TITLE:

A Placebo-controlled, Double-blinded, Randomized Pilot Study of Bupivacaine Liposome Injectable Suspension (EXPAREL) for Minimally Invasive Supracervical Hysterectomies Postsurgical Analgesia

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Protocol Description

All patients who are scheduled for a robot-assisted or traditional laparascopic supracervical hysterectomy will be identified in the beginning of the week (Sunday) through the OR scheduler. All patients go to pre-admission testing, where they meet with a nursing staff who will coordinate their blood work and take a history. The co-investigators will be able to prescreen them in this fashion and on the day of the surgery confirm that they are eligible for the study.

After obtaining informed consent, participants will be assigned to the intervention or placebo group randomly. Randomization will be performed based computer-based random number generator (www.randomizer.org) which would generate two sets of random numbers containing 26 numbers from 1 to 52 with each number in a set remaining unique, which will be given to the pharmacy assistant director. The master list will be only accessible by pharmacy personnel. Hospital pharmacy staff will prepare the numbered package of either Exparel or normal saline (based on the randomization) in bubbled wrapped amber bag that will be given to the resident/attending who will proceed to inject the given medication during the prepping. Unlike normal saline which will be used as placebo, EXPAREL is milky in color, therefore to ensure adequate blinding of study investigators and surgeons an independent resident will unpack the package prior to the surgery and administer it to the patient in the absence of study investigators and surgeons during the prepping. All OB-GYN residents will be instructed about the proper injection procedure prior to the start of the study. All resident are equally capable, however senior residents (PGY3/PGY4) are assigned to do hysterectomies (a total of 12 residents). We expect performance bias but will rehearse with a model cervix in the simulation lab in order to diminish it. Only the pharmacy staff and independent residents will have access to the random generated list; all other staff including the investigators, surgeons, anesthesiologists, and nurses as well as patients will be kept blinded to the assigned treatments.

Subjects in the intervention arm will receive paracervical block with 20 ml of extended-release liposomal bupivacaine (EXPAREL) at the 4 and 8o'clock positions. Subjects in the placebo arm will receive paracervical/intracervical block with 20 ml of saline at the 4 and 8 o'clock positions. In both study arms the injection will be administered preoperatively.

Post operative pain management will be the same for both study groups. Immediately after surgery in the recovery room they will be able to receive ketorolac 30mgIV and/or acetominophen 1000mg IV, and if needed narcotics (as requested by the patient). This will all be recorded in the anesthesia record which is accessible to the co-investigators. Robot-assisted and traditional laparoscopic supracervical hysterectomy are ambulatory cases and we expect same day discharge. At home or in the hospital, all study participants will have oral acetaminophen 650mg q4-6 hr and NSAIDS 600mg q4-6 hours, as needed. If needed they will also have percocet 5-325mg q4-6 hours, the first dose of which will be recorded as the median time to narcotics.

Post operative pain management for both groups will include a combination of oral or parenteral nonsteroidal anti-inflammatory medications, and oral or parenteral opioids to be used as needed. Since most patients who undergo minimally invasive hysterectomy are discharged few hours after the surgery, data regarding the time, type and dose of postoperative analgesics used by the patient will be collected by providing the patient with a pain diary before discharge. Patient will be instructed to record use of any analgesics (including NSAIDS) for 72 hours whether the analgesic was prescribed by the surgeon or was taken at patient's own discretion. These data regarding the time, number and type of breakthrough analgesia will be used for evaluation of median time to first

break through opioid use and total opioid analgesic requirement.

The severity of pain will be assessed preoperatively in the holding area, at the time of PACU arrival, and at 12, 24, and 48 hours postoperatively using a numeric rating scale (NRS) from 0 to 10 with 10 being the worst pain the patient has ever experienced. The first two assessments will be performed in the hospital by the principal investigators and the remaining assessments will happen through a phone conversation with the patient after discharge from hospital. The NRS has been found to be a simple and valid alternative to the visual analog scale, and has been validated by Paice and Cohen in 1997. Based on this study which examined the validity of a verbally administered NRS using convergence methods, the correlation between the VAS and the NRS was strong and statistically significant ($r = 0.847$, $p < 0.001$), supporting the validity of the verbally administered NRS. Type of pain (characterized as sharp, dull, stabbing, aching), location of pain (categorized as right upper quadrant, epigastric, left upper quadrant, right lumbar, umbilical, left lumbar, right iliac, hypogastric, left iliac) and radiation of pain will also be evaluated and recorded.

Based on the available evidence EXPAREL's adverse effects includes QT interval prolongation. The long QT prolongation syndrome usually does not manifest in any symptoms however one reported symptom is fainting, and if left persistent can lead to seizure activity and or death. To assess the incidence and severity of adverse events, patients' heart activity will be monitored during the surgery and any abnormal findings in the electrocardiogram pattern will be recorded. Additionally, before patient's discharge from hospital, the investigator will seek information on adverse event of the intervention by specific questioning and, as appropriate, by examination. Questions will include, do you feel faint and/or dizzy, do you have difficulty breathing. Information on all adverse events will be recorded immediately and the clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Any adverse event that occurs after patient discharge and is considered to be possibly related to the study intervention will also be recorded. Adverse events can include re-admission, signs and symptoms of infection, and bleeding.

The Data Safety and Monitoring Board (DSMB) will include 3 doctors, who are independent of the study. Members of DSMB will meet every 2 months at Maimonides hospital to carry out a regular assessment of the number and type of serious adverse events. They will report their findings or recommendations to the principal investigator and representatives from Maimonides Institutional Review Board (IRB). The DSMB will recommend whether to continue the study or stop it early considering the objectives of the study and subjects safety.