**STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN**

**Title:** Pharmacoeconomics and Related Patient Outcomes of Multi-dose Intravenous Acetaminophen (OFIRMEV)

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**Purpose:** In this study we examine the impact of adding IV acetaminophen to the multimodal analgesic regimen for robotic-assisted laparoscopic prostatectomy (RALP). We analyze whether adding IV acetaminophen can improve postoperative recovery time, inpatient hospital length of stay (LOS), postoperative pain scores, and opioid consumption.

## Methods:

The study design is a 2-arm, double-blind, randomized, placebo-controlled trial comparing IV acetaminophen to a control (IV placebo). All patients will be provided written informed consent. All patients in this study are scheduled to undergo robotic-assisted laparoscopic prostatectomy (RALP). Other inclusion criteria are male patients at least 18 years of age who are ASA Physical Status 1-4. Exclusion criteria include chronic opioid use, liver disease (known history of hepatitis B or C, cirrhosis, nonalcoholic steatohepatitis, history of alcoholism, ALT/AST greater than 3 times upper limit of normal in the past 3 months), allergy/hypersensitivity to acetaminophen, baseline dementia, chronic diathesis, and chronic kidney disease.

Primary outcome is PACU (post-anesthesia care unit) LOS (length of stay). Patients undergoing RALP will be enrolled in this study and randomly assigned to receive either 1 gram IV acetaminophen or IV placebo within 15 minutes following the induction of anesthesia and prior to surgical incision. All patients will undergo general endotracheal anesthesia with standardized anesthetic technique consisting of anesthesia induction with propofol 2–2.5 mg/kg, fentanyl 50–100 mcg, and a non-depolarizing neuromuscular agent. General anesthesia is maintained with an inhalational agent (either desflurane or sevoflurane). All patients receive ketorolac 30 mg, ondansetron 4 mg, as well as hydromorphone (based on anesthesia provider's decision, up to 1 mg) prior to emergence from anesthesia. Baseline pain is recorded using the Visual Analog Scale (VAS). These measures will be again recorded on transport to the PACU and again every 30 minutes for 2 hours. Pain scores will be recorded at 8 random distinct time points in the first 24 hours after discharge from the PACU and 8 time points in the second 24 hours post-PACU discharge. Repeat doses of IV acetaminophen or placebo will be given to each respective group every 6 hours for a total of 4 doses. Total opioid consumption during hospital stay was also recorded for each patient. Because opioid choice may be variable due to physician preference, total opioid use will be standardized and converted to PO morphine equivalents (based on APS equianalgesic table). PACU LOS in minutes will be calculated from the time of admission in the electronic health record (EHR) to the point where the patient was charted as "ready for discharge" from the PACU in the EHR. LOS on the hospital floor in days is calculated from the time point of "ready for discharge" from the PACU to the time point where the patient was charted as "ready for discharge" from the hospital in the EHR. For both time measurements, patients without time records or negative LOS will be removed for the analysis.

## Statistical analysis

Assuming a difference of 12 minutes of PACU LOS between IV acetaminophen and IV placebo group, with a common within group standard deviation (SD) of 24 minutes, recruiting 44 patients for each group would enable the investigators to reject the null hypothesis that the two

groups have equal mean with 90% power at significance level of 0.05. Sample size calculation was performed using SAS 9.3 software (SAS Institute Inc., Cary, NC, USA).

Specific data variables collected for the study include: LOS on the hospital floor (LOS, calculated in days), PACU LOS (measured as the time from arrival to the PACU to the exact time the patient met discharge to the inpatient floor criteria by meeting Aldrete score thresholds, as documented by the PACU staff (measured in minutes), pain scores (using numeric rating scale 0-10, VAS scale), total opioid consumption (PO or IV) in the PACU and daily during hospital stay (total measured in morphine equivalents). Baseline characteristics include smoking history (yes or no), body mass index (BMI) in $kg/m^2$, baseline pre-op pain scores (0-10, VAS scale), whether or not dexamethasone was used in surgery (yes or no), whether or not patient had chronic pain of 6 months or more (yes or no), and patient age in years. Primary endpoints for the study were total PACU LOS measured in minutes and LOS on the hospital floor measured in days. Secondary endpoints include VAS pain score and total opioid consumption (PO of IV) in morphine equivalents (APS equianalgesic table). Continuous variables will be examined using Shapiro-Wilk test for normality assumption. Both age and PACU LOS will be calculated using mean values and SDs, as well as postoperative pain scores from immediate after surgery to 24 hours after surgery, while all other continuous variables will be calculated using median values and interquartile ranges. Categorical variables (smoking history, chronic pain, dexamethasone) will be calculated using frequencies and percentages. The differences in patient preoperative characteristics, as well as postoperative outcomes, between IV acetaminophen and IV placebo groups will be compared using two-sample t-test, Wilcoxon ranksum test, Chi-square test, Fisher's exact test, repeated measures ANOVA, when deemed appropriate. Additionally, multiple linear regression will be used for evaluating the effect of IV acetaminophen on PACU LOS after adjusting for patient preoperative characteristics. Generalized linear model with gamma distribution and log link function will be used to estimate the effect of IV acetaminophen on LOS on the hospital floor, adjusting for the same set of patient preoperative characteristics. The pain scores from immediate postop to 2 hours, from immediate postop to 24 hours after surgery will be calculated at each time point respectively. The comparison of postoperative pain scores between IV acetaminophen and IV placebo groups will be performed using repeated measures ANOVA. Other comparisons between the two groups will be done using Wilcoxon ranksum test. All statistical hypothesis tests will be two sided, with p-value $<0.05$ considered statistically significant. Statistical analyses will be performed with SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA).