UW14030: Epidural Anesthesia Within an Enhanced Recovery Pathway in Reducing Pain in Patients Undergoing Gynecologic Surgery

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UW14030: Epidural Analgesia as Part of an Enhanced Recovery Pathway in Gynecologic Surgery

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DESIGN: Single-center, randomized controlled trial

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ENROLLMENT:	104
STUDY LOCATION:	University of Wisconsin Hospital and Clinics
STUDY DURATION:	36 months from initial subject enrollment
PURPOSE:	To test the hypothesis that epidural analgesia, when incorporated into an enhanced recovery pathway in gynecologic surgery, results in improved pain control, shorter hospital stay, decreased rate of complications, and increased patient satisfaction, than enhanced recovery pathway alone.
PRIMARY ENDPOINT:	Postoperative subject pain scores (mean pain score on a ten point scale in the first 24 hours following surgery)
FUNDING SPONSOR:	UW Department of Obstetrics and Gynecology

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1.0 PROJECT SUMMARY/ABSTRACT

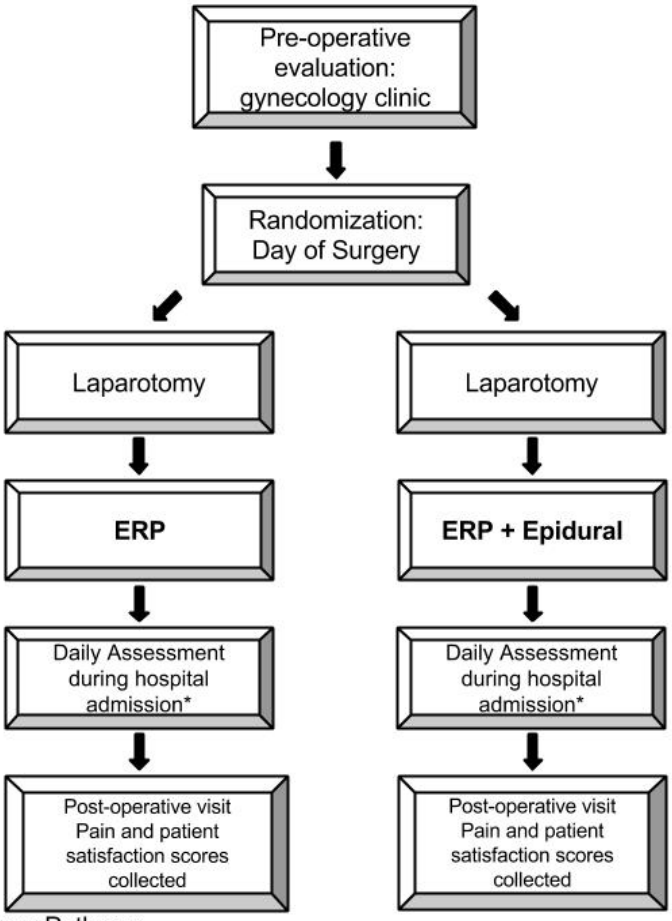
Epidural analgesia is commonly used for post-operative pain control in patients undergoing laparotomy. It has been associated with better pain control than patient-controlled analgesia with intravenous opioids and is considered the standard of care at our institution for patients undergoing surgery via vertical midline laparotomy. Epidurals are typically placed prior to the induction of general anesthesia but not used until the end of the surgery, when a combination of a local anesthetic and an opioid are started. The epidurals stay in place for several days after surgery, with a continuous dose of medication infused, and patient-controlled bolus dosing available. Once bowel function has returned, the epidural is removed and patients transition to a regimen of oral pain medications.

Recently, the concept of enhanced recovery, in lieu of patient-controlled analgesia, has been validated in the colorectal and gynecologic surgical literature. Enhanced recovery pathways include pre-operative education, elimination of mechanical bowel prep, limited drain placement, early ambulation, and structured use of intra-operative and post-operative anti-emetics and analgesics. The use of intravenous opioids is restricted.

The role of epidural analgesia within an enhanced recovery pathway has not been studied. We will randomize participants undergoing laparotomy for gynecologic indications to epidural placement vs. no epidural placement. All patients will participate in an enhanced recovery pathway as described below. We will compare pain scores, opiate use, length of hospital stay, post-operative antiemetic use, return of bowel function, patient satisfaction, post-operative complications, and readmission rates in both groups.

A translational correlate to our clinical endpoint will be examination of stress and inflammation response in patients receiving epidurals versus those who do not. There is evidence that neuroaxial blockade can decrease cytokine release (a marker for inflammation) and decrease cortisol release (a marker for stress). This is particularly important in patients with cancer, where immune function has the capability of affecting the tumor microenvironment.

1.1 Research Schema



ERP = Enhanced Recovery Pathway
* Consists of collection of primary and secondary outcome measurements

2.0 INTRODUCTION

2.1 Background and Rationale

Historically, post-operative care has lacked evidence-based support. Common practices are adopted by individual surgeons and disseminated pedagogically. Consequently, much of the dogma surrounding post-operative care has been challenged in recent years. This can perhaps be best illustrated by looking at the use of post-operative nasogastric tubes. Once routinely used to prevent ileus in all post-operative patients, nasogastric tube use was subsequently shown to increase pneumonia, atelectasis and aspiration (1) and is now used only in select patients. New, evidence-based management pathways have been developed to attenuate the stress response associated with surgery and accelerate post-operative recovery (2,3). Termed 'enhanced recovery pathways' by Dr. Kehlet, a colorectal surgeon, aspects of these pathways have slowly disseminated and have been adapted across different surgical

subspecialties as more and more data have been published demonstrating their benefits. Key elements common to all enhanced recovery pathways include: preoperative patient education, reduction of preoperative fasting, omission of bowel preparation, perioperative normovolemia, limited use of nasogastric tubes and drains, early removal of urinary catheters, aggressive multimodal analgesia to minimize opiate consumption, early postoperative mobilization, prokinetics to enhance gastrointestinal motility, and early oral intake. Recently, Kalogera et al. published a retrospective cohort study demonstrating the use of an enhanced recovery pathway in a gynecologic patient population (4). Patients undergoing laparotomy for debulking, staging and benign procedures (including vaginal prolapse surgery) were included. The described enhanced recovery pathway resulted in a 2-day reduction in mean length of hospital stay, use of fewer opioids for pain control, and significant cost savings (more than $500,000 in 81 patients). Patient satisfaction scores and 30-day outcomes were similar in both groups (4).

Individual surgeons currently adopt elements of different enhanced recovery pathways at our institution, but a rigorous multi-disciplinary system has yet to be enacted.

Many aspects of the enhanced recovery pathway are focused on hastening the return of gastrointestinal function after surgery, including minimizing opiate consumption (5). At our institution, return of bowel function after laparotomy is often the rate limiting factor impacting length of hospital stay. Like many institutions, we have explored the potential benefit of epidural analgesia to reduce systemic opioid use. The benefit of epidural analgesia in post-laparotomy pain management has been demonstrated in a number of randomized controlled trials and meta-analyses (6, 7). The 2005 Cochrane review on this subject concluded that although there was improved pain control with continuous epidural analgesia vs. patient controlled analgesia, there was no statistically significant difference in the length of hospital stay or time until return of bowel function (8). Despite data supporting its use, epidural analgesia has not been universally accepted, attributable to regional trends and physician preference. In our institution, we do not often utilize epidurals in patients who have undergone bowel resection, fearing that postoperative hypotension may lead to anastamotic ischemia and subsequent bowel leak. Many surgeons find that the frequency of epidurals being discontinued is unacceptable, and preferentially use patient-controlled analgesia (PCA), typically with hydromorphone or morphine. Epidural placement also can delay surgical start times, dependent on the availability of anesthesia staff. Further, no prospective data have been collected regarding the use of epidural analgesia within an enhanced recovery pathway.

We will test the hypothesis that patients who receive epidural analgesia as part of an enhanced recovery pathway do not experience better pain control than those who participate in an enhanced recovery pathway without regional analgesia. We have identified an exploratory translational endpoint, which examines the role of epidural analgesia in immune cell function and stress response. Serum markers of inflammation (IL-2, IL-6, TNF, CRP) will be compared between the two groups. Salivary cortisol levels (as a marker of stress) will also be obtained to make comparisons. This may be of particular interest for our subjects with a cancer diagnosis, as stress and inflammation have been shown to negatively affect tumor behavior, promoting invasion, angiogenesis and metastases.

2.2 Study Purpose

We propose to perform a randomized controlled trial to test the hypothesis that epidural analgesia in combination with an enhanced recovery pathway is not superior in providing post-operative pain control when compared with an enhanced recovery protocol alone among patients undergoing laparotomy for gynecologic surgery. We will also measure the impact of epidural analgesia on the following secondary outcomes: opiate use, length of hospital stay, post-operative antiemetic use, return of bowel function, patient satisfaction, post-operative complications, and readmission rate. To test our hypothesis that epidural analgesia decreases stress response to surgery, we will also measure serum levels of several biomarkers associated with stress, such as C-reactive protein (CRP) and salivary cortisol levels.

2.3 Study Design

Our study will be a single-center, non-blinded, randomized control trial. The study will be conducted at the University of Wisconsin Hospital and Clinics. Gynecologic patients undergoing laparotomy via midline vertical skin incision will be eligible. Given the nature of this study, it will be impossible for researchers or subjects to be blinded to research interventions.

2.4 Study Endpoints

2.4.1 Primary Endpoint

Mean postoperative pain score for the first 24 hours post-operatively, measured by the Numeric Rating Scale (NRS), which rates pain on a 1-10 scale (collected routinely on the post-operative floor) will be compared between the epidural and no-epidural groups.

2.4.2 Secondary Endpoints

2.4.2.1 Total opioid use measured in oral morphine equivalents for the first two days post-surgery

2.4.2.2 Length of hospital stay (measured in hours from admission to time of discharge order placement)

2.4.2.3 Post-operative antiemetic use and number of recorded episodes of emesis

2.4.2.4 Return of bowel function (measured in hours from completion of surgery to passage of flatus)

2.4.2.5 Subject satisfaction at the 4 week post-operative visit (as measured by two pain satisfaction questions taken from the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey)

2.4.2.6 Post-operative complications (urinary tract infections (UTIs), thromboembolic events, pneumonia, blood transfusion, myocardial infarction, falls)

2.4.2.7 Readmission rate

2.4.2.8 Epidural discontinuation rates prior to planned removal (in epidural group only)

2.4.2.9 Stress and inflammation serum markers at baseline and the first day after surgery, as well as saliva markers the first day after surgery.

3.0 MATERIALS AND METHODS

3.1 Selection of Subjects

Subjects included in this study will be women who are undergoing an exploratory laparotomy via midline vertical skin incision for gynecologic indications at UW Hospital.

3.2 Eligibility Criteria

Potential subjects will be introduced to the study during their pre-operative assessment with their operating surgeon. Eligible subjects will have a discussion with the study team about the goals and objectives of the study, and will be consented for the study at their preoperative clinic visit. There is a chance that subjects will be approached after their pre-operative assessment regarding this study. This would be conducted via phone contact by a clinical member of the research team. This would only be in circumstances that the study team is unable to initially approach a subject at her clinical pre-operative assessment, and the study team feels that the subject would be a good candidate for this study.

3.2.1 Inclusion Criteria

1. Patients undergoing gynecologic surgery via midline vertical laparotomy at UWHC.
2. Patients must be ≥18 years old.
3. Patients must be English speaking.
4. Patients must have the ability to understand visual and verbal pain scales.
5. Patients must be eligible for epidural placement

3.2.2 Exclusion Criteria

1. Known allergy to local anesthetics.
2. Known history of chronic pain disorders and/or chronic opioid use defined as > 10mg of PO morphine or equivalent used daily for at least 30 days prior to enrollment

3. Patient is a prisoner or incarcerated.
4. Significant liver disease that would inhibit prescription of opioids
5. Significant kidney disease that would inhibit administration of gabapentin
6. Patient has a history of opioid dependence requiring rehabilitation or the use of opioid antagonists
7. Patient is pregnant
8. Patients with a planned exploration with biopsies (no organs removed) will be excluded from the study.

3.3 Conduct of Study

3.3.1 Study Procedure Overview

Informed consent will be obtained at the pre-operative visit, during which time all participants will receive standardized preoperative teaching and carbohydrate loading in line with the enhanced recovery protocol. Post-surgical expectations and additional measurements within the context of the study will be explained to all participants.

They will also be informed of the risks and benefits of epidural analgesia. Subjects would leave with printed information regarding the enhanced recovery pathway, including when to drink the carbohydrate-loading drink and how to manage their daily medications in the preoperative and postoperative periods.

In the event that the initial introduction regarding the study was not completed at the subject's pre-operative assessment, the potential subject may be contacted via phone by a clinical member of the research team. An IRB-approved basic introductory telephone script will be used. If the subject is interested in learning more about the study, the study team may mail the subject a consent form and/or invite the subject to come in for a research visit. Two attempts will be made to call the potential subject. If the subject does not answer the phone, does not return the phone calls, or is not interested in participating, the study team will not make additional attempts to contact the subject.

Additionally, if a patient is admitted directly to the hospital for a laparotomy or was not recruited at the pre-op visit, she may be recruited and consented in the hospital. This is relatively rare in our patient population. Recruitment and consenting would only be considered if the patient were admitted the day prior to surgery and adequate time were available to discuss the study and obtain consent. In the hospital setting, a member of the clinical/surgical team who is also a member of the research team (e.g., resident, surgeon, fellow) would approach the potential subject. Consent would then be obtained by that same individual or another member of the research team (e.g., study coordinator).

The study staff will provide the anesthesiology team with regular notifications regarding consented subjects and their planned surgery dates. Subjects will be considered

enrolled at the time of randomization, which will preferably occur on the day of surgery, but could be performed at any time after consent. Randomization will be computer-generated via OnCore and will be performed by one of the study team members.

Sections 3.3.2-3.3.3 outline the recommended procedures to be followed throughout the pre-, peri- and post-operative periods. These guidelines are consistent with standard clinical care, for which strict adherence is not feasible. Therefore, variations from these guidelines will not be considered protocol deviations.

3.3.2 Intervention Period

Upon arrival to the hospital on the day of surgery, standard First Day Surgery procedures will be followed. Subjects will be cleared physically fit for surgery by both anesthesiology and gynecology per standard clinical practice. A peripheral intravenous catheter will be placed preoperatively, as this is customary for any operative procedure.

For subjects randomized to receive an epidural, the regional anesthesiology faculty, fellow or resident will discuss the nature of epidural analgesia with the subject. If the subject is still amenable, they will be consented for the epidural per standard practice (part of the surgical consent form) in a semi-enclosed space in the pre-operative holding area normally used for consenting all surgical and anesthetic procedures.

Subjects in both arms will receive the following medications in our pre-operative holding area:

- Celecoxib 400mg PO x 1
- Acetaminophen 1,000 mg PO x 1
- Gabapentin 600 mg PO x 1. Patients over 60 years old will be given 300 mg PO x 1 of gabapentin to avoid over-sedation.

For subjects randomized to the epidural group, an epidural will be placed in the First Day Surgery pre-operative area or similar areas suitable for insertion of epidural catheters. Subjects will receive sedative and opioid prior to epidural placement, per the anesthesia team's standard practices. The epidural will be placed by the anesthesia team using the standard protocol. The epidural will not be turned on (no medications running other than the test dose) until the end of the surgery. The first bolus dose will be given while the skin incision is being closed.

During the operation, all patients will receive the following anti-emetics:

- Haldol 1 mg IV x 1
- Dexamethasone 4 mg IV x 1
- Zofran 4 mg IV 30 minutes before skin incision closure.

Alternative medications of similar classes may be utilized in the event of a drug shortage.

The non-epidural subjects will receive an injection of a local anesthetic (.25% bupivacaine or equivalent) into their incision after fascial closure. IV opioid medication will be administered at the discretion of the anesthesiologist.

In the post-operative anesthesia care unit, subjects with epidurals may receive medication via the epidural in boluses on an as needed basis, as determined by the anesthesia team. Medications will be titrated based on patient comfort and blood pressures.

Standard epidural medications and dosage are as follows:

- 0.1% ropivicaine + 10 mcg/mL hydromorphone at 6 mL/hr continuous rate
- 3 mL/hr RN bolus, to be used as needed based on pain ratings
- 3 mL/30 minutes patient bolus, which is available on patient demand.

Hypotension is a common side effect of epidural analgesia, and is the most common reason that epidurals are turned off post-operatively. In order to standardize dose adjustments related to hypotension, hypotension will be defined as follows:

- >20mmHg drop in systolic blood pressure from the patient's pre-operative ambulatory clinic visit.
- Other evidence of hypotension, such as evidence of reduced end-organ perfusion (ie neurologic changes, demand cardiac ischemia, urine output of < 10 mL/hr)

If subjects with epidurals develop hypotension, they will be evaluated by the gynecology resident on-call. Other causes of hypotension (hypovolemia, acute hemorrhage) will be ruled out. An intravenous fluid bolus will be given based on the MD's clinical evaluation. If the patient's blood pressure does not respond, the anesthesia team will be called and the epidural rate will be decreased from 6 mL/hr to 4 mL/hr. In the event of severe hypotension of instability, the epidural may be discontinued or halted as dictated by standard clinical practice. If these interventions fail to normalize the patient's blood pressure to within 20 mmHg of their baseline, the epidural will be turned off. The patient will continue to receive medications through the enhanced recovery pathway and may receive patient controlled opioid analgesia if indicated. The future use of the epidural will be determined by the surgical and anesthesia team.

3.3.3 Postoperative Care Guidelines: For all subjects

3.3.3.1 *Activity*

Patients will spend >2 hours out of bed (including 1 or more walk and sitting in chair) within the first 12 hours following surgery. From POD 1 until discharge, the patient will be out of bed greater than 8 hours including four or more walks and sitting in chair each day. The patient will be up in a chair for all meals. The urinary catheter will be removed as soon as the patient demonstrates the ability to walk with assistance and the treating team does not have a clinical indication to measure urine output with the accuracy of a catheter. In the case of radical hysterectomy, where post-operative bladder

dysfunction is common, the catheter will be removed at the physician's discretion.

3.3.3.2 *Diet*

If a gastric emptying device (orogastric or nasogastric tube) was used intraoperatively, it will be removed at extubation. The first meal of low residual diet will be ordered 4 hours after completion of surgery (or upon arrival to floor). Within the first 12 hours after surgery, one box of liquid Ensure will be ordered for the patient. Patients will be encouraged to have oral intake of at least 800mL, but not more than 2,000mL on POD 0. Continue 2 boxes of liquid Ensure per day until discharge. There will be a daily oral intake goal of 1500-2500mL of fluids. Scheduled senna, docusate and polyethylene glycol will be ordered to promote post-operative bowel function.

3.3.3.3 *Fluid balance*

Upon arrival to the floor IV fluids will be infused at 40 mL/h. A nursing communication will be sent to peripheral lock IV when patient has had 600 mL orally intake or at 8:00 AM on post-operative day (POD) #1, whichever comes first. Fluid boluses will be given at the discretion of the physician.

3.3.3.4 *Analgesia*

There will be a goal of no IV patient-controlled analgesia. In the epidural group, dosing and rate of standardized medication will be managed by the anesthesia team until the epidural is removed. This will include the standard order set for patients who receive epidurals on any hospital service. Medications will include the epidural solution of local anesthetic and narcotic, oral narcotic on an as needed basis, scheduled acetaminophen, and as-needed anti-emetics. The dose of ropivicaine (either the concentration or the rate) can be increased on post-operatively based on blood pressures, pain scores and sensory exam. In the non-epidural group (and in the epidural group after epidural removal), suggested pain medication regimen guidelines are as follows:

Oral opioids
Oxycodone 5–15 mg orally will be administered every 3 hours as needed for pain rated 4 or greater or greater than patient stated comfort goal (5 mg for pain rated 4–5, 10 mg for pain rated 6-7, or 15 mg for pain rated 8-10). If 15 mg every 3 hours is inadequate for pain control as evidenced by a need for IV opioids the dose will be escalated by increasing the dose available by 10mg increments.

Scheduled acetaminophen

Acetaminophen 1,000 mg will be given orally every 8 hours for subjects with no or mild hepatic disease (acetaminophen 1,000 mg orally twice daily for patients with moderate hepatic disease). Maximum acetaminophen should not exceed 3,000 mg/24 hours from all sources

Scheduled NSAIDs
Ketorolac 15 mg IV will be given every 6 h for four doses (start no sooner than 6 hours after last intraoperative dose). Six hours after last dose of ketorolac, ibuprofen 800 mg will be given orally every 6 hours on a scheduled basis.

If a subject is unable to take NSAIDs, Tramadol 100 mg will be given orally 4 times a day (start at 6:00 AM POD 1) for subjects younger than 65 years of age with no history of renal impairment or hepatic disease. The dose of tramadol will be reduced to 100 mg orally twice daily for subjects 65 years of age or older or whose creatinine clearance is less than 30 mL/min

All medications above may be substituted for a similar drug in the same class if a medication shortage occurs or an allergic reaction is documented.

Breakthrough pain
If pain is rated greater than 7 more than 30 minutes after receiving 15 mg oxycodone, the subject will receive an IV narcotic as a rescue dose. This dose may be repeated after 20 minutes of the first dose if the pain score remains above 5. Patient-controlled analgesia utilizing an IV opioid will be initiated if the 2 IV narcotic doses are deemed insufficient to keep the patient's pain score less than 5 using the NRS.

3.3.4 Biological outcome measures

Biological correlates will include assessment of salivary cortisol levels, systemic levels of inflammatory cytokines (IL-2, IL-6, TNF and CRP), and changes in the phenotype of circulating immune cells, in order to quantify changes in stress and inflammation in patients who receive epidural analgesia versus those who do not.

Blood samples from enrolled subjects will be collected at the following specific time-points: prior to surgery and the 1st day following surgery. Whenever possible, these research blood draws will coincide with routine laboratory draws in order to avoid additional venipuncture. We will collect 3 tubes of blood (~30mL) at each time point to measure serum markers for inflammation and stress response (IL-2, IL-6, TNF, CRP). Salivary cortisol levels will also be measured three times on the first post-operative day (morning, afternoon, evening).

The standard of care for patients on our gynecologic service is to draw a routine set of serum laboratory studies, including blood count and comprehensive metabolic panel, on the first post-operative day.

3.3.5 Post-operative data collection

The Pain Numeric Rating Scale (NRS) is routinely performed by nursing staff at least once per shift and is included in the electronic medical record. In addition, a member of the research team will collect a Brief Pain Inventory (short form) on the first post-operative day. Missed pain scores will not constitute a protocol violation, though every attempt will be made by the study team to ensure they are collected. Total opioid equivalents used will be recorded. Total anti-emetic use and episodes of emesis will be recorded. Post-operative complications, including infections, bowel obstructions, deep vein thromboses, and pulmonary emboli, will be recorded. Time until return of bowel function (as defined by passage of flatus or gas visualized in the ostomy bag) will be recorded.

Stress and inflammation serum markers will be drawn as part of the standard POD#1 morning lab draw. Salivary cortisol levels will be measured at three time-points on the first post-operative day (morning, afternoon and night). A Perceived Stress Scale (PSS) will be administered on the first day after surgery, to correlate perceived stress with salivary cortisol levels. Subjects will fill out a patient satisfaction survey related to pain control (HCAHPS) at their post-operative visit. BPI will also be collected at this visit. If the study team is unable to administer the questionnaires at the time of the post-operative clinic visit, the study team may call the patient to administer the survey/questionnaires over the phone or mail the survey/questionnaires to the subject within one month of the postoperative clinic visit.

3.3.6 Study Table of Events

	Pre-op Visit[1]	Day of Surgery	Post-Op Day 1	Discharge	Post-Op Clinic Visit
Consent	X				
Eligibility	X				
Randomization		X[2]			
Enhanced Recovery Pathway (ERP)	X	X	X	X	X
Epidural placement		X[3]			
Serum (~ 30mL)[6]	X[4]		X		
Salivary swab[6]			X[5]		
Pain Numeric Rating Scale (NRS)		X[7]	X	X[7]	
Brief Pain inventory			X		X[8]
Perceived Stress Scale			X		
AE check				X	
Patient Satisfaction Survey (HCAHPS)					X[8]

1. Study recruitment may occur over the phone after the pre-operative assessment using an IRB approved phone script, or recruited from the hospital if admitted the day prior to surgery.
2. Randomization to occur at any point after consent and eligibility is determined, but as close to surgery as possible. Preferably to occur the morning of surgery.
3. For subjects randomized to receive an epidural
4. Pre-op serum sample may be collected at the pre-operative visit or on the day of surgery.
5. Salivary swab will be performed on POD #1 at three time points: morning, afternoon and evening
6. Every attempt should be made to collect blood and salivary samples as outlined. However, if a subjects refuses or the sample is unable to be collected for another reason (e.g., no lab staff available to process sample, or unable to obtain sufficient sample), it will not be considered a protocol violation.
7. Every attempt will be made to collect the Pain Numeric Rating Scale (NRS) on Day of Surgery and Discharge date, if available. The Pain Numeric Rating Scale (NRS) will be collected daily during admission.
8. If the study team is unable to administer the questionnaires at the time of the post-operative clinic visit, the study team may call the patient to administer the survey/questionnaires over

the phone or mail the survey/questionnaires to the subject within one month of the postoperative clinic visit.

4.0 STATISTICAL CONSIDERATIONS

4.1 Randomization

Simple unstratified complete randomization will be performed electronically by study staff using OnCore after consent, as close to surgery as possible, preferably on the day of surgery.

4.2 Analyses

The primary endpoint of relative pain scores between the epidural and non-epidural group will be analyzed by calculating a two-sided 95% confidence interval on the difference in mean scores between the two groups and concluding non-inferiority if this lies entirely below 2 points (mean non-epidural pain score proven, within a 95% confidence limit, to be at most 2 points worse than mean pain score in the epidural group). Secondary outcomes of length of hospital stay, patient satisfaction scores, average daily pain score for two days following surgery, length of time until return of bowel function, total opioid use, and stress and inflammation serum markers will be compared using two-sided 95% confidence intervals for their mean differences. Superiority tests at the two-sided .05 level, where specified in Section 2.4, will be conducted by determining whether these confidence intervals overlap 9. Post-operative complications and epidural discontinuation rates will be tabulated and presented for each group (where applicable).

All analyses will be performed on an intent-to-treat basis, although as stated below noncompliance and losses follow-up are expected to be rare.

4.3 Sample Size Calculations

With 52 patients in each group and using a two-sided 0.5 critical value, there is 87% power to detect non-inferiority of the non-epidural group to the epidural group as defined by a mean difference in post-operative pain scores of 2 points or less, under the alternative hypothesis that the treatments are identical. Thus this study is well-powered to show non-inferiority of the patient group who does not receive an epidural as part of the enhanced recovery pathway, with respect to postoperative pain within a margin of 2 points. These calculations used a post-operative pain score standard deviation or 3.3 units, obtained from unpublished data on similar patients at this institution.

Because randomization will be performed as close to surgery as possible and the primary outcome is obtained within one day of surgery, minimal loss to follow-up is anticipated. We will increase the number of subjects enrolled in order to meet our power calculations if a subject is lost to follow-up. Therefore, up to 6 additional subjects may be accrued.

4.4 Interim Analysis

No formal interim analysis will be made for efficacy or futility. Adverse events and other aspects of safety will be monitored as described in Section 7.

5.0 RECORDS TO BE KEPT

All subjects will be entered into OnCore, the UWCCC research database. The following fields will be completed in OnCore: demographics, MR number, insurance type, consent information, study ID#, subject statuses and dates, disease site and histology, enrolling staff. Subject data will be managed by the PI, resident researchers (Co-Investigators) and the UW Gyn-Oncology Research Office.

Each subject will be assigned a unique, study ID number. Study data will be stored with study ID numbers and will be kept indefinitely. Study data will be collected and managed using REDCap electronic data capture tools hosted at the University of Wisconsin-Madison, School of Medicine and Public Health. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Once the study is complete and REDCap is no longer needed, data will be exported from the system and stored on the departmental network, which is secure and password protected. Access is limited to the study team and IT support staff. Data within REDCap is maintained and archived per ICTR policy.

Data will be collected directly from subjects, from study interventions and from medical record review. Data elements to be collected will include demographics, details of the enhanced recovery protocol, details of surgery and hospital course, diagnosis, pain scores, and adverse events (a complete data sheet is attached).

Blood and salivary samples are collected as part of this study. Tissue banking is optional for study participants. All specimens will be stored at UW Hospital in the Division of Gynecologic Oncology laboratories. These laboratory areas have limited access and remain locked when no laboratory personnel are present. Subject samples will be coded, removed of all direct identifiers, and linked to the password-protected study database.

Since the UW Gyn-Oncology lab does not have the ability to test for cortisol levels, saliva samples will be sent to an outside lab for testing. The UW lab will extract saliva from the collection swabs and then store the samples for batch shipment to the Laboratory for Biological Health Psychology at Brandeis University where cortisol measurements are conducted on a fee-for-service basis. Samples for shipment will be labeled with study number, subject ID number, specimen code (e.g., morning, afternoon, evening). Brandeis will not have access to any direct identifiers or the code that links samples back to identifiers. Salivary samples will be exhausted or discarded after testing at Brandeis and only cortisol results will be returned to the UW study team.

Additionally, 1-2 mL of serum will be sent to an outside laboratory at Brigham and Women's Hospital in Boston, MA. Samples for shipment will be labeled with study number, subject ID number, specimen code (e.g., pre-op or POD#1). The lab will not have access to any direct identifiers or the code that links samples back to identifiers. Samples will be exhausted or discarded after testing at Brigham and only results will be returned to the UW study team. Samples will be centrifuged and then frozen at -70-80°C and held for batch shipment to the lab of:

Kevin Elias, MD and Kathy Hasselblatt, MS
Brigham and Women's Hospital
221 Longwood Avenue
Boston, MA 02115

After the available protocol testing from blood samples is complete, leftover samples will be stored for future IRB-approved research if subjects consent to specimen banking. Future research will be limited to research studying cancer and surgical stress and immune response. No future research will be conducted on leftover samples without obtaining separate IRB approval. Subjects may request to withdraw samples at any time by contacting our research office.

Blood samples will be used to analyze soluble molecules present in the serum and plasma. We will isolate immune and other cells present in the blood to determine if epidural analgesia affects immune response. The soluble molecules present in the blood will be analyzed by using techniques such as mass spectroscopy, NMR, ELISA, western blotting, and biochemical activity assays. The cells present in the blood will also be used in different immunological assays. At the lab at Brigham and Women's Hospital, serum will be analyzed for circulating microRNAs. Serum cytokine, CRP and cortisol levels may also be evaluated, to ensure results are similar to those collected in our own laboratories. Salivary samples will be used to measure cortisol levels. Cortisol is a marker of physiologic stress, which also may be altered by epidural analgesia.

Blood collection: 30 mL of blood will be drawn from the patient prior to surgery. We will use this blood to examine the patient's baseline immune response, by measuring natural killer cell and other immune activity. A second blood draw (again, 30mL) will occur the first day after surgery. Whenever possible, blood samples will be drawn in conjunction with other clinically required blood tests in order to avoid unnecessary venipuncture.

Salivary collection: A cotton swab will be brushed against the inside of the mouth (the buccal mucosa) at three different time points (morning, afternoon, and evening) on the first post-operative day.

6.0 PATIENT CONSENT AND PEER JUDGMENT

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

7.0 DATA AND SAFETY MONITORING

7.1 Oversight and Monitoring Plan

The UWCCC Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all UWCCC clinical studies. A summary of DSMC activities follows:

- Reviews all clinical trials conducted at the UWCCC for subject safety, protocol compliance, and data integrity.
- Reviews all Serious Adverse Events (SAE) requiring expedited reporting, as defined in the protocol, for all clinical trials conducted at the UWCCC, and studies conducted at external sites for which UWCCC acts as an oversight body.
- Reviews all reports generated through the UWCCC DSMS elements (Internal Audits, Quality Assurance Reviews, Response Reviews, Compliance Reviews, and Protocol Summary Reports) described in Section II of this document.
- Notifies the protocol Principal Investigator of DSMC decisions and, if applicable, any requirements for corrective action related to data or safety issues.
- Notifies the CRC of DSMC decisions and any correspondence from the DSMC to the protocol Principal Investigator.
- Works in conjunction with the UW Health Sciences IRB in the review of relevant safety information as well as protocol deviations, non-compliance, and unanticipated problems reported by the UWCCC research staff.
- Ensures that notification is of SAEs requiring expedited reporting is provided to external sites participating in multi-institutional clinical trials coordinated by the UWCCC.

7.2 Monitoring and Reporting Guidelines

Subjects will be assessed for toxicity throughout the study period. All grade 3 or greater adverse events, regardless of causality, that occur during hospitalization will be collected. Data Safety Monitoring Protocol Summary Reports will be provided to the UWCCC DSMC annually.

7.3 Review and Oversight Guidelines

7.3.1 Serious Adverse Event – Reported Within 48 hours

Serious Adverse Events requiring reporting within 48 hours (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu within one business day. A 48 hr. initial "SAE Details" Report, generated in the UWCCC database, must be attached to the email along with any pertinent information available at the time of initial reporting. The Committee Chair will review the information and determine if immediate action is required. Within 10 working days, all subsequent SAE documentation must be submitted electronically along with a 48 hour follow-up "SAE Details" Report and a completed UWCCC SAE Routing Form to saenotify@uwcarbone.wisc.edu. All information is entered and tracked in the UWCCC database.

The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB (as necessary) and provides documentation of these notifications to the DSMC.

See Section 7.4 for detailed instructions on SAE reporting.

7.3.2 Serious Adverse Event – Reported Within 10 Days

Serious Adverse Events requiring reporting within 10 days (as described in the protocol) must be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (any documentation available at that time of initial reporting). The DSMC Chair will review the information and determine if further action is required. All information is entered and tracked in the UWCCC database.

The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB (as necessary) and provides documentation of these notifications to the DSMC.

See Section 7.4 for detailed instructions on SAE reporting.

7.3.3 Study Progress Review

Protocol Summary Reports (PSR) are required to be submitted to the DSMC in the timeframe determined by the risk level of the study (quarterly; semi-annually; or annually). The PSR provides a cumulative report of SAEs, as well as instances of non-compliance, protocol deviations, and unanticipated problems, toxicities and responses that have occurred on the protocol in the timeframe specified. PSRs for those protocols scheduled for review are reviewed at each DSMC meeting.

Protocol Summary Reports enable DSMC committee members to assess whether significant benefits or risks are occurring that would warrant study suspension or closure. This information is evaluated by the DSMC in conjunction with other reports of quality assurance activities (e.g., reports from Internal Audits, Quality Assurance Reviews, etc.) occurring since the prior review of the protocol by the DSMC. Additionally, the DSMC requires the study team to submit external DSMB or DSMC reports, external monitoring findings for industry-sponsored studies, and any other pertinent study-related information.

In the event that there is significant risk warranting study suspension or closure, the DSMC will notify the PI of the DSMC findings and ensure the appropriate action is taken for the protocol (e.g., suspension or closure). The DSMC ensures that the PI reports any temporary or permanent suspension of a clinical trial to the sponsor (e.g., NCI Program Director, Industry Sponsor Medical Monitor, Cooperative Group Study Chair, etc.) and other appropriate agencies. DSMC findings and requirements for follow-up action are submitted to the CRC.

7.4 Expedited Reporting of Serious Adverse Events

Subjects will be assessed for SAEs in real-time during the hospital admission until the time of discharge. All Grade 3 events considered at least possibly related to the study intervention (except grade 3 hypotension) will be reported to the UWCCC DSMC within at least 10 working days. Grade 4-5 events considered as least possibly related (including hypotension) must be reported within 48 business hours. All SAEs must be reported to the UWCCC Data and Safety Monitoring Committee Chair (as above) and the UW IRB (if applicable; consult the UW-IRB website for reporting guidelines). For submission of SAEs on this protocol, reference the UWCCC SAE SOP and the SAE Reporting Workflow for DOWGs on the UWCCC website (http://www.uwccc.wisc.edu) for specific instructions on how and what to report to the UWCCC.

For this protocol, the following entities are required to be notified:

a) saenotify@uwcarbone.wisc.edu
b) Study PI (Dr. Lisa Barroilhet)
c) Study Co-Investigators
d) UWCCC Gynecologic Oncology Research Program Manager
e) Any other appropriate parties listed on the SAE Routing Form (for follow-up reports only)

For each SAE, research staff will consult the UW-IRB website to determine if reporting to the IRB is required.

8.0 REFERENCES

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