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NCT number: 04429022
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Multimodal Pain Management After Robotic-Assisted Total Laparoscopic Hysterectomy

National Clinical Trial (NCT) Identified Number: 04429022

UB Protocol Number: 00004549

Principal Investigator: Sarah Andres, D.O.

Sponsor: University at Buffalo

Funded by: Not applicable

Version Number: v.1.0

10 May 2023

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

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STATEMENT OF COMPLIANCE

The trial was conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator assured that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.
The protocol, informed consent form(s), recruitment materials, and all participant materials were submitted to the IRB for review and approval. Approval of both the protocol and the consent form were obtained before any participant was enrolled. During this study, no amendments were made to the protocol or consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

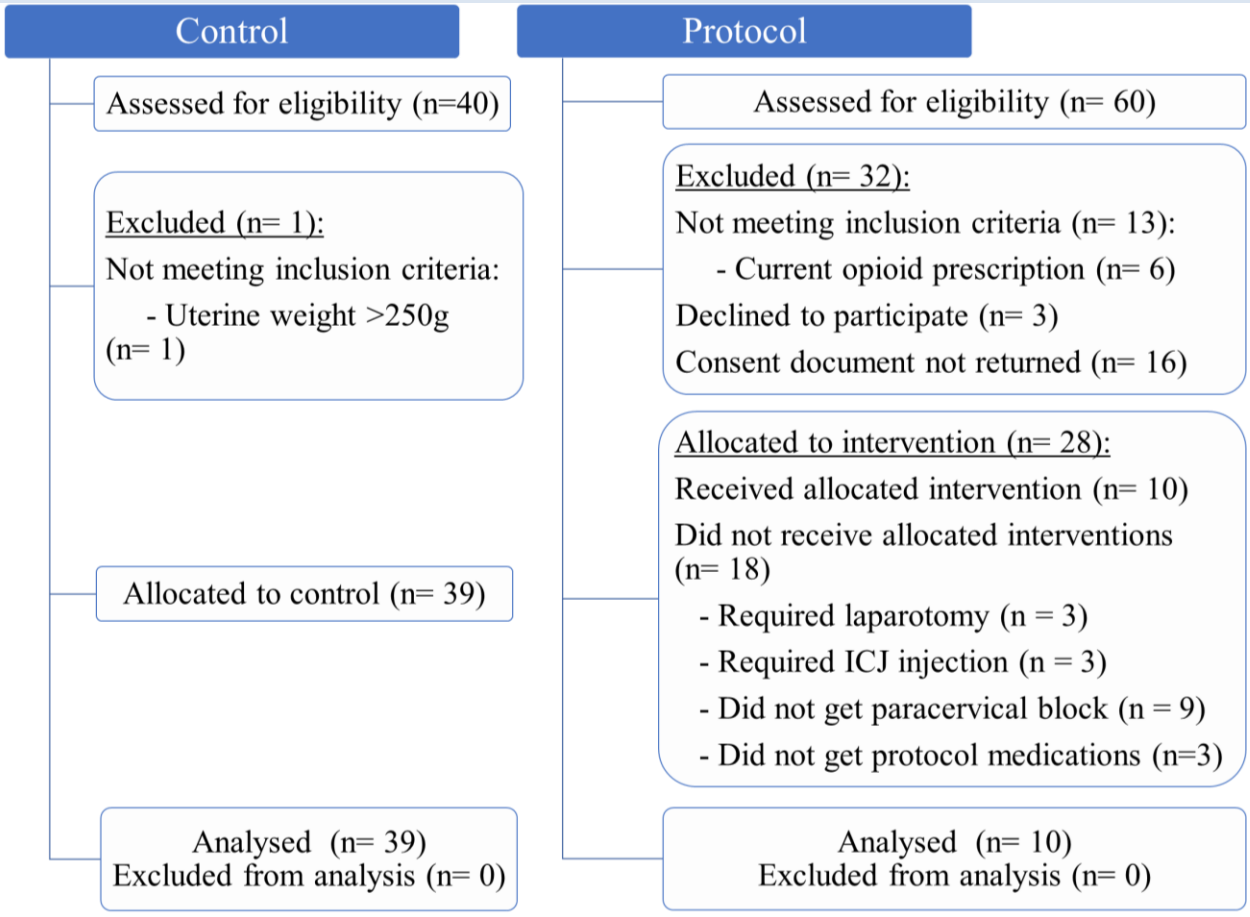
Title:	Multimodal Pain Management After Robotic-Assisted Total Laparoscopic Hysterectomy
Study Description:	The standard of care for pain management after laparoscopic hysterectomy is non-specific, however in light of the ongoing opioid epidemic, a transition to non-opioid pain medication regimens is desired by both physicians and patients. This study aims to create a standardized non-opioid multimodal pain management regimen for women undergoing robotic hysterectomy with the goal of minimizing postoperative opioid usage. Using a prospective cohort with historical controls study design, a traditional opioid based pain medication was compared to a multimodal pain protocol which included an emphasis on non-opioid pain medications.
Objectives:	Primary Objective: To decrease opioid use (measured in morphine milligram equivalents or MME) following Robotic-Assisted Total Laparoscopic Hysterectomy (RA-TLH) Secondary Objectives: To decrease inpatient length of stay (LOS) and pain following RA-TLH
Endpoints:	Primary Endpoint: Total opioid pain medications required hour 0-3 post-operatively in morphine milligram equivalents (MME), Total opioid pain medications required through hours 3-24 post-operatively in MME. Secondary Endpoints: Length of stay in hours, pain scores, return to the clinic or emergency department (ED) due to post-operative pain within two weeks of hospital discharge.
Study Population:	Adult women undergoing robotic-assisted total laparoscopic hysterectomy with a single surgeon in Western New York
Description of Sites/Facilities Enrolling Participants:	Single site study enrolling at an academic-affiliated community hospital
Description of Study Intervention:	A standardized non-opioid multimodal pain management regimen was designed for women undergoing robotic hysterectomy with the goal of minimizing postoperative opioid usage. Using a prospective cohort with

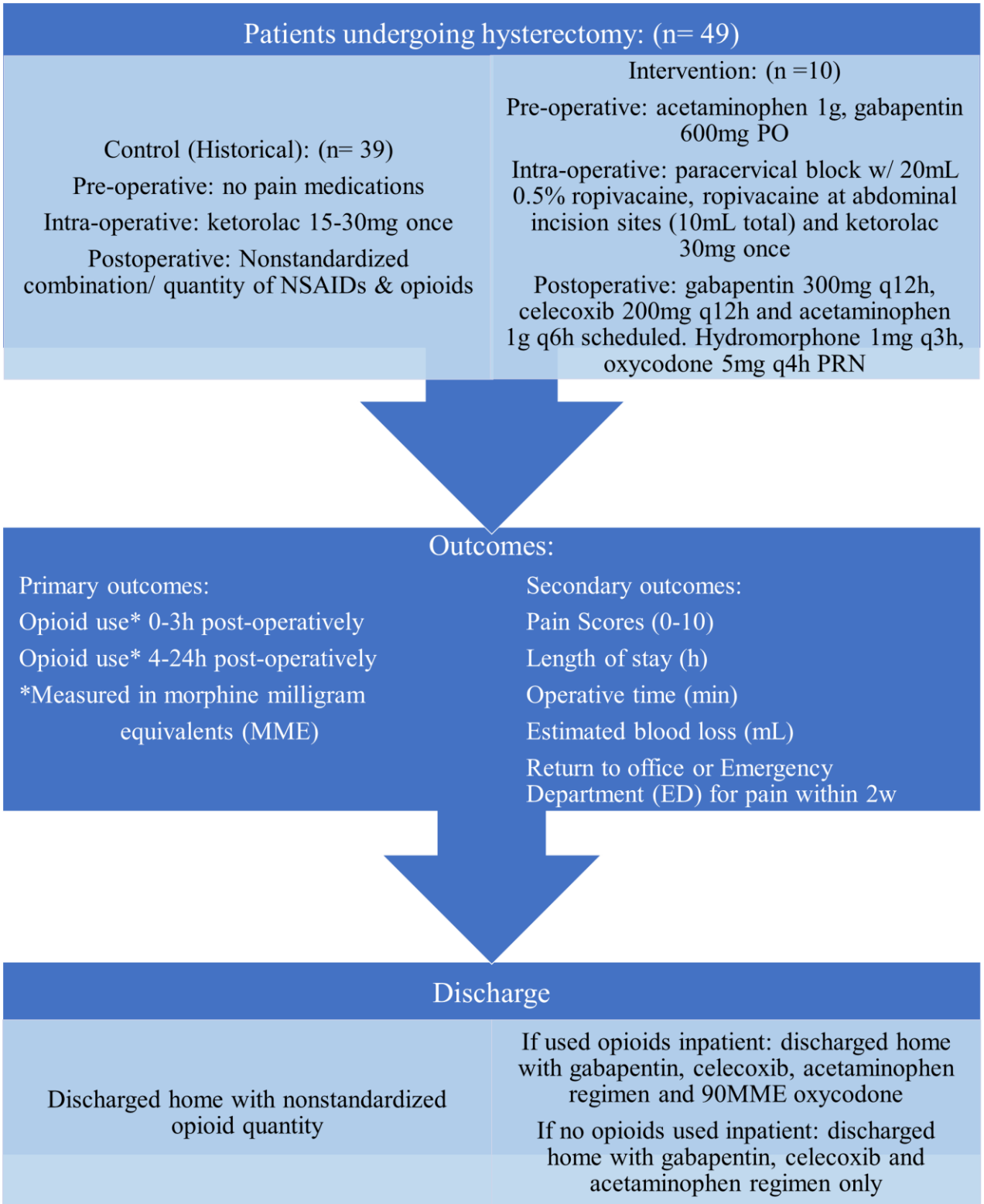
historical controls study design, a traditional opioid based pain medication was compared to a multimodal pain protocol which included an emphasis on non-opioid pain medications. Pain medications were given pre-operatively, intra-operatively and post-operatively, via oral, intravenous and intramuscular or subcuticular routes.
Describe the study intervention. If the study intervention is a drug or biologic, include dose and route of administration.

Study Duration: 11.27.2018- 5.24.2022

Participant Duration: seven days

1.2 SCHEMA




Patients undergoing hysterectomy: (n= 49)
Control (Historical): (n= 39)
Pre-operative: no pain medications
Intra-operative: ketorolac 15-30mg once
Postoperative: Nonstandardized combination/ quantity of NSAIDs & opioids
Intervention: (n =10)
Pre-operative: acetaminophen 1g, gabapentin 600mg PO
Intra-operative: paracervical block w/ 20mL 0.5% ropivacaine, ropivacaine at abdominal incision sites (10mL total) and ketorolac 30mg once
Postoperative: gabapentin 300mg q12h, celecoxib 200mg q12h and acetaminophen 1g q6h scheduled. Hydromorphone 1mg q3h, oxycodone 5mg q4h PRN
Outcomes:
Primary outcomes:
Opioid use* 0-3h post-operatively
Opioid use* 4-24h post-operatively
*Measured in morphine milligram equivalents (MME)
Secondary outcomes:
Pain Scores (0-10)
Length of stay (h)
Operative time (min)
Estimated blood loss (mL)
Return to office or Emergency Department (ED) for pain within 2w
Discharge
Discharged home with nonstandardized opioid quantity
If used opioids inpatient: discharged home with gabapentin, celecoxib, acetaminophen regimen and 90MME oxycodone
If no opioids used inpatient: discharged home with gabapentin, celecoxib and acetaminophen regimen only

2 INTRODUCTION

2.1 STUDY RATIONALE

The standard of care for pain management after laparoscopic hysterectomy is non-specific, however in light of the ongoing opioid epidemic, a transition to non-opioid pain medication regimens is desired by both physicians and patients.

2.2 BACKGROUND

Hysterectomy is the most common major gynecologic surgery performed in the US and is performed for a variety of indications including malignancy, pelvic mass, endometriosis, leiomyoma, and pelvic organ prolapse (5). The standard of care for pain management after laparoscopic hysterectomy is non-specific. This includes general anesthesia and a focus on non-opioid pain medications. Unfortunately, there is no standardized medication regimen as standard of care and pain management after hysterectomy varies widely from surgeon to surgeon. The traditional regimen for post-operative pain control is opioid-based, however there is limited research regarding the necessary amount of opioids required for adequate pain relief postoperatively. Some studies suggest that patients only take 28% of prescribed opioids (4). A recent case-control cohort study by Dr. Mark from Roswell Park regarding ultra-restrictive opioid prescribing after laparoscopic or robotic surgery showed no change in pain scores, complications or medication refill requests; suggesting that far fewer opioids can be prescribed after surgery (7). New persistent opioid use is a common and under-recognized surgical complication which occurs in 6.5% of patients undergoing major surgery (3). In light of the ongoing opioid epidemic, a transition to non-opioid pain medication regimens is desired by both physicians and patients alike.

A recent quality improvement study by Adajar showed a reduction in post-operative opioid use with a pain medication regimen using gabapentin, celecoxib, acetaminophen and local ropivacaine at laparoscopic port sites (1). Multiple small randomized control trials have shown a reduction in post-operative opioid use when a paracervical block is used in the setting of a vaginal hysterectomy (2). The goal of our study is to assess the effect of a multimodal non-opioid pain medication regimen- including gabapentin, celecoxib, acetaminophen, ketorolac, ropivacaine at port sites combined with a paracervical block- on postoperative opioid use after robotic assisted total laparoscopic hysterectomy. We chose this regimen after considering success in prior studies, cost minimization and resource availability. While NSAIDs such as celecoxib and ketorolac are associated with risks of renal insufficiency and gastric ulcers, these risks are dose dependent and these medications are well-tolerated in the majority of our patient population. NSAIDs have become a staple in pain medication regimens due to their capacity to effectively treat pain after hysterectomy while minimizing opioid use (5). Ropivacaine was chosen due to its longer half- life than lidocaine as well as its cost and resource availability as compared to liposomal bupivacaine. An emphasis was placed on pain medications taken by mouth or per os (PO) to facilitate post-operative milestones and decreased length of stay. The pain medications chosen in the above multimodal regimen are largely well-tolerated by patients, effectively treat pain and show promise in reducing opioid use-postoperatively.

Our primary outcomes are total opioid pain medications required hours 0-3 and hours 3- 24 post-operatively in morphine milligram equivalents (MME). Opioid pain medications will be reported in MME, as it is most often reported in literature, to increase generalizability and applicability.

Our study design is a prospective cohort study with historical controls. While a randomized control trial would be ideal, the expected variation in outcomes precludes this possibility at this institution. Because

of the wide variation in opioid needs postoperatively, an adequately powered randomized control trial would require significantly higher case numbers than available at this institution.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

When taking any medication, there is a risk of allergic reaction. Standard of care medications after hysterectomy include Tylenol and NSAIDs such as ibuprofen. As with the above medications and any medication in general, the medications in this study inherently carry a potential risk of allergic reaction. There is a risk of allergic reaction gabapentin and celecoxib. Most allergic reactions are minimal and treated quickly with a resolution of allergic symptoms in less than 4 hours. There is a risk of toxicity from local anesthetic, ropivacaine. All medications are considered safe in study outlined dosages and regimen.

The paracervical block carries small, preventable risks to the patient. The dosage of ropivacaine local anesthetic has been titrated to provide maximal pain relief and minimize chance of toxicity. Toxicity is always possible however all steps to minimize toxicity (e.g. ensuring injection into cervical stroma not blood vessel) will be undertaken.

During any surgery, there is an inherent risk of needle stick. There is a risk to surgeons and staff of needle-stick during paracervical block. As a whole, the paracervical block does not significantly increase the risk profile of the procedure.

Breach of confidentiality is always a risk however collected information in this study is generally benign. Assigning a number to each record in the spreadsheet and coding the record will minimize it risk for breach of confidentiality.

2.3.2 KNOWN POTENTIAL BENEFITS

Subjects may decrease need for opioid medication for pain management. This may decrease their risk of opioid addiction. They may have lower pain scores and therefore decreased pain after surgery. They may have a decreased length of hospital stay.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Potential risks and benefits were discussed with all patients in an informed consent discussion with their surgeon. Overall, risk of harm during participation in this study was deemed minimal. Subjects were monitored in the hospital while taking prescribed study medications. No new medications were prescribed for the patient to take at home; all medications had been trialed by the patient in the hospital.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To decrease opioid use (measured in morphine milligram equivalents or MME) following RA-TLH	1. Total opioid pain medications required hour 0-3 post-operatively in MME 2. Total opioid pain medications required through hours 3-24 post-operatively in MME	Objective measurement of opioid use in the immediate and longer term postoperative periods
Secondary		
To decrease inpatient length of stay (LOS) and pain following RA-TLH. To minimize postoperative complications related to pain management. To establish safety and efficacy of the intervention.	1. Length of stay in hours 2. Pain scores 3. Return to the clinic or emergency department (ED) due to post-operative pain within two weeks of hospital discharge	Objective markers of post-operative complications

4 STUDY DESIGN

4.1 OVERALL DESIGN

The purpose of this study was to create a non-opioid multimodal pain regimen for women undergoing gynecologic robotic surgery with the goal of minimizing postoperative opioid usage. We hoped to create a protocol that was feasible for implementation in a majority of gynecologic practices.

We hypothesized that there is no difference in post-operative opioid use between a multimodal pain medication regimen and traditional opioid-based pain medication regimen.

This study is a single site, prospective cohort study with historical controls. While a randomized control trial would be ideal, the expected variation in outcomes precludes this possibility at this institution. Because of the wide variation in opioid needs postoperatively, an adequately powered randomized control trial would require significantly higher case numbers than available at this institution. Our study took place from November of 2018 to December of 2022.

To prevent bias in our interventional group, patients will be monitored in the same manner as historical controls. No changes will be made to the patient's ability to obtain pain medications nor assessing their pain scores.

The study interventions included a multimodal pain management protocol with an emphasis on non-opioid pain medications. Standardized protocol is listed below.

Pre-op: Gabapentin 600mg PO once and Acetaminophen 1000mg per os (PO) once
Intra-op: Paracervical block with 0.5% ropivacaine; 10mL bilaterally for total of 20mL
Ropivacaine 0.5% injection at laparoscopic port sites; 10mL spread equally between all port sites

Operate at goal of intraabdominal pressure of 12mmHg; max 15mmHg
Ketorolac 30mg IV once at end of procedure

Post-op: Gabapentin 300mg PO twice daily (BID) for seven days
Acetaminophen 975mg PO every six hours (q6h) for two days then 975mg q6h as needed (PRN)
Celecoxib 200mg PO q12h for seven days
Hydromorphone 1mg IV PRN q3h
Oxycodone 5mg PO PRN q4h while inpatient

Discharge home medications: Gabapentin 300mg PO BID for seven days
Acetaminophen 975mg PO q6h x 2d then 975mg q6h PRN
Celecoxib 200mg PO q12h for seven days
+/- oxycodone 5mg PO q4h x 12 tablets*

*If patient uses opioid medication while hospitalized, will discharge home with oxycodone 5mg PO q4h x 12 tablets

Patients in the prospective cohort group were compared to historical controls who underwent surgery without a standardized pain management protocol.

No interim analysis was planned and no sub-group analyses were performed.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A recent quality improvement study by Adajar showed a reduction in post-operative opioid use with a pain medication regimen using gabapentin, celecoxib, acetaminophen and local ropivacaine at laparoscopic port sites (1). Multiple small randomized control trials have shown a reduction in post-operative opioid use when a paracervical block is used in the setting of a vaginal hysterectomy (2). The goal of our study is to assess the effect of a multimodal non-opioid pain medication regimen- including gabapentin, celecoxib, acetaminophen, ketorolac, ropivacaine at port sites combined with a paracervical block- on postoperative opioid use after robotic assisted total laparoscopic hysterectomy. We chose this regimen after considering success in prior studies, cost minimization and resource availability.

While NSAIDs such as celecoxib and ketorolac are associated with risks of renal insufficiency and gastric ulcers, these risks are dose dependent and these medications are well-tolerated in the majority of our patient population. NSAIDs have become a staple in pain medication regimens due to their capacity to effectively treat pain after hysterectomy while minimizing opioid use (5). Ropivacaine was chosen due to its longer half- life than lidocaine as well as its cost and resource availability as compared to liposomal bupivacaine. An emphasis was placed on pain medications taken by mouth or per os (PO) to facilitate post-operative milestones and decreased length of stay. The pain medications chosen in the above multimodal regimen are largely well-tolerated by patients, effectively treat pain and show promise in reducing opioid use-postoperatively.

Our primary outcomes are total opioid pain medications required hours 0-3 and hours 3- 24 post-operatively in morphine milligram equivalents (MME). Opioid pain medications will be reported in MME, as it is most often reported in literature, to increase generalizability and applicability.

Our study design is a prospective cohort study with historical controls. While a randomized control trial would be ideal, the expected variation in outcomes precludes this possibility at this institution. Because of the wide variation in opioid needs postoperatively, an adequately powered randomized control trial would require significantly higher case numbers than available at this institution.

To prevent bias in our interventional group, patients will be monitored in the same manner as historical controls. No changes will be made to the patient's ability to obtain pain medications nor assessing their pain scores.

4.3 JUSTIFICATION FOR DOSE

Standard NSAID, acetaminophen and gabapentin dosing was chosen for their established safety. Ropivacaine dosing was standardized at a weight-safe dose.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study when seven days postoperative as this was deemed the standard immediate postoperative recovery period. Participants were monitored until postoperative day 14, to collect all data on return to clinic or the emergency department for pain.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

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

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Female, of reproductive age or postmenopausal, undergoing hysterectomy
4. In good general health as evidenced by medical history and without below exclusion criteria
5. Uterine weight <325g on postoperative pathologic report
6. Ability to take oral medication and be willing to adhere to the study intervention regimen

5.2 EXCLUSION CRITERIA

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

1. Current use of opioid prescription or current opioid addiction
2. Presence of contraindication to study medication; eg: gastric bypass, gastric ulcers, chronic kidney disease
3. Known allergic reactions to study medications
4. Non-English speaking patients, cognitively impaired adults

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

Not applicable, due to study design.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The target study sample size was 200 women, with 100 subjects in the prospective intervention group and 100 subjects in the historical control group. We anticipated screening 200 subjects to reach the target sample for the prospective intervention group and screening 200 subjects to reach the target sample for the historical control group.

We expected 200 eligible prospective intervention subjects to be available within the anticipated recruitment period therefore only one in two potential subjects must agree. We expected to review 200 charts within the anticipated collection period to obtain 100 historical control subjects.

For the prospective intervention group, subjects undergoing hysterectomy were screened by the surgeon and the PI at their pre-operative visit. Patients were screened with a thorough history and physical to ensure they have no contraindication to the study intervention medications (ex: allergy, h/o gastric bypass, gastric ulcers, chronic kidney disease). Patients with current opioid prescription and current opioid addiction were excluded from both the historical controls and intervention arm. Cognitively impaired and non-English speaking patients were excluded. If eligible, patients were given verbal and written information regarding the study protocol.

Historical controls were identified through EMR chart search for RA-TLH procedure performed by the surgeon. A review of the electronic chart via Surginet was used to screen for historical control eligibility. Reports were run to identify potential participants with the following criteria: date, physician and procedure. Further screening by the PI to exclude patients with exclusion criteria was then applied. Patients with contraindication to any study medications (ex: allergy, h/o gastric bypass, gastric ulcers, chronic kidney disease) were excluded. Patients with current opioid prescription and current opioid addiction were excluded from both the historical controls and intervention arm. Cognitively impaired and non-English speaking patients were excluded.

As the study population included only adult women undergoing planned hysterectomy, pregnant women were excluded. Vulnerable participants including those who lack consent capacity, such as the mentally ill, prisoners, cognitively impaired participants and children were excluded.

Participants were not compensated or provided any compensation.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

As a preface, the standard of care for pain management after laparoscopic hysterectomy is non-specific. This includes general anesthesia and a focus on non-opioid pain medications with adequate treatment of pain. Unfortunately, there is no standardized medication regimen as standard of care after hysterectomy. As a result, pain management after hysterectomy varies widely from surgeon to surgeon and historically, there has been a heavy reliance on opioid pain medications.

Intervention:
Pre-op: Gabapentin 600mg PO PO x 1 prior to surgery (in pre-op), Acetaminophen 1000mg PO x1 prior to surgery (in pre-op)
Intra-Op: Paracervical block with local anesthetic (0.5% ropivacaine); 10 mL bilaterally (2 injection sites) for total of 20mL. Local anesthetic (0.5% ropivacaine) injected at all laparoscopic port sites; 10mL spread equally between laparoscopic port incisions. Will operate at <15mmHg intra-abdominal pressure with a goal of <12mmHg. At end of procedure during closure of fascia, 30mg ketorolac IV will be given once.
Post-Op: Gabapentin 300mg PO BID for 7 days, Acetaminophen 1000mg PO q6h x 2 days then 1000mg q6h PRN, Celecoxib 200mg PO q 12h x 7d. Hydromorphone 1mg IV PRN q3h and oxycodone 5mg PO PRN q4h while inpatient. Oxycodone 5mg PO x 12 tabs upon discharge (90MME) if patient needed opioid medications while hospitalized; if no opioid used while inpatient, patient will be discharged home with

only non-opioid pain medications. Patients will receive standard post-operative medications such as zofran, metoclopramide. Per standard of care, patients will be asked to rate their pain, on a scale from 1 to 10, by nursing staff prior to administration of pain medications.
After discharge, the patient's opioid use while inpatient will be calculated in MME in addition to LOS in hours. MME will be calculated using the MDCalc MME calculator which uses the Centers for Disease Control and Prevention (CDC) conversion for various opioids to morphine equivalents. Pain scores are recorded in the medication administration record (MAR); pain scores from hour 0 – 3 and hour 3 to 24 postoperatively will be averaged, respectively.

Control:
Patients may or may not have received Toradol during or after their procedure. The mainstay of pain medication regimen was opioid containing medications such as hydromorphone and oxycodone. Patients received standard post-operative medications such as zofran, metoclopramide. Per standard of care, patients were asked to rate their pain, on a scale from 1 to 10, by nursing staff prior to administration of pain medications.

After discharge, the patient's opioid use while inpatient will be calculated in MME in addition to LOS in hours. MME will be calculated using the MDCalc MME calculator which uses the Centers for Disease Control and Prevention (CDC) conversion for various opioids to morphine equivalents. Pain scores are recorded in the medication administration record (MAR); pain scores from hour 0 – 3 and hour 3 to 24 postoperatively will be averaged, respectively.

6.1.2 DOSING AND ADMINISTRATION

Pre-op: Gabapentin 600mg PO PO x 1 prior to surgery (in pre-op), Acetaminophen 1000mg PO x1 prior to surgery (in pre-op)

Intra-Op: Paracervical block with local anesthetic (0.5% ropivacaine); 10 mL bilaterally (2 injection sites) for total of 20mL. Local anesthetic (0.5% ropivacaine) injected at all laparoscopic port sites; 10mL spread equally between laparoscopic port incisions. Will operate at <15mmHg intra-abdominal pressure with a goal of <12mmHg. At end of procedure during closure of fascia, 30mg ketorolac IV will be given once.

Post-Op: Gabapentin 300mg PO BID for 7 days, Acetaminophen 1000mg PO q6h x 2 days then 1000mg q6h PRN, Celecoxib 200mg PO q 12h x 7d. Hydromorphone 1mg IV PRN q3h and oxycodone 5mg PO PRN q4h while inpatient. Oxycodone 5mg PO x 12 tabs upon discharge (90MME) if patient needed opioid medications while hospitalized; if no opioid used while inpatient, patient will be discharged home with only non-opioid pain medications.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Medications will originate from a Kaleida pharmacy at Millard Fillmore Suburban Hospital and be stored in the Pyxis medication dispensing station. The Pyxis machine is password and badge protected with medications assigned to specific study patients.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The study intervention is a multimodal pain medication regimen including gabapentin, acetaminophen, celecoxib, ketorolac, oxycodone, paracervical block with 0.5% ropivacaine, and 0.5% ropivacaine at all

robotic port sites. No changes were made to the standard formulation, appearance, packaging or labeling to the above standard Kaleida administered medications.

6.2.3 PRODUCT STORAGE AND STABILITY

The study intervention is a multimodal pain medication regimen including gabapentin, acetaminophen, celecoxib, ketorolac, oxycodone, paracervical block with 0.5% ropivacaine, and 0.5% ropivacaine at all robotic port sites. No changes were made to the standard product storage of the above Kaleida administered medications in the Pyxis medication dispensing station.

6.2.4 PREPARATION

The study intervention is a multimodal pain medication regimen including gabapentin, acetaminophen, celecoxib, ketorolac, oxycodone, paracervical block with 0.5% ropivacaine, and 0.5% ropivacaine at all robotic port sites. No preparation for any of these medications was required; no thawing, diluting, mixing, or reconstitution was required. All medications administered during the intervention protocol were administered without additional preparation after being obtained from the Pyxis medication dispensing station.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable due to study design.

6.4 STUDY INTERVENTION COMPLIANCE

Consent documents were doubly reviewed by two providers. Adherence to the study protocol was verified by a double provider review of the patients' EMR chart and medication administration summary. The surgeon was additionally present during all portions of the patients' hysterectomy.

6.5 CONCOMITANT THERAPY

All medications taken for chronic medical conditions were continued during the study period in both the intervention and control groups. No independent effects were expected from these medications and no effect on study outcomes was anticipated.

6.5.1 RESCUE MEDICINE

Not applicable as no rescue medications were used.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from the intervention arm does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- medications administered
- reason for study discontinuation

- time and date of discontinuation

Data will be reviewed on a weekly basis by the PI to ensure no adverse events are occurring. All subjects will have their study data reviewed within a week of their surgery. The surgeon will report any adverse events throughout the study duration to the PI should a patient call or present to their office with an adverse event. All adverse events including medication reactions will be reviewed. Safety endpoints include allergic reaction to medications. Safety information will be collected in a case report form, on a weekly basis. The PI will review safety data. Cumulative safety data will be reviewed every 6 months. The safety data will be analyzed with rate of adverse events to determine if harm is occurring.

A serious adverse event in response to a paracervical block will trigger an immediate suspension of research.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive study intervention

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form but do not receive the study intervention may be replaced. Subjects who sign the informed consent form and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for her post-operative visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 1 week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

For the prospective intervention group, subjects undergoing hysterectomy were screened by the surgeon and the PI at their pre-operative visit. Patients were screened with a thorough history and physical to ensure they have no contraindication to the study intervention medications (ex: allergy, h/o gastric bypass, gastric ulcers, chronic kidney disease). Patients with current opioid prescription and current opioid addiction were excluded from both the historical controls and intervention arm. Cognitively impaired and non-English speaking patients were excluded. If eligible, patients were given verbal and written information regarding the study protocol. Subjects were given the consent form at their pre-operative visit, then asked to sign and return the consent form prior to their surgery. Timing between pre-operative visit and surgery ranged from 14 to 60 days.

Historical controls were identified through EMR chart search for RA-TLH procedure performed by the surgeon. A review of the electronic chart via Surginet was used to screen for historical control eligibility. Reports were run to identify potential participants with the following criteria: date, physician and procedure. Further screening by the PI to exclude patients with exclusion criteria was then applied. Patients with contraindication to any study medications (ex: allergy, h/o gastric bypass, gastric ulcers, chronic kidney disease) were excluded. Patients with current opioid prescription and current opioid addiction were excluded from both the historical controls and intervention arm. Cognitively impaired and non-English speaking patients were excluded.

For both the intervention and control groups, all hospital oral medications were administered by a registered nurse (RN). Once discharged, patients self-administered oral medications.

For the intervention group, subjects were given oral acetaminophen and gabapentin in the pre-operative holding area, prior to surgery. After general anesthesia was administered, the paracervical block with local anesthetic (0.5% ropivacaine) was administered by a physician; 10 mL of 0.5% ropivacaine was injected bilaterally (2 injection sites) for total of 20mL. Local anesthetic (0.5% ropivacaine) injected at all laparoscopic port sites by a physician; 10mL spread equally between laparoscopic port incisions. The surgeon operated at <15mmHg intra-abdominal pressure with a goal of <12mmHg. At end of procedure during closure of fascia, 30mg ketorolac IV was given once, by the anesthesia provider (physician or certified nurse anesthetist).

Postoperatively for the intervention group, the following medications were given in a scheduled fashion: gabapentin 300mg PO BID for 7 days, acetaminophen 1000mg PO q6h x 2 days, and celecoxib 200mg PO q 12h x 7d. As needed medications for break through pain included: hydromorphone 1mg IV PRN q3h and oxycodone 5mg PO PRN q4h while inpatient.

For the intervention group, oxycodone 5mg PO x 12 tabs was prescribed upon discharge (90MME), if patient needed opioid medications while hospitalized. If no opioid was used while inpatient, the patient was discharged home with only non-opioid pain medications. After 2 days of scheduled acetaminophen, patients were instructed to take acetaminophen 1000mg q6h PRN.

For the control group, patients received a non-standardized pain medication regimen including opioids, acetaminophen and nonsteroidal anti-inflammatory medications (NSAIDs). They did not receive a paracervical block, nor did they receive local anesthetic at port site incisions.

In both the intervention and control groups, patients received standard post-operative medications such as zofran, metoclopramide. Per standard of care, patients will be asked to rate their pain, on a scale from 1 to 10, by nursing staff prior to administration of pain medications.

Our primary outcomes are total opioid pain medications required hours 0-3 and hours 3- 24 post-operatively in morphine milligram equivalents (MME). Opioid pain medications will be reported in MME, as it is most often reported in literature, to increase generalizability and applicability. Secondary outcomes include pain scores (1-10), length of stay in hours and return to the clinic or emergency department due to post-operative pain within a two-week period.

Patient demographics collected included: age, BMI, smoking status (yes/no/prior), prior pelvic surgeries, preinvasive or benign vs malignant indication for surgery, history of diabetes, history of substance use disorder, pre-operative glucose level and pre-operative albumin.

Financial identification number (FIN) was collected for subject identification during data collection as it is unique to the patient and the encounter.

Operative variables collected included: operative time in minutes, docked robot time, quantitative blood loss as calculated by the change in pre- and post- hemoglobin in g/dL, estimated blood loss, intraoperative complications, and whether staging performed.

Study outcome data collected included: total opioid pain medications required hour 0-3 post-operatively in morphine milligram equivalents (MME), total opioid pain medications required through hour 3-24 post-operatively in MME, pain scores (1-10), length of stay in hours and return to the clinic or emergency department due to post-operative pain within a two-week period.

All medications administered were logged in the patient's MAR. Total opioid medication administration was calculated from the MAR. Pain scores were collected prior to and after receiving any pain medication- per hospital policy.

All patients had a one to two week postoperative visit with the surgeon to assess compliance and tolerance of regimen. All patients had pre-operative blood work, including a complete blood count and basic metabolic panel, collected one to two weeks prior to their surgery. All patients who stayed overnight in the hospital had postoperative day one blood work, including a complete blood count and basic metabolic panel, completed.

8.2 SAFETY AND OTHER ASSESSMENTS

An initial safety meeting was held with the research team to educate research staff on the study protocol. Additionally, monthly meetings occurred with research mentor the surgeon, to ensure proper progress. Obstetric and gynecology resident physicians who were involved in care for hysterectomy patients received education and instructional materials on the study protocol.

Subject screening for eligibility was completed and verified by the PI, the research mentor and a research team member. As the study population included only adult women undergoing planned hysterectomy, pregnant women were excluded. Vulnerable participants including those who lack consent capacity, such as the mentally ill, prisoners, cognitively impaired participants and children were excluded.

For the intervention arm, recruitment and follow up occurred in the surgeon's office. In a private room, with the surgeon, information regarding the trial will be given to potential subjects. All potential subjects will be reminded that participation is voluntary and regardless of enrollment, their postoperative pain will be treated. Data will be de-identified and no identifiable data will be published. Recruitment and follow up will occur in private exam rooms where subjects' confidentiality will be ensured. The interventions will occur in an operating room equipped with Da Vinci robotic system at Millard Fillmore Suburban Hospital, a fully accredited tertiary care institution within New York State, equipped with badge access security system.

For the control arm, retrospective data pulls will occur in a private, non-public setting. All data will be collected from Cerner electronic medical record (Powerchart and Surginet). All electronic medical resources are password protected with two-factor authentication sign in. Study consent forms will be scanned into the two-factor password security authentication protected UB domain. The electronic copy of consent forms will be retained however the paper copy will be destroyed following the creation of the scanned electronic form.

An in-hospital Obstetrics & Gynecology physician was present at all times during this study. Data analysis for the project as a whole will occur in a private, non-public setting.

Data will be reviewed on a weekly basis by the PI to ensure no adverse events are occurring. All subjects will have their study data reviewed within a week of their surgery. The surgeon will report any adverse events throughout the study duration to the PI should a patient call or present to their office with an adverse event.

Collected study data will be stored in a password-encrypted datasheet, on a UB domain that is also password security protected with two-factor authentication sign-in. Only the research team will have access to the password protected spreadsheet. Once all data collection has been completed, all data identifiers will be deleted from the data collection sheet to create a de-identified data set. Individual results will not be shared with subjects. The results of this study will be presented and potentially published in aggregated format.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

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

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

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

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

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

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

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

8.3.3.3 EXPECTEDNESS

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

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

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

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

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

8.3.5 ADVERSE EVENT REPORTING

Data will be reviewed on a weekly basis by the PI to ensure no adverse events are occurring. All subjects will have their study data reviewed within a week of their surgery. The surgeon will report any adverse events throughout the study duration to the PI should a patient call or present to their office with an adverse event. Adverse events including medication reactions will be reviewed. Safety endpoints include allergic reaction to medication. The safety information will be collected on a weekly basis in a case report form. The safety data will be analyzed with rate of adverse events to determine if harm is occurring.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Individual results will not be shared with subjects however AEs and SAEs related to the study will be shared with participants. The results of this study will be presented and potentially published in aggregated format.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable for this study.

8.3.9 REPORTING OF PREGNANCY

Not applicable.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

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

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

8.4.2 UNANTICIPATED PROBLEM REPORTING

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

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

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

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 7 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 30 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 30 days of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Individual results will not be shared with subjects however AEs and SAEs related to the study will be shared with participants.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Efficacy Endpoint: There is no difference in post-operative opioid use between a multimodal pain medication regimen and traditional opioid-based pain medication regimen.

Secondary Efficacy Endpoints:

- A multimodal pain medication regimen does not change length of stay.
- A multimodal pain medication regimen does not change pain scores.
- A multimodal pain medication regimen does not change rate of return to the clinic or emergency department (ED) due to post-operative pain within two weeks of hospital discharge

9.2 SAMPLE SIZE DETERMINATION

We planned a study of opioid (measured in morphine milligram equivalents) use postoperatively from independent control and experimental subjects with 4 controls per experimental subject. Previous studies suggest the response within each subject group was normally distributed with standard deviation 3. If the true difference in the experimental and control means is 3, we will need to study 10 experimental subjects and 40 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05.

We expected to screen 50 subjects to reach my target sample for the prospective intervention group. We expected to screen 100 subjects to reach my target sample for the historical control group.

Due to the COVID-19 pandemic, surgical volume drastically dropped, and during our study and recruitment period, only 60 subjects were available for screening in the prospective arm. Of the 60 subjects, only 28 were eligible for the intervention arm. Of the 28 subjects who were assigned to the intervention, ten underwent the protocol as intended.

This study was not powered for secondary endpoints.

9.3 POPULATIONS FOR ANALYSES

Participants included and analyzed were those who satisfied the Per-Protocol Analysis Dataset. These patients complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of study intervention according to the underlying scientific model.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

In general, continuous variables will be summarized with standard descriptive statistics including means, standard deviations, medians, and ranges. Categorical variables will be summarized with frequencies and percentages. Analysis of outcome measures will primarily be based on general linear models such as t-tests and multiple regression. For markedly non-normally distributed data, nonparametric methods will be used. An overall alpha-level of 0.05 will be used as a cut-point for statistical significance and all statistical tests will be two-sided. All data will be analyzed using SPSS.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Our primary outcome includes total opioid pain medications required 0-3 hours (h) and 3-24h post-operatively in morphine milligram equivalents (MME). MME is measured on a continuous scale. Comparisons will be made using either t-test or the non-parametric Mann-Whitney U test depending upon the skewness of the data. Skewness will be determined by visual inspection of the histograms. Results will be presented as means and standard deviations or medians and ranges.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Our secondary outcomes include pain scores (1-10), length of stay in hours and return to the clinic or emergency department due to post-operative pain within a 2-week period. Pain scores were averaged from 0-3 hours and 3-24 hours post-operatively, for two separate data points. Comparisons for pain scores and length of stay will be made using either t-test or the non-parametric Mann-Whitney U test depending upon the skewness of the data. Skewness will be determined by visual inspection of the histograms. Results will be presented as means and standard deviations or medians and ranges. Return to clinic or emergency department will be compared using the chi-squared test.

9.4.4 SAFETY ANALYSES

No adverse events or serious adverse events occurred during this study.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Demographic information collected included age, BMI, smoking status (yes/no/prior), prior pelvic surgeries, preinvasive or benign vs malignant indication for surgery, history of diabetes, history of substance use disorder, pre-operative glucose level and pre-operative albumin. Comparisons will be made using t-tests, Mann-Whitney U-tests, and/or chi-squared tests as appropriate.

9.4.6 PLANNED INTERIM ANALYSES

No interim analysis was planned or performed.

9.4.7 SUB-GROUP ANALYSES

No subgroup analyses were performed.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be listed. Instead, all individual participant data was aggregated in a de-identified manner.

9.4.9 EXPLORATORY ANALYSES

No exploratory analyses were conducted.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting

intervention/administering study intervention. The following consent materials are submitted with this protocol:

- UB IRB HRP 502 Consent Document Toolkit

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

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

10.1.2 STUDY DISCONTINUATION AND CLOSURE

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

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

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

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

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

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

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

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

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored on an Excel electronic datasheet, saved on secure Kaleida domain, password encrypted, to be maintained for 3 years after the study closes. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived on a password encrypted, secure Kaleida domain.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored in an Excel electronic datasheet, on a password encrypted, secure Kaleida domain. After the study is completed, the de-identified, archived data will be stored for three years however will not be used by other researchers.
No de-identified biological samples will be stored.
When the study is completed, access to study data and/or samples will be provided to authorized parties through the PI.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Sarah Andres, D.O., Resident physician	George Danakas, M.D., Research mentor & attending physician
University at Buffalo	General Physicians, Adjunct faculty at the University at Buffalo
1001 Main St, Buffalo, NY	1001 Main St, Buffalo, NY
(716) 323-0631	(716) 323-0631
seandres@buffalo.edu	gdanaka@buffalo.edu

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of the University at Buffalo IRB. Members of the IRB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The IRB was updated annually with safety and efficacy data on each arm of the study.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- The PI conducted weekly monitoring of patient data.
- Due to the small nature of this study, independent audits were not conducted.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the PI for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data is documented (recorded) and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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

Data recorded in the password encrypted Excel sheet derived from the EMR should be consistent with the data recorded in the EMR.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be reported to the University at Buffalo IRB.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of three years after the formal discontinuation of study intervention. These documents should be retained for a longer period, however, if required by local regulations.

10.1.10 PROTOCOL DEVIATIONS

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

These practices are consistent with ICH GCP:

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

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

10.1.11 PUBLICATION AND DATA SHARING POLICY

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

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

10.1.12 CONFLICT OF INTEREST POLICY

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

10.2 ADDITIONAL CONSIDERATIONS

Not applicable.

10.3 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem

US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

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