PennState

HRP-592 - Protocol for Human Subject Research with Use of Test Article(s) IRB 8663

Protocol Title:

Erector spinae plane block (ESPB): A new technique for perioperative pain control in patients undergoing surgery through a flank or anterior subcostal incision.

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1.0 Objectives

1.1 Study Objectives

Using a randomized double-blinded study design, our goal is to evaluate the superiority of Erector Spinae Plane block (ESPB) in the peri-operative pain management in patients undergoing surgery through flank or anterior subcostal incisions as compared to the standard of care of using IV and oral opiates.

1.2 Primary Study Endpoints

1. Pain scores using the Visual analogue scale (VAS) 0-10 on postoperative day 1. (VAS scale document attached)

1.3 Secondary Study Endpoints

1. Pain scores using the Visual analogue scale (VAS) 0-10 on postoperative day (POD) 2 and 3.
2. Total dose of IV and oral opiate and study drug use at the completion of POD 1, 2 and 3.
3. Length of hospital stay
4. Patient satisfaction survey of pain control given on POD 1, at discharge and at time of postoperative visit (within 14 days of discharge)—(survey document attached)
5. Amount of oral opiates used from discharge to postoperative visit
6. Total cost of hospital stay

2.0 Background

2.1 Scientific Background and Gaps

Despite the advances in less invasive surgical techniques, the flank or anterior subcostal incision remains a widely used surgical approach for surgeries performed on upper urinary tract.(1) Post-operative pain control is a fundamental part of care for any patient undergoing surgery and is often challenging. These incisions, in particular, are known to lead to increased postoperative pain due to the multiple layers of abdominal musculature incised. It has been shown that inadequate peri-operative pain control can lead to chronic pain in postoperative patients.(2,3) Whereas, proper management of post-operative pain has shown benefits such as improved patient satisfaction, earlier mobilization, decreased length of hospital stay and even decreased hospital costs.(4,5,6)

Opioids are the most commonly used agents for peri-operative pain control. Despite being effective, opioid use is associated with a long list of side effects and its overuse may be a driver for chronic addiction. The use of neuro-axial techniques, especially epidural-analgesia, offered a successful alternative to opioid narcotic use. Yet, its use can be limited by coagulopathy, infection and anatomical abnormalities. Additionally, the use of an epidural, at times, can delay a patient's progress to hospital discharge. Thus, the need for developing alternative safe and effective opioid sparing pain management techniques has grown.

The goals of reducing postoperative narcotic requirements, in addition to the availability and high safety profile of the US-guided peripheral nerve block techniques, has provided a fertile landscape for studying new alternatives to epidural analgesia.(7) It is promising that the exploration of new techniques for perioperative pain management may improve patient satisfaction and outcomes through avoiding deleterious side effects, decreasing length of hospital stay and may overall decrease total costs.

2.2 Previous Data

Recently, the erector spinae plane block (ESPB) has been described in multiple case studies. In 2016, Mauricio and colleagues presented ESPB as a novel analgesic technique in thoracic neuropathic pain. The authors used the proposed block successfully to manage thoracic pain in 4 patients presenting with chronic thoracic pain (2 cases) and postoperative pain control following video assisted thoracoscopic procedures (2 cases).(8) The same group has also utilized the same technique for postoperative pain control following ventral hernia repair and thoracotomy.(9,10)

2.3 Study Rationale

Opioid analgesia is associated with multiple side effects and its overuse may be a driver of chronic addiction. Establishing opioid sparing techniques for perioperative pain control is crucial for providing effective and safe patient care after surgery.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

1. Subjects undergoing open nephrectomy using a flank or anterior subcostal incision.
2. Consenting adults age 18-85
3. Patients weighing over 60 kg.
4. American Society of Anesthesiologists (ASA) Physical Status classification I to III
5. Planned to be hospitalized for at least 24 hours post-op
6. Cognitive capacity to use the visual analogic scale (VAS) and complete the patient satisfaction survey

3.2 Exclusion Criteria

1. Patient refusal
2. Patients with allergies to ropivacaine, local anesthetics, specifically amide anesthetics, or opiates (hydromorphone or oxycodone)
3. Scoliosis
4. Patients with chronic pain syndromes or who are on chronic pain medications/other neurologics of more than 3 months or whom have neuromodulators/stimulators
5. Concurrent surgeries requiring additional incisions on the body
6. Pregnant females (pregnancy testing included in study procedures)
7. Individuals with any clinically relevant history or the presence of neurological deficits or cardiovascular disease
8. Patients with a history of liver dysfunction

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

1. If the block cannot be placed/technically performed in the patient
2. If the subject does not follow protocol
3. If they are unable to participate cognitively after the surgery.
4. Any inpatient Clavian III or greater surgical complication
5. If surgery needs to be carried out via an incision other than flank or anterior subcostal
6. If the subject has an adverse event, such an allergic reaction attributed to the study drug, causing the patient to become unblinded
7. If the patient has pain requirements which exceed all options available in this protocol.

3.3.2 Follow-up for withdrawn subjects

If subjects need to be withdrawn from the study based on the above reasons, they will transition to following the clinical standard of care that is medically required for their particular situation. The block that is in place will be unblinded to the physician and patient. Unblinding will help the physician and patient understand if it may be worth trying to continue with the block in such circumstances as a means of pain control. Continuation with the blinding procedures could only delay achievement of adequate pain control and removal of unnecessary hardware, if the block ends up containing the control—normal saline. The remainder of the hospital course for these withdrawn subjects will continue according to standard medical practice. Their course will continue to be tracked for research purposes and they will be included and reported in the study results.

4.0 Recruitment Methods

4.1 Identification of subjects

The urology surgeons and members of the research team will identify potential study candidates as they present to the urology clinic to discuss their upcoming surgery. Identification of potential subjects can occur both prior to clinic by using the patient medical record, as well as at the patient clinical encounter.

4.2 Recruitment process

After identification of potential subjects, at their clinic visit, the urology surgeons will confirm their eligibility and interest in participating. Study information and a copy of the consent form will be provided to the patient to review. Official enrollment of eligible and interested patients will occur in the urology clinic by the end of their preop visit. Consent to participate in the study will formally be obtained during this visit by a member of the research team. Attestation of the subject enrollment/consent will be signed by the principal investigator.

4.3 Recruitment materials

Patient consent form

4.4 Eligibility/screening of subjects

All potential subjects will be screened for initial study eligibility according to the inclusion and exclusion criteria, listed above—3.1,.3.2, during their urology clinic visit prior to their scheduled surgery.

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

Written consent will take place in the urology clinic following confirmation of patient eligibility and agreement to participate in the research study.

5.1.1.2 Coercion or Undue Influence during Consent

It will be explained to the patient that research is voluntary. The patient will be encouraged to ask questions and it will be explained to the patient that their decision to participate or not participate will have no effect on their level of care.

5.1.2 Waiver or alteration of the informed consent requirement

Not applicable

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

Written consent will be obtained. The patient will retain a signed and dated copy. A signed and dated copy will also be stored in the locked office of the research team and stored in the patient's medical record.

5.2.2 Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)

Partial waiver requested for review of schedules/charts for recruitment purposes.

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects

Not applicable

5.3.2 Cognitively Impaired Adults

5.3.2.1 Capability of Providing Consent

Not applicable

5.3.2.2 Adults Unable To Consent

Not applicable

5.3.2.3 Assent of Adults Unable to Consent

Not applicable

5.3.3 Subjects who are not yet adults (infants, children, teenagers)

5.3.3.1 Parental Permission

Not applicable

5.3.3.2 Assent of subjects who are not yet adults

Not applicable

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Identifiers will be destroyed by unlinking the subject ID code numbers from their MRNs and deleting this information from the database. This will occur following full analysis and publication.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Use of PHI is necessary to identify eligible patients and link them to their clinical data.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

Waiver of Authorization is requested for assessing patient eligibility prior to review of the consent document and enrollment in the research study.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

The study will be prospective, randomized, controlled, and double blinded.

7.2 Study Procedures

After study approval and prior to study start, Kathy Lehman will be responsible for educating the clinical head nursing staff of the inpatient wards, Same Day Unit (SDU) and Post Anesthesia Care Unit (PACU) of this study and its protocol requirements. She will also provide an educational session to both the division of Urology as well as to the department of Anesthesiology on the study and protocol requirements.

7.2.1 Day 1 –Screening and Consent

The urology surgeon and/or study coordinator will identify potential patients according to the inclusion/exclusion criteria (3.1-3.2) prior to or on the day of clinic. These will be patients scheduled for surgery using a flank or anterior subcostal incision. A copy of the consent form will be provided to the subject at the time of their clinic visit. Patient eligibility and interest in participation will be confirmed by the urology surgeon at the clinic visit prior to surgery. If they meet the criteria to be included into the study, a member of the research team will obtain written consent from the patient during this preop clinic visit.

7.2.2 Working Day prior to surgery

A member of the research team will call the patient to ensure that they are planning on coming in for their scheduled surgery (i.e.: not sick, running a fever, has transportation). Members of the research team who will perform the block will be notified to confirm coordination of this procedure in the Same Day Unit (SDU).
The subject will then be randomized by the study statistician using a computer-generated randomization list using SAS software (SAS Institute, Cary, NC) into two groups:

- Group 1. Erector spinae plane block (ESPB)
- Group 2. Sham Erector spinae plane block. (SESPB)

7.2.3 Day of Surgery - Pre-op

In the SDU, Kathy Lehman will be present to ensure the current surgery and anesthesia team for the study patient are sufficiently educated on the protocol requirements and to ensure safety and protocol adherence. The patient will receive a study bracelet with the study ID and patient's specific randomization ID. The block procedure will be performed in the SDU by a member of the anesthesia block team, who is also part of the research team. The placement of the erector spinae catheter will occur according to standard practice guidelines using strict sterile conditions and is similar regardless of type of study medication that the patient will be randomly receiving. After the block catheter is placed, a member of the research team will pick up the study drug from the pharmacy, deliver it to the SDU and ensure the correct coordination of study drug to the patient using the patient's study ID bracelet. The ESP catheters will be bolused with 20 ml of Ropivacaine 0.5% vs 20ml of normal saline (placebo). Following this initial bolus, the ESP catheter will be connected to a pump containing Ropivacaine 0.2% or normal saline which will

deliver automatic boluses of 15ml of either study medication or normal saline every 3 hours. The automatic bolus dosing of 0.2% Ropivacaine is based on the standard dosing for all adults weighing between 50-120kg.

7.2.4 Day of Surgery -Operating Room

Once in the operating room, general anesthesia will be induced according to the standard of care for the patient and surgery. The ESPB pump will continue to deliver automatic boluses of 15ml of either study medication or normal saline every 3 hours throughout the duration of surgery. Intraoperatively, anesthesia is required to use only Fentanyl, a short acting opioid, for additional pain control and requested to refrain from using hydromorphone or morphine. At the completion of the case, Ondansetron will be administered for postoperative nausea. Dexamethasone will not be routinely administered as this can also have analgesic effects. All medications administered by the anesthesia team during the operative case will be recorded in the anesthesia record and reviewed and documented by a member of the research team.

7.2.5 Postoperative hospital stay

As per standard of care, the patient will be taken to the post anesthesia care unit (PACU). Here, Kathy Lehman will be present to ensure the PACU team for the study patient are sufficiently educated on the protocol requirements and to ensure safety and protocol adherence. The ESPB pump will be delivering the automatic boluses of study drug (15ml every 3 hours) and additionally allow the patient to self-administer an on demand dose of study drug (0.2% Ropivacaine vs. normal saline) 5ml every 30 minutes throughout their hospital stay. The pump will permanently lock out and cease administration of both the automatic and self-administered boluses if the total dose of study drug reaches 770mg. The patient will still be able to initiate a demand dose, but no medication will be provided. If a lock out occurs prior to POD3, when the pump is scheduled to be removed, it will remain in place until the schedule day of removal. In the PACU, if the patient has additional pain requirements beyond the patient's previously determined acceptable pain score (asked pre-operatively per hospital standard) the PACU team may start a patient controlled analgesia (PCA) containing a set demand dose of hydromorphone 0.2mg every 6 mins. The pump will lock out if the maximum dose of 2mg per hour is reached. Bolus IV dosing of hydromorphone may be administered at the start of the PCA and throughout the hospital stay if deemed necessary by the treating physician team to control patient pain needs. One gram of acetaminophen IV every 8hrs will also be started in the PACU and continued through the patient's hospital stay. Acetaminophen will be converted over to oral regimen on POD 1. When transferred to the inpatient wards, Kathy Lehman will ensure the nurse assigned to the study patient is aware and properly educated on the protocol requirements on a daily basis. She will also monitor for subject safety and protocol adherence while the study patient remains in the hospital by both identifying the patient room as on a research study as well as through daily interaction with the nursing team. While on the inpatient wards, additional pain control adjuncts will be provided using oral oxycodone 5-10mg every 4 hours administered based on a pain scale: pain 3-6 translates to 5mg tab and pain 7-10 translates to a 10mg tab. The PCA, as outlined above, may be started later in the hospital course, if needed, based on the patient's needs. The ESP block will be discontinued between 6AM-9AM on POD 3. Specific research order sets for this study will be created by the principal investigator for use of the study drug/placebo, narcotics and acetaminophen. All medications and dosages administered during the hospital stay (PACU and inpatient ward) will be reviewed and documented by a member of the research team to tabulate the total IV and oral opioid and study drug requirement of all study patients. Daily pain scales using the Visual analogue scale (VAS) 0-10 will be provided to the patient by a member of the research team, each morning between 9AM-12PM, on POD 1, 2 and 3 (scale attached). Additionally, on POD 1, between 9AM-12PM, a brief patient satisfaction survey (which has been previously validated (11)) will be provided to the patient to complete by a member of the research team (document attached).

On day of discharge, the same brief patient satisfaction survey will be provided again for the patient to complete prior to leaving the hospital. Each patient will be provided with a standard home pain regimen which will include use of acetaminophen 500mg oral tabs every 6 hours as needed, oxycodone 5mg oral tabs every 4 hours as needed with a quantity of 30 tabs dispensed.

7.2.6 Postoperative clinic visit

Due to the COVID pandemic, a member of the research team will perform a telephone visit at 14 days postoperatively to determine and document the number of oral oxycodone tablets remaining out of a total of 30 tabs dispensed. Additionally, this member of the research team will also have the study patient fill out the same brief patient satisfaction survey (document attached). It is at this time that the patient's participation in this study will be concluded.

7.3 Duration of Participation

The patient will remain in the study until their telephone postoperative visit occurring within 14 days from discharge from the hospital.

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

Ropivacaine Hydrochloride injection 0.2% is FDA approved for use in surgery as a field block (infiltration) regional anesthesia. We will use the Penn State Health standard of care ambulatory pump to provide the automatic and demand boluses of the study drug through the ESP catheters.

7.4.2 Treatment Regimen

Group	Drug mixture
ESPB	Ropivacaine 0.2%
SESPB	Normal saline

7.4.3 Method for Assigning Subject to Treatment Groups

On the working day prior to surgery, subjects consented for the study will be randomized from a computer-generated randomization list using SAS software (SAS Institute, Cary, NC) and using block stratification with block sizes of two and four to allow an equal number of participants in each of the study groups.

7.4.4 Subject Compliance Monitoring

Members of the research team will verify that the label on the study drug that they receive in the SDU matches the study ID and patient's specific randomization ID on their study bracelet.

7.4.5 Blinding of the Test Article

The study drugs will be prepared and provided by the investigational pharmacy who will be unblinded in this study. Post randomization of study patients (randomization will occur the working day prior to scheduled operative date), the study drug will be packaged in a cartridge which will be nonspecific to the medication type (Ropivacaine or Normal saline). The cartridge will be labeled both with the study ID and the patient's specific randomization number.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

The Investigational Drug Service Pharmacy will maintain a study-specific supply of ropivacaine and normal saline for this study.

7.4.6.2 Storage

The investigational pharmacy will handle storage and distribution of study drugs according to their approved handling protocols.

7.4.6.3 Preparation and Dispensing

Following randomization of study patients (randomization will occur the working day prior to scheduled operative date), the study drug will be packaged both in a syringe which will contain the initial bolus dose and also in a cartridge which will contain the automatic pump boluses. Both the syringe and cartridge which will be nonspecific to the medication type (Ropivacaine or Normal saline). The syringe and cartridge will be labeled both with the study ID and the patient's specific randomization number. The ESPB syringe and cartridge will contain Ropivacaine 0.2% and the SESPB syringe and cartridge will contain normal saline. All preparation, dispensing of drug into cartridges and cartridge labeling will occur by the investigational pharmacy, who will remain unblinded. The day of surgery, a member of the research team will pick up both the syringe and cartridge and deliver it to the SDU. Here, the syringe followed by the cartridge will be connected to the block catheters allowing administration to begin in the SDU.

7.4.6.4 Return or Destruction of the Test Article

Study drug will be discarded as per standard procedures.

7.4.6.5 Prior and Concomitant Therapy

See section 7.2 Study Procedures for full details on concomitant medical therapy administered both during the operation, perioperative period and at hospital discharge.

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8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

40 patients, 20 per group.

8.2 Sample size determination

A total of N=17 patients in each group (N=34 total) yields 80% power to detect a 2-point mean decrease in pain scores using a 2-sided t-test conducted at a significance level of 0.05 and assuming that the standard deviation (in each group) is 2. The standard deviation was selected to be slightly smaller than the standard deviation (2.5) under the assumption that all pain scores are equally likely (uniform

distribution). In order to account for potential patient withdrawals from the study (see section), we have expanded the number to 20 patients randomized in each group.

8.3 Statistical methods

For the primary endpoint, a 2-sided t-test will be used. T-tests will also be used for all secondary endpoints, unless the assumption of normality does not hold, in which case a Wilcoxon Rank Sum Test will be used.

9.0 Confidentiality, Privacy and Data Management

See the Research Data Plan Review Form

9.1 Confidentiality

9.1.1 Identifiers associated with data and/or specimens

9.1.1.1 Use of Codes, Master List

9.1.2 Storage of Data and/or Specimens

9.1.3 Access to Data and/or Specimens

9.1.4 Transferring Data and/or Specimens

9.2 Subject Privacy

10.0 Data and Safety Monitoring Plan

10.1 Periodic evaluation of data

The PI and research coordinator will review cumulative adverse events, early termination of study participation, and accrual every six months and report any issues requiring modification of the study or alteration of the risk: benefit ratio to the IRB immediately. A summary of adverse events, study progress and protocol modifications will be included for IRB review in the continuing review.

10.2 Data that are reviewed

The data to be reviewed will be:

- Safety data
- Untoward events
- Efficacy data

10.3 Method of collection of safety information

Safety information will be collected by the research staff preoperatively and post operatively as described in Section 7.2.

10.4 Frequency of data collection

Data will be collected via the electronic medical record and begin following patient randomization. Total IV and oral opiate during the hospitalization will be collected post discharge. The VAS pain scales will be administered between 9AM-12AM on POD 1, 2 and 3 and collected daily. The patient satisfaction

survey will be collected on POD 1, day of discharge and at the telephone post operative visit, within 14 days from discharge.

10.5 Individuals reviewing the data

The PI will provide oversight for the conduct of the study, and the research coordinator will monitor the data. They will ensure that all eligible criteria and consent requirements are met prior to a subject's participation in the study and that the procedures and adverse event reporting occur according to the IRB approved protocol.

10.6 Frequency of review of cumulative data

The PI and research coordinator will review cumulative adverse events, early termination of study participation, and accrual every six months and report any issues requiring modification of the study or alteration of the risk: benefit ratio to the IRB immediately. A summary of adverse events, study progress and protocol modifications will be included for IRB review in the continuing review.

10.7 Statistical tests

Not applicable.

10.8 Suspension of research

Not applicable.

11.0 Risks

Risks specific to this study include:

- Risk of randomization - patient will be assigned to a treatment program by chance. The treatment received may prove to be less effective than the other research treatment(s) or other available treatments.
- Loss of confidentiality associated with being part of a research study collecting personal health information.
- Complications of ESPB: local hematoma, local infection, pneumothorax, local anesthetic toxicity.
- Adverse effects related to the study medications at proposed dosing are uncommon. Most adverse effects noted were at higher dosing; there is limited literature noting adverse effects at proposed dosing.

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

Potential benefits of being a subject in the study include improved pain control, less nausea/vomiting, less sedation, fewer side effects from opiates, and decreased length of hospital stay.

12.2 Potential Benefits to Others

This study will provide data that may potentially create improved pain management protocols in patients undergoing general anesthesia for surgery using a flank or anterior subcostal incision.

13.0 Sharing Results with Subjects

not applicable

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

not applicable

15.0 Economic Burden to Subjects

15.1 Costs

There will be no costs to the subject associated with their participation in the study other than those associated with normal standard of care. The study drugs will be provided by Hershey Medical Center.

15.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Such charges may be paid by the study sponsor as outlined in the research agreement and explained in the consent form.

16.0 Resources Available

16.1 Facilities and locations

This study will be completed at Penn State Hershey Medical Center. This is a large university based tertiary care center where kidney surgery is frequently completed.

16.2 Feasibility of recruiting the required number of subjects

The required number of patients (see Section 9) needed should be attainable in 18-24 months according to current numbers being operated on at Hershey Medical Center. The project will continue until this number is obtained. The access to these patients will not be limited by the surgical team.

16.3 PI Time devoted to conducting the research

The PI enjoys protected academic time as well as access to urology-specific research infrastructure for full support.

16.4 Availability of medical or psychological resources

All resources needed for the protocol, as well as for any possible adverse event, are available at Penn State Hershey Medical Center.

16.5 Process for informing Study Team

Meetings will be held periodically as needed to ensure all research team members are informed about the protocol and their duties. Team emails will also be used to keep team members updated.

17.0 Other Approvals

17.1 Other Approvals from External Entities

Not applicable

17.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of HRP-902 - Human Tissue For Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – Hershey only – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes, but are no longer needed for clinical use. Upload a copy of HRP-901 - Human Body Fluids for Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Clinical Research Center (CRC) Advisory Committee– All campuses – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of HRP-903 - Radiation Review Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/investigator

18.0 Multi-Site Research

Not applicable

19.0 Adverse Event Reporting

19.1 Adverse Event Definitions

For drug studies, incorporate the following definitions into the below responses, as written:	
Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction". • *Reasonable possibility.* For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that 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 patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

For device studies, incorporate the following definitions into the below responses, as written:	
Unanticipated adverse device effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

19.2 Recording of Adverse Events

Research subjects will be routinely questioned about adverse events at study visits.

All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy

NOTE: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.

- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study

The test finding is considered an adverse event by the investigator.

19.3 Causality and Severity Assessments

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

19.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

19.4.1 Written IND/IDE Safety Reports

The Sponsor-Investigator will submit a written IND Safety Report (i.e., completed FDA Form 3500A) to the responsible new drug review division of the FDA for any observed or volunteered adverse event that is determined to be a serious and unexpected, suspected adverse reaction. Each IND Safety Report will be prominently labeled, "IND Safety Report", and a copy will be provided to all participating investigators (if applicable) and sub-investigators.

Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

For each written IND Safety Report, the Sponsor-Investigator will identify all previously submitted IND Safety Reports that addressed a similar suspected adverse reaction experience and will provide an analysis of the significance of newly reported, suspected adverse reaction in light of the previous, similar report(s) or any other relevant information.

Relevant follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the information is available and will be identified as such (i.e., "Follow-up IND Safety Report").

If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting; the Sponsor-Investigator will

submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days, after the determination was made.

19.4.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions **UNDER REVIEW**

In addition to the subsequent submission of a written IND Safety Report (i.e., completed FDA Form 3500A), the Sponsor-Investigator will notify the responsible review division of the FDA by telephone or facsimile transmission of any unexpected, fatal or life-threatening suspected adverse reaction.

The telephone or facsimile transmission of applicable IND Safety Reports will be made as soon as possible but in no event later than 7 calendar days after the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting

19.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

19.6 Unblinding Procedures

Unblinding of the study drug would occur if a patient developed an adverse reaction, such as an allergic reaction, attributed to the study drug. Documentation of the adverse reaction would ensue and the patient would be unblinded and then withdrawn from the study. Such a patient would then be cared for in context of standard medical practice and their remainder of their medical course would continue to be tracked for research purposes and reported in final study results. Additionally, in any instance that the subject is being withdrawn from the study, as listed in section 3.3.1, the subject will also be unblinded. Unblinding will help the physician and patient engage in a more meaningful and effective clinical interaction for pain control. There will be no confusion as to if the block may or may not contain active medication, Ropivacaine, and thus could be effective for the clinical scenario.

19.7 Stopping Rules

Not applicable.

20.0 Study Monitoring, Auditing and Inspecting

20.1 Study Monitoring Plan

20.1.1 Quality Assurance and Quality Control

This is a low risk therapeutic study using techniques and agents with a known safety profile. The PI will ensure that this study is conducted, and that the data are generated, documented (recorded), and reported, in compliance with this protocol, with institutional and IRB policies, with Good Clinical Practice guidelines and any other applicable regulatory requirements.

20.1.2 Safety Monitoring

The **Principal Investigator** will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the

coordinators may have concerning AEs; and will notify the IRB, FDA, sponsor and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

The **Research Coordinator** will complete the appropriate report forms and logs; assist the PI to prepare reports and notify the IRB, FDA, and/or DSMB of all Unanticipated Problems/SAE's.

21.0 Future Undetermined Research: Data and Specimen Banking

Not applicable

21.1 Data and/or specimens being stored
not applicable

21.2 Location of storage
not applicable

21.3 Duration of storage
not applicable

21.4 Access to data and/or specimens
not applicable

21.5 Procedures to release data or specimens
not applicable

21.6 Process for returning results
not applicable

22.0 References

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