.3 At any point in the study, will you request, use, or access PII from the Military Health System (MHS)?

◉ Yes ○ No

10.4 Have you consulted with an MHS data expert to determine the data elements to be extracted or the information system(s) to access?

Consulting with a data expert often saves time later in the compliance process because the data expert can advise on the data available in the numerous MHS information systems, the quality of that data and the methods for encrypting and collapsing data. To schedule a consult with an MHS data expert, send an email to: (**dha.ncr.pcl.mbx.privacyboard@mail.mil**)

○ Yes, then complete the questions below according to the data consult

◉ No, then complete the questions below according to the best of your knowledge (NOTE: It is highly recommended that you work with an MHS data expert)

10.5 Indicate whether you plan to receive a data extract from the MHS or plan to access an information system directly to create a data set:

A data extract is when the MHS or a contractor provides the data set directly to the researcher. When receiving a data set through data extract, the researcher may indicate whether the data elements should be provided as is, encrypted or collapsed. In contrast to a data extract, access to an information system means that the researcher may directly access an MHS information system and create a data set for the research study

☐ Data Extract
☑ Access

10.6 Do you intend to use only de-identified data from the MHS in your research study?

There are different two methods for de-identifying data pursuant to HIPAA:
1) Safe Harbor Method: Removing all of the identifiers listed in Table 1 below, provided that the researcher does not have actual knowledge that the remaining data can be used alone or in combination with other information to identify the individual who is the subject of the information
2) Statistical Method: An expert, with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable, determines that the data is not individually identifiable

○ Yes ◉ No

10.7 If your research study requires access to an MHS information system, please indicate the system to obtain data:

If you do not know which system(s) contain the data elements you need, refer to the Guide for DoD Researchers on Using MHS Data or seek guidance from an MHS data expert:

PHI Systems:

MHS Information System	Requesting Data
: ESSENTRIS	: Yes
: AHLTA	: Yes
: CHCS	: Yes

PII-Only Systems:

MHS Information System	Requesting Data
No records have been added	

De-Identified Data & Other Systems:

Information System	Requesting Data
Expense Assignment System	: No
List other system(s):	
List other system(s):	

10.8 Do you intend to merge or otherwise associate the requested data with data from any sources outside of the MHS, including other DoD systems that are not part of the MHS?

- ○ Yes, will merge data
- ◉ No, will not merge data

10.9 Indicate the categories of data that you will request from MHS systems or MHS health care providers about research participants or relatives, employers, or household members of the research participants.

Data Element(s)	MHS	Non-MHS Systems
1. Names	☑	☐
2. Postal address with only town, city, state and zip code	☐	☐
3. Postal address with all geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of Census: 1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and 2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000	☐	☐
4. Dates including all elements (except year) directly related to an individual, including birth date, admission date, discharge date, and date of death	☑	☐
5. Ages over 89 and all elements of dates (including year) indicative of such age, unless you will only request a single category of "age 90 or older"	☑	☐
6. Telephone numbers	☑	☐

7. Fax numbers	☐	☐
8. Electronic mail addresses	☑	☐
9. Social Security numbers (SSNs)	☑	☐
10. Medical record numbers	☑	☐
11. Health plan beneficiary numbers	☐	☐
12. Account numbers	☐	☐
13. Certificate/license numbers	☐	☐
14. Vehicle identifiers and serial numbers, including license plate numbers	☐	☐
15. Device identifiers and serial numbers	☐	☐
16. Web Universal Resource Locators (URLs)	☐	☐
17. Internet Protocol (IP) address numbers	☐	☐
18. Biometric identifiers, including finger and voice prints	☐	☐
19. Full-face photographic images and any comparable images	☐	☐
20. Any other unique identifying number, characteristic, or code (DEERs ID, EDIPN, Rank)	☑	☐

If you are obtaining SSNs, provide a justification as to why and explain why a substitute cannot be used

Plan to utilize DOD ID numbers where available. CHCS, AHLTA requires SSNsto access charts; and Essentris utilizes DoD ID to find the patient.

Social security numbers will be collected to properly identify the subject during surgery, to order prescriptions, for pharmacy to monitor study medication, and to write physician orders/notes in AHLTA/Essentris/CHCS if unable to utilize DOD ID number.

10.10 Is it possible that the data will become identifiable because of triangulation, a small cell size, or any unique data element(s)?

Triangulation means using different data elements that are not themselves identifiable but that when combined can be used to identify an individual. For example, triangulation would be using rank and race together to determine the identity of an individual with a particular health condition.
Small cell size means that there are only a small number of eligible individuals that satisfy the category description. Guidance for acceptable cell size is available from the Centers for Medicare and Medicaid Services. For example, the rank category of four star generals with a particular diagnosis may be less than 30 so the rank category may need to be expanded to include lower ranks
A unique data element includes any unique features that are not explicitly enumerated in the categories of data in rows 1 – 19 of Table 1 above, but that could be used to identify an individual. Examples of unique data elements include: 1) a unique number, such as a medical record number or EDIPN; 2) a unique code, such as a diagnosis code or a bar code on an electronic health record; and 3) any unique characteristic, such as the rank of general or admiral, or a race or gender combined with another unique characteristic

- (●) Yes, there is a reasonable possibility the data will become identifiable
- ( ) No, there is no reasonable possibility the data will become identifiable

10.11 HIPAA Privacy Rule and Use of Protected Health Information in Research:

- ( ) N/A – will not use or disclose protected health information (PHI)
- (●) HIPAA Authorization will be obtained
- ( ) Use of a limited data set where a data use agreement will be obtained
- ( ) Waiver/alteration of HIPAA Authorization is being requested

10.12 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for this Study:

Include in this section the plan for acquiring data (both electronic and hard copy), access during the study, data/specimen storage and length of time stored, shipment/transmission, and the plan for storage and final disposition at the conclusion of the study. Describe any data agreements in place for accessing data within and/or outside of your institution (e.g., Data Sharing Agreement, Data Use Agreement, Business Agreements, etc.)

Initial data will be collected at the pre-operative counseling and study consenting appointment. Information to include PHI will be annotated on Data Collection Sheet (entitled Posterior Colporrhaphy Data Sheet). Subject will be asked past medical and surgical history. Will also obtain information from ALTHA, Essentris, and CHCS1. Pre-operative pain level will be annotated using the visual analog pain scale (0-10) at the pre-operative appointment, on post-operative day one, two, and three. Subjects will be contacted either by telephone or by email (via Relay Health) on post-operative day one, two, and three. All information will be recorded on the Data Collection Sheet.

All data sheets will be collected at the completion of each surgical day and placed in the locked cabinet in a locked office. The data sheets will be kept in a locked cabinet within the Urogynecology Clinic on the 2nd floor of building 10 in a room locked during off-hours. A master list of subjects' full names, electronic email addresses, and sponsor's last four of the social security number will be kept on a computer in the Urogynecology office that is password protected and can only be access by the Research Team (PI, AIs, study coordinators, and nurses). Members of the surgical team and the Associate Investigators will have access to sheets to record data as it is collected. The Primary Investigator, will be available for debriefing of any subject after the study is completed if the subject desires. The PI will also be available for any questions during the course of the study.

All data will be entered into an Excel spreadsheet, analyzed with the assistance of a biostatistician, and recorded on a government issued computer excel database that is password and CAC card protected,

These sheets will be stored here for the duration of the study and required time per the IRB after completion of the study.

Maintain Study Files: Principal Investigator agree to maintain a Study File that must be kept for three years from the date the study is closed (32 CFR 219.115(b) and that HIPAA authorizations will be retained for 6 years after the study is closed and provided to WRNMMC upon request. PI acknowledges that research data are the property of the Command and will not be removed without prior approval. When PI is scheduled to permanent change of station (PCS) or end of time in service (ETS), study records will be given to a new PI, the Department Chief.

10.13 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for Future Research:

If the study involves collecting, storing, or banking human specimens, data, or documents (either by the Investigator or through an established repository) for FUTURE research, address. How the specimens/data will be used, where and how data/specimens will be stored (including shipping procedures, storage plan, etc.), whether and how consent will be obtained, procedures that will fulfill subjects' request as stated in the consent, whether subjects may withdraw their data/specimens from storage, whether and how subjects may be recontacted for future research and given the option to decline, whether there will be genetic testing on the specimens, who will have access to the data/specimens, and the linkage, the length of time that data/specimens will be stored and conditions under which data/specimens will be destroyed

N/A

11.0 Statistical/Data Analysis Plan

11.1 Statistical Considerations:

List the statistical methods to be used to address the primary and secondary objectives, specific aims, and/or research hypotheses. Explain how missing data and outliers will be handled in the analysis. The analysis plan should be consistent with the study objectives. Include any sub-group analyses (e.g., gender or age group). Specify statistical methods and variables for each analysis. Describe how confounding variables will be controlled in the data analysis

Refer to section 11.2 and 11.3 for statistical consideration.

11.2 Sample Size Estimation:

In a previous randomized placebo-controlled study of the effect of Bupivacaine extended-release liposome injection in patients undergoing hemorrhoidectomy, the mean (standard deviation) for the total amount of opioid rescue medication (in morphine equivalents) for the bupivacaine and placebo groups were:
Time post-surgery Bupivacaine (long acting) 1.3% Placebo
through 12 hours 6.2(8.2) 14.7(10.7)
through 24 hours 11.3(11.8) 20 (13.5)
through 72 hours 22.3 (21.0) 29.1 (20.7)

Controlling the probability of a Type I error at alpha = 0.05, a sample of 21 subjects per group (total of 42 subjects) would have 80% power to detect an effect size similar to what was seen in the Gorfine study at 12 hours: For the difference seen at 24 hours, a total of 70 subjects would be required, and for the 72 hour difference, a total of 300 subjects would be required.
In the Gorfine study, the overall pain level for the entire 72 hour period was reported as 141.8 for the bupivacaine group compared to 202.5 for the placebo group. The common standard deviation is assumed to be 104.3. This corresponds to a 30% improvement in pain from placebo. Controlling the probability of a Type I error at alpha = 0.05, a sample of 48 subjects per group

would have 80% power to detect a similar difference in pain scores (total of 96 subjects). Allowing for a 20% dropout rate, of up to 120 subjects will be recruited for the study.

11.3 Data Analysis Plan:

1. As per the CONSORT guidelines for randomized controlled trials, a patient flow diagram will be presented to describe recruitment, exclusions, randomization, dropouts, loss to follow-up and subjects included in the analysis.
2. Distributions of continuous data will be examined for normality using the Shapiro-Wilk test, and histograms. Baseline demographic and clinical characteristics for the bupivacaine alone and bupivacaine plus Exparel® groups will be presented using means with standard deviations for normally distributed data, medians with interquartile ranges or counts with proportions.
3. Blinding will be described using the proportion of surgeons who guessed correctly.
4. The primary outcome of interest is the subject's vaginal pain score on a numerical rating scale from 0-10, completed preoperatively, and on postop day 1, 2, 3. Postoperative day one will be the same for all patients, defined as the day after surgery. This will be the same regardless if patients are discharged home the same day of surgery or stay overnight. Groups will be compared using generalized estimating equations (GEE), with the within subject factor 'time' and the between subject factor, treatment. Additional confounders may be added to the model to include type of surgery (vaginal alone vs. vaginal+abdominal) pain medication use, and age. It is assumed that pain levels will differ between groups through postop day 1, and then approach similar levels by days 2 and 3. Pain scores for day 3 will be analyzed separately and compared using the Wilcoxon rank sum test. Abdominal pain scores will be analyzed using the same methods.
5. A secondary aim will be additional pain medications used, converted to morphine equivalent levels, as of each postop period (i.e. day 1, day 2, day 3). Postoperative day one will be the same for all patients, defined as the day after surgery. This will be the same regardless if patients are discharged home the same day of surgery or stay overnight. Groups will be compared using a GEE model as specified above.
6. To fulfill our third aim, voiding outcomes will be compared between groups using Fisher's exact test.
7. A fourth aim to be explored will be the impact of pain on quality of life based on a rating scale from 0-10, completed on admission, and on postoperative day 1, 2, and 3.

12.0 Participant Information

12.1 Subject Population:

Female, DEERS eligible subjects over the age of 18 who receives care at WRNMMC to undergo surgery for posterior colporrhaphy at the Urogynecology Service.

The maximum number of subjects that will be enrolled/consented at WRNMMC is 120 individuals.

12.2 Age Range:

- ☐ 0-17
- ☑ 18-24
- ☑ 25-34
- ☑ 35-44
- ☑ 45-54
- ☑ 55-64
- ☑ 65-74
- ☑ 75+

12.3 Gender:

☐ Male
☑ Female

12.4 Special categories:

☐ Minors /Children - "You must also consider the requirements of 45 CFR 46 Subpart D and DoDI 3216.02, Enclosure 3, paragraph 7.d."
☑ Students
☑ Employees - Civilian - "You must also consider the requirements of DoDI 3216.02, paragraph 7.e."
☐ Employees - Contractor
☑ Resident/trainee
☑ Cadets /Midshipmen - "You must also consider the requirements of DoDI 3216.02, Enclosure 3, paragraphs 7.e. and 12."
☑ Active Duty Military Personnel - "You must also consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e."
☑ Wounded Warriors - "Depending on your intended subjects' status, you may also need to consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e."
☐ Economically Disadvantaged Persons - "You must also consider the requirements of 32 CFR 219.111(b)."
☐ Educationally Disadvantaged Persons - "You must also consider the requirements of 32 CFR 219.111(b)."
☐ Physically Challenged (Physical challenges include visual and/or auditory impairment)
☐ Persons with Impaired Decisional Capacity - "You must also consider the requirements of 10 USC 980."
☐ Prisoners - "You must also consider the requirements of 45 CFR 46 Subpart C and DoDI 3216.02, Enclosure 3, paragraphs 7.b. and 7.c."
☐ Pregnant Women, Fetuses, and Neonates
☐ Non-English Speakers
☐ International Research involving Foreign Nationals - Headquarters Review is necessary

12.5 Inclusion Criteria:

Order Number	Criteria
1	Females >18 years of age
2	Patients are DEERS eligible health care beneficiaries.
3	Patients undergoing Urogynecologic surgery involving the posterior vaginal wall mucosa or muscularis including posterior colporrhaphy at Walter Reed National Military Medical Center.
4	Patients must be able to read and understand written English or have an appropriate certified medical translator available.

12.6 Exclusion Criteria:

Order Number	Criteria
1	Known allergy to amide local anesthetics
2	Unstable cardiac arrhythmia

3	Hepatic impairment (including but not limited to patients under the care of their physician for severe hepatic disease, cirrhosis or hepatic cancer)	
4	Known pregnancy at time of surgery (pregnancy test morning of surgery if applicable)	
5	Regular use of narcotic pain medication, defined as use on most days of week at any time in the three months prior to surgery	
6	Significant history of opioid or alcohol abuse or addiction (requiring treatment)	
7	Concurrent pain management requiring the use of epidural anesthesia	

13.0 Recruitment and Consent

13.1 Identification and Selection of Subjects:

All female subjects 18 years of age or older eligible to receive care at WRNMMC and who are scheduled to undergo surgery with the Urogynecology Service will be screened for potential recruitment in our locally injected anesthetic postsurgical pain medicine trial prior to their pre-operative appointment. The Urogynecology Service surgical calendar will be reviewed for any upcoming surgeries that involve a posterior colporrhaphy under general anesthesia. The Walter Reed S3 operating room scheduling system will be reviewed to confirm the planned procedures. Those subjects who meet inclusion criteria for the study will be recruited at the time of their pre-operative visit. Discussion of the study will occur after the surgical consent form for the scheduled surgery has been signed and when discussion of post-operative pain management is addressed. Consents will be signed at that time.
These functions will be perfomed by the PIs and AIs who are health care providers here at WRNMMC.

All discussion of the study will take place after the clinical appointment has ended.

13.2 Recruitment Process:

Refer to section 13.1 for more information regarding recruitment process.

All discussion of the study will take place after the clinical appointment has ended.

13.3 Compensation for Participation:

There is no monetary payment for joining the study

13.4 Eligibility Assessment Process:

Refer to section 13.1 for more information regarding recruitment process.

13.5 Consent Process:

Are you requesting a waiver or alteration of informed consent?

○ Yes ◉ No

Please explain the consent process:

Informed Consent Process

Discussion of the study will occur after the surgical consent form for the scheduled surgery has been signed and when discussion of post-operative pain management is addressed. Study participants will review the study consent form in detail with the member of the surgical team or the Associate Investigators, in the study. The subject will be given a copy of the signed consent and a copy will remain on file in a locked cabinet in the Urogynecology Clinic. Regardless of the decision to participate in the study or which treatment group assignment, all subjects will have the same options for post-operative pain medications. Subjects may choose to leave the study at any point during the study without consequence. They will still receive the same high standard of care from our Service. There will be no additional time spent under anesthesia as result of being enrolled in our study.

On the day of surgery, the operating surgeon and team will meet with subject prior to the administration of anesthesia, review the operating plan and the consent for enrollment in our study. We will review our requirement to contact the subject on day one, two, and three. Any last minute questions can be answered for the subject's understanding and she may withdraw from the study at this time if desired.

13.6 DoDI 3216.02 requires an ombudsman to be present during recruitment briefings when research involves greater than minimal risk and recruitment of Service members occurs in a group setting. If applicable, you may nominate an individual to serve as the ombudsman.

- (•) N/A
- ( ) Propose ombudsman

13.7 Withdrawal from Study Participation:

Explain the process for withdrawal and specify whether or not the subjects will be given the opportunity to withdraw their data their data/specimens in the event they wish to withdraw from the study

On the day of surgery, the operating surgeon and team will meet with subject prior to the administration of anesthesia, review the operating plan and the consent for enrollment in our study. We will review our requirement to contact the subject on day one, two, and three. Any last minute questions can be answered for the subject's understanding and she may withdraw from the study at this time if desired. Withdrawal from the study will not cancel scheduled surgery. Subject can decided to withdraw from study participation at any time by informing the PI or research staff via phone, in-person, in wiriting, or electronic mail.

14.0 Risks and Benefits

14.1 Risks of Harm:

Identify all research-related risks of harm to which the subject will be exposed for each research procedure or intervention as a result of participation in this study. Consider the risks of breach of confidentiality, psychological, legal, social, and economic risks as well as physical risks. Do not describe risks from standard care procedures; only describe risks from procedures done for research purposes

Potential risks associated with participating in this study are the risks associated with the drug itself, which is FDA approved for surgical site anesthesia[13]. We will not be utilizing more than 20mL of local injectable bupivicaine in either group. Either 20mL of 0.25% plain bupivacaine or combined 10 mL of 0.25% plain bupivacaine plus 10mL (266 mg) volume of the 1.3% long-acting liposomal bupivacaine in our study. An anesthesiologist will be monitoring the subject's vitals (subject will still be under anesthesia) during the injection of the study medications and while in the immediate post-operative

period to evaluate for possible acute allergic reaction. The surgeon will be alerted immediately of any change per Walter Reed protocol.

The safety of Exparel® was evaluated in ten randomized, double blind, local administration into the surgical site clinical studies involving 823 patients undergoing various surgical procedures. Patients were administered a dose ranging from 66 to 532 mg of Exparel®1.3%. In these studies, the most common adverse reactions (incidence greater than or equal to 10%) following Exparel® administration were nausea, constipation, and vomiting. The common adverse reactions (incidence greater than or equal to 2% to less than 10%) following Exparel® administration were pyrexia, dizziness, edema peripheral, anemia, hypotension, pruritus, tachycardia, headache, insomnia, anemia postoperative, muscle spasms, hemorrhagic anemia, back pain, somnolence, and procedural pain.

Risks are associated with any surgery to include infection. If subject experiences a fever greater than 100.4°F, increase in redness or swelling to the surgical site or an increase in discharge, she should contact the surgeon immediately or go to the emergency room. We will not be deviating from standard operating procedures for the subject's surgery.

The principal investigator will keep all research records. The records may be looked at by staff from the Walter Reed (WRNMMC) Department of Research Programs, the Walter Reed (WRNMMC) Institutional Review Board (IRB), the DoD Higher Level Review, and other government agencies, such as the Food and Drug Administration (FDA), as part of their duties.

These duties include making sure that the research participants are protected. Confidentiality of all records will be protected to the extent possible under existing regulations and laws but cannot be guaranteed. Complete confidentiality cannot be promised, particularly for military personnel, because information bearing on subject's health may be required to be reported to appropriate medical or command authorities. Information about the code will be kept in a secure location and access limited to authorized research study personnel.

14.2
Measures to Minimize Risks of Harm (Precautions, safeguards):

For each research procedure or intervention, describe all measures to minimize and/or eliminate risk of harms to subjects and study personnel

1. Safety Monitoring Plan
We will be placing a sticker label in every subject's surgical chart identifying her as a participant in our study and they are NOT to receive any additional local anesthetic for 96 hours. This is to ensure subject does not receive more than recommended dose in 96 hours.

We will also be counseling subjects at their pre-operative appointment and prior to discharge home on the signs of infection (fever, increased operative site pain, purulent discharge), which is a risk of any surgery in the urogenital tracts (cited as 2.4-7.7% with all clean-contaminated surgeries). All subjects will receive operative antibiotics as indicated. All subjects will be given written instructions for standard post-operative care on their discharge paperwork along with phone numbers to contact the Urogynecology Division, the Gynecology on-call physician and the Walter Reed Emergency room if any concerns arise. Subjects will be questioned at each interaction regarding the concern for infection and evaluated as soon as possible, as is customary in our Service.

Our surgical technique and choice of antibiotics for our subjects will not be changed based on their enrollment in the study. The only difference is the injection of either plain bupivacaine versus bupivacaine plus Exparel®.

2. Safety Analysis Plan
We will perform an interim analysis after 30 subjects to assess safety. Discontinuation or temporary suspension will be discussed with safety monitor, research team and investigational pharmacy if we see an infection rate of 15% higher than the typical surgical infection rate of 2.4-7.7% (clean-contaminated surgeries) at this interim analysis and this will be reported to IRB within the required time frame.

14.3 Confidentiality Protections (for research records, data and/or specimens):

Describe in detail the plan to maintain confidentiality of the research data, specimens, and records throughout the study and at its conclusion (e.g., destruction, long term storage, or banking). Explain the plan for securing the data (e.g., use of passwords, encryption, secure servers, firewalls, and other appropriate methods). If data will be shared electronically with other team members/collaborators outside the institution, describe the method of transmission and safeguards to maintain confidentiality. Explain whether this study may collect information that State or Federal law requires to be reported to other officials or ethically requires action, e. g., child or spouse abuse

Subject data will be stored in a locked cabinet in an office in the Urogynecology Division clinic, Building 9. A master list of subjects' full names and the last four of their social security number will be kept on a computer in the Urogynecology office that is password protected. All data will be recorded on a government issued computer excel database that is password and CAC card protected. Once a patient is enrolled in the study, the PI or AIs will assign a subject identifier (001, 002, 003, etc) and enter this identifier on the data sheet. All data sheets will be collected at the completion of each surgical day and placed in the locked cabinet.

The data sheets, data files and master code will be held for a minimum of three years and then shredded and disposed in a HIPAA compliant recepticale per WRNMMC protocol. The combined informed consent document with HIPAA Authorization will be held for a minimum of 6 years and then shredded and disposed in a HIPAA compliant recepticale per WRNMMC protocol. The Principal Investigator will be responsible for destroying this information.

All electronic data will be deleted from the computer and then the trash bin after the mandatory storage time.

14.4 Potential Benefits:

Describe any real and potential benefits of the research to the subject and any potential benefits to a specific community or society

If the individuals in the research are considered experimental subjects (per 10 USC 980), and they cannot provide their own consent, the protocol must describe the intent to directly benefit all subjects

Subjects may benefit by having a decrease in the postsurgical pain, pain medication use, decrease risk of opioid associated adverse effects, and improved quality of life.

14.5 Privacy for Subjects:

Describe the measures to protect subject's privacy during recruitment, the consent process, and all research activities, etc.

The subject's privacy will be protected by performing all study procedures in a private room; this includes obtaining consent and medical history, performing exams, and test. The only personnel that will be present will be the study investigators, research coordinator, and staff, such as nurses, who will perform procedures under the direction of the study investigator. The subject and his or her family member(s) or spouse will be made to feel at ease by limiting the number of personnel present, and encouraging the subjects to ask questions and notify the staff if he or she is uncomfortable in any way.

14.6

Incidental or Unexpected Findings:

Describe the plan to address incidental findings and unexpected findings about individuals from screening to the end of the subject's participation in the research. In cases where the subject could possibly benefit medically or otherwise from the information, state whether or not the results of screening, research participation, research tests, etc., will be shared with subjects or their primary care provider. State whether the researcher is obligated or mandated to report results to appropriate military or civilian authorities and explain the potential impact on the subject

Participants will be informed of any incidental findings. Depending on the type of incidental finding, the participant may be contacted by phone. In the case of a potential serious emergency, the PI or designee will be responsible for informing the participant right away. Participants will not have an option to decline receiving information about an incidental finding. A qualified person (usually a member of the research team) will talk with the participant if there is an incidental finding. The participant will be referred to an appropriate doctor for further evaluation.

15.0 Study Monitoring

15.1 Data Monitoring Plan:

Describe the plan to monitor the data to verify that data are collected and analyzed as specified in the protocol. Include who will conduct the monitoring, what will be monitored and the frequency of monitoring

The PI and associate investigators will conduct a weekly review of the data sheets.

During the review, they will assess the data sheets for completion to ensure patients have been contacted and pain scores, QOL scores, number of remianing medication have been recorded for days 1, 2, and 3.

15.2 Safety Monitoring Plan:

Describe the plan to monitor the data to ensure the safety of subjects

We will be placing a sticker label in every subject's surgical chart identifying her as a participant in our study and they are NOT to receive any additional local anesthetic for 96 hours. This is to ensure subject does not receive more than recommended dose in 96 hours.

We will also be counseling subjects at their pre-operative appointment and prior to discharge home on the signs of infection (fever, increased operative site pain, purulent discharge), which is a risk of any surgery in the urogenital tracts (cited as 2.4-7.7% with all clean-contaminated surgeries). All subjects will receive operative antibiotics as indicated. All subjects will be given written instructions for standard post-operative care on their discharge paperwork along with phone numbers to contact the Urogynecology Division, the Gynecology on-call physician and the Walter Reed Emergency room if any concerns arise. Subjects will be questioned at each interaction regarding the concern for infection and evaluated as soon as possible, as is customary in our Service.

Our surgical technique and choice of antibiotics for our subjects will not be changed based on their enrollment in the study. The only difference is the injection of either plain bupivacaine versus bupivacaine plus Exparel®.

15.3 Does your study require independent data and safety monitoring?

○ Yes ◉ No

16.0 Reportable Events

16.1 Reportable Events:

Consult with the research office at your institution to ensure requirements are met
• Describe plans for reporting expected adverse events. Identify what the expected adverse events will be for this study, describe the likelihood (frequency, severity, reversibility, short term management and any long term implications of each expected event)
• Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the research protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event

Expected adverse events which are not serious are reported on the Continuing Review (CR) Progress Report CR is generally performed on a 12-month cycle. More frequent Progress Reports may be required at the discretion of the IRB.

Serious Adverse Events: The PI, within 24 hours, must report all related or possibly-related AND serious adverse events (SAE) occurring in subjects enrolled at WRNMMC . This is accomplished by submitting an adverse event report to the IRB via IRBNet. For protocols involving investigational drugs or devices, the investigator must also report a serious adverse event to the sponsor of the IND or IDE immediately (within 24 hours). Serious adverse events must be reported even if the PI believes that the adverse events are unrelated to the protocol.

Unexpected (but not serious) adverse events occurring in subjects enrolled at WRNMMC which, in the opinion of the PI, are possibly related to participation AND places subjects or others at a greater risk of harm that was previously known or recognized in the protocol must be reported by the PI within 24 hours of discovery by email or phone to the IRB and the Research Monitor. A follow-up written report within five business days to the IRB and the Research Monitor through IRBNet is required.

Unanticipated problems involving risks to subjects or others (UPIRTSOs) must be reported to the IRB and Research Monitor via email or telephone within 24 hours of discovery and a written follow up report within five business days.

When a deviation occurs, the investigator shall report the occurrence to the IRB. The investigator is required to make the determination whether the deviation meets the criteria for an unanticipated problem involving risks to subjects or others. The IRB Chair or IRB staff member shall also make the determination if the protocol deviation meets the definition of an unanticipated problem involving risks to participants or others. If the IRB Chair or IRB Staff member determines and documents that the deviation is an unanticipated problem involving risks to subjects or others or the deviation resulted from serious or continuing noncompliance, the IRB staff member shall place the deviation on the agenda of the next available IRB meeting for review. If the IRB Chair or IRB Staff member determines and documents that the deviation is not an unanticipated problem involving risks to subjects or others, the IRB Chair or staff member shall acknowledge the submission and complete the review through an administrative review procedure.

As a reminder, according to DoDI 3216.12 (November 8, 2011), the IRB shall approve an independent research monitor by name for all DoD-conducted research involving human subjects, determined by the IRB to involve more than minimal risk to human subjects. Additionally, the research monitor may be identified by an investigator or appointed by an IRB or IO for research involving human subjects determined to involve minimal risk.

The research monitor may perform oversight functions and will report their observations to the IRB or a designated official. The research monitor may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research. The research monitor shall have the authority to stop a research protocol in progress, remove individual subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report. Research monitors shall have the responsibility to promptly report their observations and findings to the IRB or other designated official. The research monitors shall have expertise consonant with the nature of risk(s) identified within the research protocol, and they shall be independent of the team conducting the research involving human subjects.

17.0 Equipment/non-FDA Regulated Devices

17.1 Does the study involve the use of any unique non-medical devices/equipment?

○ Yes ◉ No

18.0 FDA-Regulated Products

18.1 Will any drugs , dietary supplements, biologics, or devices be utilized in this study?

☑ Drugs
☐ Dietary Supplements
☐ Biologics
☐ Devices
☐ N/A

18.2 Drug Details:

☑ Are drug(s) in this research being used in accordance to the approved labeling?
☐ Are drug(s) in this research being used in a manner other than its approved labeling?

When adding a drug indicate in the details section of the drug if the use is either used in accordance to the approved labeling or in a manner other than it's approved labeling

View Details	Drug Name	FDA Approved	A new drug or a new use of approved drug:	IND Number
⊟	**Trade Drug Name:** Exparel **Generic Drug Name:** **Investigational Drug Name:**	Yes	No	

Trade Drug Name:	Exparel
Generic Drug Name:	
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Pacira Pharmaceuticals
Is the drug supplied at no cost?	Yes
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	No
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	Drug approved by FDA and utilized at WRNMMC already.

Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Dose Range:	
Frequency:	
Route of administration:	
Will the investigational pharmacy be dispensing?	Yes
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	N/A
Identify who will be preparing the investigational drug /biologic for administration and describe in detail how it will be prepared:	Investigational pharmacy
Indication(s) under Investigation:	N/A
Where will the drug be stored	Investigational pharmacy
Drug Storage Restrictions (including temperature, etc.):	
Administration Instructions:	
Possible Untoward Effects, Their Symptoms & Treatment:	
Potential or Actual Antidotes for Excessive or Adverse Drug Effect:	
Contraindications and Interactions, If Known:	
Investigators Authorized to Prescribe:	Katherine Dengler.

⊟	**Trade Drug Name:** Marcaine **Generic Drug Name:** **Investigational Drug Name:**	Yes	No	

Trade Drug Name:	Marcaine
Generic Drug Name:	
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Hospira
Is the drug supplied at no cost?	Yes
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	No
Is an IND necessary	No
IND Number	

Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	Drug approved by FDA and utilized at WRNMMC already.
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Dose Range:	
Frequency:	
Route of administration:	
Will the investigational pharmacy be dispensing?	Yes
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	
Identify who will be preparing the investigational drug /biologic for administration and describe in detail how it will be prepared:	
Indication(s) under Investigation:	
Where will the drug be stored	Investigational Pharmacy
Drug Storage Restrictions (including temperature, etc.):	
Administration Instructions:	
Possible Untoward Effects, Their Symptoms & Treatment:	
Potential or Actual Antidotes for Excessive or Adverse Drug Effect:	
Contraindications and Interactions, If Known:	
Investigators Authorized to Prescribe:	Katherine Dengler.

18.4 Reporting Requirements for FDA-regulated research under IND and IDE:

Describe the process for complying with FDA regulatory requirements for adverse event reporting and adverse device effects reporting to the sponsor

N/A

18.5 Sponsor (organization/institution/company):

☑ N/A

If applicable, provide sponsor contact information:

19.0 Research Registration Requirements

19.1 ClinicalTrials.gov Registration:

- ○ Registration is not required
- ◉ Registration pending
- ○ Registration complete

19.2 Defense Technical Information Center Registration (Optional):

- ◉ Registration is not required
- ○ Registration pending
- ○ Registration complete

20.0 References and Glossary

20.1 References:

1. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg. 2003;97:534–540.
2. The Joint Commission. Facts about pain management. Available from: http://www.jointcommission.org/pain_management/. Accessed February 1, 2014.
3. Food and Drug Administration. FDA Drug Safety Communication: Prescription Acetaminophen Products to be Limited to 325 mg Per Dosage Unit; Boxed Warning Will Highlight Potential for Severe Liver Failure. Available from: **http://www.fda.gov/drugs/drugsafety/ucm239821.htm**. Accessed February 1, 2014.
4. Lyu H, Wick EC, Housman M, Freischlag JA, Makary MA. **Patient satisfaction as a possible indicator of quality surgical care.** JAMA Surg. 2013 Apr;148(4):362-7.
5. Wheeler M, Oderda GM, Ashburn MA, Lipman AG. **Adverse events associated with postoperative opioid analgesia: a systematic review.** J Pain. 2002 Jun;3(3):159-80.
6. Bramlett K, Onel E, Viscusi ER, Jones K. **A randomized, double-blind, dose-ranging study comparing wound infiltration of DepoFoam bupivacaine, an extended-release liposomal bupivacaine, to bupivacaine HCl for postsurgical analgesia in total knee arthroplasty.** Knee. 2012 Oct;19(5):530-6.
7. Dasta J, Ramamoorthy S, Patou G, Sinatra R. **Bupivacaine liposome injectable suspension compared with bupivacaine HCl for the reduction of opioid burden in the postsurgical setting.** Curr Med Res Opin. 2012 Oct;28(10):1609-15.
8. Marcet JE, Nfonsam VN, Larach S. **An extended paIn relief trial utilizing the infiltration of a long-acting Multivesicular liPosome foRmulation Of bupiVacaine, EXPAREL® (IMPROVE): a Phase IV health economic trial in adult patients undergoing ileostomy reversal.** Journal of Pain Research. 6: 549-555.
9. Vogel JD. **Liposome bupivacaine (EXPAREL®(R)) for extended pain relief in patients undergoing ileostomy reversal at a single institution with a fast-track discharge protocol: an IMPROVE Phase IV health economics trial.** Journal of Pain Research. 6: 605-610.
10. Hu D, Onel E, Singla N, Kramer WG, Hadzic A. **Pharmacokinetic profile of liposome bupivacaine injection following a single administration at the surgical site.** Clin Drug Investig. 2013 Feb;33(2):109-15.
11. Gorfine SR, Onel E, Patou G, Krivokapic ZV. **Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: a multicenter, randomized, double-blind, placebo-controlled trial.** Dis Colon Rectum. 2011 Dec;54(12):1552-9.

12. Bergese SD, Ramamoorthy S, Patou G, Bramlett K, Gorfine SR, Candiotti KA. **Efficacy profile of liposome bupivacaine, a novel formulation of bupivacaine for postsurgical analgesia.** J Pain Res. 2012;5:107-16.
13. Yeung J, Crisp C, Mazloomdoost D, Kleeman S, Pauls R. Liposomal Bupivacaine During Robotic Colpopexy and Posterior Repair: A Randomized Controlled Trial. Obstetrics and Gynecology. 2018, 131(1);39-46.
14. Exparel® (bupivacaine liposome injectable suspension) [package insert]. San Diego, CA: Pacira Pharmaceuticals Inc; 2011.
15. Mazloomdoost D, Pauls R, Hennen P, Yeung J, Smith B, Kleeman S, Crisp C. Liposomal bupivacaine decreases pain following retropubic sling placement: a randomized placebo-controlled trial. American Journal of Obstetrics and Gynecology. 2017, 217(5):598,e1-e11.
16. Emanuel A, Rai S, Rai K. A Content Incontinent: Report of Liposomal Bupivacaine Induced Fecal Incontinence. Case Reports in Surgery, 2016. Article ID 7164983.
17. Baxter R, Bramlett K, Onel E, Daniels S. **Impact of local administration of liposome bupivacaine for postsurgical analgesia on wound healing: a review of data from ten prospective, controlled clinical studies.** Clin Ther. 2013 Mar; 35(3):312-320.
18. Book NM, Novi B, Novi JM, Pulvino JQ. **Postoperative voiding dysfunction following posterior colporrhaphy.** Female Pelvic Med Reconstr Surg. 2012 Jan-Feb;18(1):32-4.
19. Buckenmaier CC 3rd, Galloway KT, Polomano RC, McDuffie M, Kwon N, Gallagher RM. **Preliminary validation of the Defense and Veterans Pain Rating Scale (DVPRS) in a military population.** Pain Med. 2013 Jan;14(1):110-23.

20.2 Abbreviations and Acronyms:

N/A

Protocol No. 11111
Current Version: 1.4
Date: March 10, 2020

WALTER REED NATIONAL MILITARY MEDICAL CENTER (WRNMMC)
BETHESDA, MARYLAND

This consent form is valid only if it contains the IRB stamped date

Consent for Voluntary Participation in a Research Study Entitled: Efficacy of Injectable Local Anesthetics on Postsurgical Analgesia Following Posterior Colporrhaphy: A Prospective, Randomized, Double-Blinded Trial

Principal Investigator:
MAJ(P) Katherine L Dengler, MC, USA
Female Pelvic Medicine and Reconstructive Surgery Fellow (Post GraduateYear-6)
OB/Gyn Department, Division of Female Pelvic Medicine and Reconstructive Surgery
Office: (301)400-2468; Cell (352) 262-6861
Walter Reed National Military Medical Center

Study site: _X_WRNMMC, __ FBCH, __USUHS, ___WRAIR, ___NMRC, ___JPC, ___OTHER

"A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

Are you participating in any other research studies? _____ Yes _____No

1. INTRODUCTION OF THE STUDY

You are being asked to be in this research study because you are scheduled for surgery involving the posterior wall of your vagina with the Urogynecology Service at WRNMMC.

Taking part in this study is voluntary. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your benefits to which you are otherwise entitled. Leaving the study will not

affect your medical care. Please read the information below, and ask questions about anything you do not understand, before deciding whether to take part in the study.

If significant new findings develop during the course of this study that may relate to your decision to continue participation, you will be informed.

2. PURPOSE OF THE STUDY:

The purpose of this study is to learn how well the treatment drug works on controlling pain following surgery. A numbing medication either a short-acting local anesthetic solution, bupivacaine or a combination of both bupivacaine plus a long-acting local anesthetic solution, Exparel® will be injected into your vagina while you are under anesthesia in the operating room prior to the start of your Urogynecologic surgery. Participation in our study will not increase the amount of time you spend under anesthesia. We will also be studying how much pain medication you used to control your post-surgery pain during the first three days after your surgery, whether you have any pain associated with bowel movements, and whether or not you had any difficulty with emptying your bladder.

This study involves the use of FDA approved-drugs bupivacaine and Exparel®, a long-acting liposomal bupivacaine injection. This means that the drug has been approved by the Food & Drug Administration (FDA) for treatment of post-operative pain for surgeries involving soft-tissue and is currently being used at WRNMMC as one of many options available from our pharmacy. While the drug has not been studied extensively in surgeries such as the one you are scheduled for, it has been studied in numerous other surgical procedures. The same operating techniques will be used regardless of study enrollment.

3. PROCEDURES TO BE FOLLOWED:

As a subject, you will undergo the following procedures:

Screening: You have been selected for our study because you are scheduled for surgery involving your posterior vagina (back wall of the vagina). We have ensured that you do not have any of the following conditions:

- Known allergy to amide local anesthetics
- Unstable cardiac arrhythmia also known as unstable irregular heart rate
- Known liver impairment

- Known pregnancy at time of surgery (a pregnancy test will be done the morning of surgery if applicable)
- Regular use of narcotic pain medication, defined as use on most days of week at any time in the three months prior to surgery
- Significant history of opioid or alcohol abuse or addiction (requiring treatment)
- Concurrent pain management requiring the use of epidural anesthesia

As a research subject, you will be randomly assigned to one of two groups by the pharmacy on the day of your surgery; Group A or Group B. Randomization is a process like flipping a coin and means you will have a one in two chance of being assigned to either group. Both groups will receive an injection into the vagina at the beginning of your surgery in the operating room.

- Group A will receive a dose of short-acting bupivacaine injected into the vagina at the beginning of surgery.
- Group B, will receive a combination of the short acting bupivacaine and the long-acting liposomal bupivacaine injection (Exparel®), injected into the vagina at the beginning of surgery.

Neither you nor your surgeon will know which Group you are assigned to. You will have a 50% chance of being in either group. We use short acting bupivacaine routinely in our surgeries. You will not be under anesthesia longer as a result of choosing to participate in our study. As standard of care, no other portion of your surgery or post-operative care will be different or experimental. You will receive the same post-operative pain medications, regardless if you are Group A or B or if you choose not to participate.

On the day after surgery, you be asked to rate the pain in your abdomen and vagina using an 11-point visual analog scale. We will keep track of how much pain medication you use after your surgery; any pain with bowel movements and any difficulty emptying your bladder after the bladder catheter is removed. We will contact you on days two and three after your surgery, either by phone or through email (Relay Health) and ask you once again to rate your pain using the same visual analog scale. We will also ask you four quality of life questions using the visual analog scale along with a count of how many pain tablets you have used since your surgery. You will have the same post-operative appointments regardless of study participation or if you choose not to participate. Providers from the Urogynecology Service will be available at any time to discuss your post-operative care, pain issues or any medications questions (other than study group assignment).

This study is a double blind study, which means that neither you nor your study investigator will know what medication you are receiving. In the event of an emergency, there is a way to determine which solution you received.

4. ALTERNATIVES TO PARTICIPATION:

Choosing not to participate in this study is your alternative to participating for the study.

The medication involved in this study may also be available without the need for you to volunteer to participate in this study.

5. AMOUNT OF TIME FOR YOU TO COMPLETE THE STUDY

You will be part of this study for three days. During this time, you will be asked at three different times to rate your pain, quality of life questions and how much pain medication you have taken. This will be on post-operative day one, two and three.

6. NUMBER OF PEOPLE THAT WILL TAKE PART IN THIS STUDY

A total of 120 female subjects are expected to take part in this study.

7. POSSIBLE RISKS AND DISCOMFORTS FROM BEING IN THIS STUDY

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the study investigator if you have any questions.

There are adverse side effects associated with Exparel to include nausea, vomiting, and constipation, occurring in 10% of patients. These are also common side effects associated with any surgery and you will be treated appropriately. Exparel is intended to cause numbness at the injection sites and surrounding areas for the duration of the medication effect. This is similar to the how it feels while having your teeth numbed at the dentist. This localized numbness is how this medication helps reduce pain. Adverse reactions that can occur in 2-10% of patients following EXPAREL administration include fever, dizziness, peripheral swelling, anemia (low blood count), low blood pressure, itching, fast heart rate, headache, difficulty sleeping, muscle spasms, back pain, sleepiness, and pain at injection site. If you have any concerns during your post-operative course, please contact your surgeon.

Your post-operative pain will still be addressed and managed in the same manner, regardless of which study group you are assigned to.

Additional risks are associated with any surgery to include infection. If you experience a fever greater than 100.4°F increase in redness or swelling to the surgical site or an increase in discharge, please contact your surgeon or go to the Emergency Room.

We will contact you at home on post-operative day one, two, and three either by phone or email via Relay Health. We will contact you between the hours of 8 am and 8 pm for information regarding your pain and the number of pain tablets you have used.

Many of our patients are having a hysterectomy at the time of their surgery. If you are not scheduled for a hysterectomy and are still capable of becoming pregnant (have a uterus and are NOT postmenopausal, that is, you are still having menstrual cycles), we do not recommend becoming pregnant for six months following surgery. This is to promote healthy surgical site healing. There are no human data studies to date which have shown bupivacaine or Exparel® to cause birth defects or issues with fertility.

If you are a FEMALE OF CHILD BEARING POTENTIAL wishing to participate in this research study, you must understand that Exparel® might be harmful to (1) an unborn child if you are pregnant, or (2) an infant if you are breast-feeding. Therefore, you may not be pregnant and will take a pregnancy test before you participate in this study on the morning of your surgery. You must also agree to take precautions to prevent pregnancy during the course of this study due to the possible severe harm the drug/procedure may cause your unborn child. The only completely reliable methods of birth control are total abstinence or surgical removal of the uterus. Other methods, such as the use of condoms, a diaphragm or cervical cap, birth control pills, IUD, or sperm killing products are not totally effective in preventing pregnancy. Also, you may not be actively breast-feeding and participate in this study.

If you become pregnant or feel you might be pregnant, contact your provider and the study investigator. Your surgery will be cancelled if you are pregnant.

8. POSSIBLE BENEFITS FROM BEING IN THIS STUDY:

You may benefit from taking part in this study because you may experience less post-operative discomfort, require less pain medication and have a decreased risk of adverse side effects from narcotic medications. Better long-term pain control may lead to less stress, less interference with normal activity, and improved sleep. The information we

learn will help us learn about providing better pain relief after surgery in the posterior aspect of the vagina. The information we learn will help us learn about providing better pain relief after Urogynecologic surgery.

However, no benefit can be guaranteed.

9. CONFIDENTIALITY/PRIVACY OF YOUR IDENTITY AND YOUR RESEARCH RECORDS

The principal investigator will keep your research records stored in a locked cabinet (hard copies) in a locked office and stored on a password-protected CAC enabled computer. These records may be looked at by staff from the Walter Reed (WRNMMC) Department of Research Programs, the Walter Reed (WRNMMC) Institutional Review Board (IRB), the DoD Higher Level Review, and other government agencies, such as the Food and Drug Administration (FDA), as part of their duties.

These duties include making sure that the research subjects are protected. Confidentiality of your records will be protected to the extent possible under existing regulations and laws but cannot be guaranteed. Complete confidentiality cannot be promised, particularly for military personnel, because information bearing on your health may be required to be reported to appropriate medical or command authorities. Your research records may be disclosed outside of WRNMMC, but in this case, only a unique code number will identify you. Information about the code will be kept in a secure location and access limited to authorized research study personnel.

By signing this consent document, you give your permission for information gained from your participation in this study to be published in medical literature, discussed for educational purposes, and used generally to further medical science. You will not be personally identified; all information will be presented as anonymous data. So, your name will not appear in any published paper or presentation related to this study.

This research study meets the confidentiality requirements of the Health Insurance Portability and Accountability Act (HIPAA).

The purpose of this research study is to obtain data or information on the safety and effectiveness of Exparel; the results will be provided to the Food and Drug Administration and other federal and regulatory agencies as required.

10. CONDITIONS UNDER WHICH YOUR PARTICIPATION IN THIS STUDY MAY BE STOPPED WITHOUT YOUR CONSENT

Your taking part in this study may be stopped without your consent if remaining in the study might be dangerous or harmful to you. Your taking part in this study may also be stopped without your consent if the military mission requires it, or if you lose your right to receive medical care at a military hospital.

The study investigator may also withdraw you from the study and the study medication may be stopped [if applicable], without your consent for one or more of the following reasons:

- Failure to follow the instructions of the study staff.
- The study investigator decides that continuing your participation could be harmful to you.
- Pregnancy.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

11. ELIGIBILITY AND PAYMENT FOR BEING IN THIS STUDY

You will not receive any payment for being in this study.

12. COMPENSATION IF INJURED AND LIMITS TO MEDICAL CARE

You will not receive any compensation (payment) if you are injured as a direct result of being in this study. You should understand that this is not a waiver or release of your legal rights. You should discuss this issue thoroughly with the study investigator before you enroll in this study.

Should you be injured as a result of your participation in this study, you will be given medical care for that injury at no cost to you.

Medical care is limited to the care normally allowed for Department of Defense health care beneficiaries (patients eligible for care at military hospitals and clinics). Necessary medical care does not include in-home care or nursing home care. If you need to be

hospitalized, you may have to pay the normal fees for subsistence (hospital meals), as per standard regulations.

If at any time you believe you have suffered an injury or illness as a result of participating in this research study, you should contact the Human Protections Administrator, Department of Research Programs, at Walter Reed National Military Medical Center at 301-295-8273

13. COSTS THAT MAY RESULT FROM TAKING PART IN THIS STUDY

There is no charge to you for taking part in this study.

14. IF YOU DECIDE TO STOP TAKING PART IN THIS STUDY AND THE INSTRUCTIONS FOR STOPPING EARLY

You have the right to withdraw from this study at any time. If you decide to stop taking part in this study, you should tell the study investigator as soon as possible. By leaving this study at any time, you in no way risk losing your right to medical care and there will be no penalty to you and you will not lose any of your benefits to which you are otherwise entitled. Your post-operative pain will continue to be treated in accordance with acceptable standards of medical treatment. We will keep and analyze already collected data until the study closes to maintain the integrity of our study.

Should you choose to withdraw, you must notify the study team or principal investigator. You will be given a short form to complete.

15. AUTHORIZATION FOR RESEARCH USE OF PROTECTED HEALTH INFORMATION

The Federal Health Insurance Portability and Accountability Act (HIPAA) includes a Privacy Rule that gives special safeguards to Protected Health Information (PHI) that is identifiable, in other words, can be directly linked to you by your name, your Social Security Number or date of birth. We are required to advise you how your PHI will be used. This authorization is effective until the end of the research study.

(1) What information will be collected?

For this research study, we will be collecting information about your pain level after your surgery and any pain medications you took to treat this pain. We will be collecting this information for three days after your surgery. We additionally will be collecting basic

data like your age, a weight and height calculation (BMI or Body Mass Index), date of surgery, type of surgery, and any difficulty you had emptying your bladder after your surgery. PHI data elements collected:

- Names
- Dates including all elements (except year) directly related to an individual, including birth date, admission date, discharge date, and date of death
- Ages over 89 and all elements of dates (including year) indicative of such age, unless you will only request a single category of "age 90 or older"
- Telephone numbers
- Social Security numbers (SSNs)
- Medical record numbers
- Any other unique identifying number, characteristic, or code (DEERs ID, EDIPN, Rank)

(2) Who may use your PHI within the Military Healthcare System?

The members of the research team will have access to your health information in order to find out if you qualify to participate in this study, to administer research procedures, to monitor your progress, and/or to analyze the research data. Additionally, your PHI may be made available to groups such as the WRNMMC Department of Research programs and the WRNMMC Institutional Review Board.

(3) What persons outside of the Military Healthcare System who are under the HIPAA requirements will receive your PHI?

The study team has no plans to share data outside of WRNMMC.

(4) What is the purpose for using or disclosing your PHI?

The members of the research team need to use your PHI in order to analyze the information to find out whether the drug we are testing is effective and to monitor your safety.

(5) How long will the researchers keep your PHI?

The research team in the Urogynecology Division will keep the research data for up to three years after the end of the study. At that time all the information will be destroyed. The master code, linking your study number with your personal identifying information, will be destroyed as soon as all data collection is completed.

This consent form and HIPAA authorization will be maintained for a period of six years after the study is completed.

(6) Can you review your own research information?

You will not be able to look at your research information until the study has ended.

(7) Is your health information requested for future research studies?

No, your health information is not requested for future research studies.

(8) Can you cancel this Authorization?

Yes. If you cancel this Authorization, you will no longer be included in the research study. However, the research team will use the study information collected prior to this cancellation unless you indicate otherwise. No further data will be collected.

If you want to cancel your Authorization, please contact the Principal Investigator in writing:

Katherine Dengler, MD, FACOG
MAJ(P), USA, MC
Department of Obstetrics and Gynecology/Division of Female Pelvic Medicine and Reconstructive Surgery
8901 Wisconsin Ave
Bethesda MD 20889

(9) Does this Authorization expire?

Yes, it expires at the end of the research study.

(10) What will happen if you decide not to grant this Authorization?

If you decide not to grant this Authorization, you will not be able to participate in this research study. Refusal to grant this Authorization will not result in any loss of medical benefits to which you are otherwise entitled.

(11) Can your PHI be disclosed to parties not included in this Authorization who are not under the HIPAA requirements?

There is a potential that your research information will be shared with another party not listed in this Authorization in order to meet legal or regulatory requirements. Examples of persons who may access your PHI include representatives of the DoD Higher Level Review, the Food and Drug Administration, the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP), and the DHHS Office for Civil Rights. This disclosure is unlikely to occur, but in that case, your health information would no longer be protected by the HIPAA Privacy Rule.

(12) What else may you want to consider?

- No publication or public presentation about the research described above will reveal your identity without another signed Authorization from you.
- If all information that does or can identify you is removed from your health information, the remaining de-identified information will no longer be subject to this Authorization and may be used or disclosed for other purposes.
- In the event your health information is disclosed to an organization that is not covered by HIPAA, the privacy of your health information cannot be guaranteed.

(13) Who should you contact if you have any complaints?

If you believe your privacy rights have been violated, you may file a written complaint with the WRNMMC Privacy Officer, located at 8901 Wisconsin Ave, Bethesda, MD 20889, Telephone: 301-319-4775

Your signature at the end of this document acknowledges that you authorize WRNMMC personnel to use and disclose your Protected Health Information (PHI) collected about you for research purposes as described above.

16. CONTACTS FOR QUESTIONS ABOUT THE STUDY:

If you have questions about the study, or if you think you have a study-related injury you should contact Dr. Katherine Dengler at WRNMMC, Urogynecology Division at (301) 400-2468. For questions about your rights as a research subject, contact the Human

Protections Administrator, WRNMMC Department of Research Programs in Building 17 at (301) 295-8239 or WRNMMC Staff Judge Advocate Office at (301) 295-2215.

A signed copy of this consent form will be given to you.

SIGNATURE OF SUBJECT

You have read (or someone has read to you) the information in this consent form. You have been given a chance to ask questions and all of your questions have been answered to your satisfaction.

BY SIGNING THIS CONSENT FORM, YOU FREELY AGREE TO TAKE PART IN THE RESEARCH IT DESCRIBES.

_____
Printed Name of Subject

_____ _____ _____
Signature of Subject Date Time

SIGNATURE OF RESEARCH TEAM MEMBER OBTAINING CONSENT

My signature is intended to attest that the information in the consent document and any other information was explained to and apparently understood by the subject that questions and concerns were addressed and that informed consent was freely given.

_____
Printed Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date (must be same as subject)

_____
Time

Phone Script

1. **VOICEMAIL**: Hello! This is Dr._____at the WRNMMC (Walter Reed National Military Medical Center) OB/GYN Department regarding a research study you are participating in. Please return my call at your earliest convenience at (Give name and #). Thank you!

2. **ANSWERED:** Hello, may I speak with (rank/patient name)?

a. NOT AVAILABLE – May I leave a message for (rank/patient)? My name is Dr._____. I am calling from Walter Reed National Military Medical Center regarding a research study (Patient's name) is participating in. Please return my call at (name, #). Thank you so much for passing this message along. (End call.)

b. AVAILABLE – Hello (rank/patient name)! My name is (Research Team Member). I am calling from Walter Reed National Military Medical Center's OB/GYN Department on behalf of Dr. Dengler who is the Principal Investigator of a research study you are participating in. Do you have a few minutes to talk? (If no, ask for a good time to call back.)

We are working with Dr. Dengler to follow-up with individuals who are participating in her study. The purpose of this follow-up call is to discuss your postsurgical pain in accordance with our research study.

Would you please locate your visual analog pain scale and the bottles of pain medication we prescribed at the time of your discharge? Looking at the pain scale, would you please rate your pain in your vagina from 0-10. Ms. _____, have you had a bowel movement since surgery? Did you experience pain during your bowel movement? If yes, what was the pain associated with this, using the same scale? How has the pain interfered with your usually activity from 0-10? Please rate how your pain interferes with your ability to sleep using the same scale. How has the pain affected your mood from 0-10? How has the pain contributed to your stress from 0-10?

I would now like you to look at each of your pill bottles and tell me the names of the medications. Please count for me the number of pills remaining in that bottle. Thank you Ms._____. I will contact you again on postoperative day_____, and ask you the same questions." Thank You! Have a good day.

1.**VOICEMAIL**: Hello! This is Dr._____at the WRNMMC (Walter Reed National Military Medical Center) OB/GYN Department regarding a research study you are participating in. Please return my call at your earliest convenience at (Give name and #). Thank you!

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Initial for agreement to leave voicemail._____