CLINICAL RESEARCH PROTOCOL

INVESTIGATIONAL PRODUCT(S):		None
STUDY NUMBER(S):	**IRB Number**	Pending
	Other Protocol Identifiers	UPCC 27224
PROTOCOL(S) TITLE:		Efficacy of the Erector Spinae Plane Block for Abdominal Pain from Gastrointestinal Malignancies
REGULATORY SPONSOR:		None
FUNDING SPONSOR(S):		None
MEDICAL DIRECTOR		Michael Shalaby, MD
ORIGINAL PROTOCOL DATE:		7/24/2025
VERSION NUMBER:		v 1.0
VERSION DATE:		7/24/2025

PRINCIPAL INVESTIGATOR SIGNATURE

STUDY SPONSOR:	Department of Emergency Medicine
STUDY TITLE:	Efficacy of the Erector Spinae Plane Block for Abdominal Pain from Gastrointestinal Malignancies
STUDY ID	pending
PROTOCOL VERSION	v 1.0

I have read the referenced protocol. I agree to conduct the study in accordance to this protocol, in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP), and all applicable regulatory requirements and guidelines.

Principal Investigator Name	Michael Shalaby, MD	Signature	
Affiliation:	Department of Emergency Medicine	Date	7/24/2025

Abbreviations

APS-POQ-R	Revised American Pain Society Patient Outcome Questionnaire
BMI	Body Mass Index
Cedar	Hospital of the University of Pennsylvania Cedar
CFR	Code of Federal Regulations
CRC	Clinical Research Coordinator
ED	Emergency Department
EDC	Electronic Data Capture
EMR	Electronic Medical Record
ESPB	Erector Spinae Plane Block
GI	Gastrointestinal
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HUP	Hospital of the University of Pennsylvania
ICH	International Conference on Harmonization
ICH GCP	International Conference on Harmonization Good Clinical Practice
IQR	Interquartile Range
LAST	Local Anesthetic Systemic Toxicity
LOS	Length of Stay
MME	Milligram Morphine Equivalent
MRN	Medical Record Number
NRS	Numeric Rating Scale
PAH	Pennsylvania Hospital
PI	Principal Investigator
PPMC	Penn Presbyterian Medical Center
QC	Quality Control
RA	Research Assistant
SOP	Standard Operating Procedures
SSN	Social Security Number

UGRA	Ultrasound-Guided Regional Anesthesia
UPHS	University of Pennsylvania Health System
WHO	World Health Organization

1 STUDY SUMMARY

1.1 Synopsis

Title:	Efficacy of the Erector Spinae Plane Block for Abdominal Pain from Gastrointestinal Malignancies
Short Title:	ESPB for GI Malignancy Pain
Study Description:	This study will target patients with gastrointestinal (GI) malignancy who present to any of 4 Penn Medicine emergency departments (EDs) with intractable abdominal pain. We will offer eligible patients an erector spinae plane block (ESPB), a regional anesthesia technique which is already offered to such patients in the ED at the University of Pennsylvania Healthy System (UPHS), for their intractable abdominal pain. We will compare the outcomes of this prospective cohort of patients to a matched historical control of patients with GI malignancy who were treated in the ED during the same time period as recruitment, but who were not recruited to partake in the study and who were managed with standard of care. Opioid consumption as measured by total milligram morphine equivalents (MMEs) over a 24-hour period and hospital length of stay (LOS) will be compared between cohorts. Additionally, for the ESPB cohort, pain level pre/post ESPB, and functionality and satisfaction with pain management at 24 hours will also be examined. Given that the ESPB is currently offered to patients with GI malignancy as part of standard of care in the ED within UPHS, this protocol is being submitted for expedited review because we are consenting participants to provide and to allow the research team to abstract the following data: pain levels and satisfaction scores, data on total LOS (ED + hospital) and their opioid consumption. Patients who wish not to provide this information, and therefore not to participate in the study, will still be offered the ESPB for their abdominal pain.
Objectives:	Primary objective: To determine whether patients with GI malignancy receiving an ESPB for intractable abdominal pain consume less opioids (measured in MMEs) in a 24-hour period compared to standard of care analgesia. Secondary objectives:

	• To determine whether patients who receive an ESPB have shorter hospital LOS compared to standard of care analgesia. • Within the cohort receiving the ESPB, to determine whether there was a change in pain level as measured by the numeric rating scale (NRS) pre/post block. Exploratory: Within cohort receiving the ESPB, to determine level of patient satisfaction and functionality as measured by the Revised American Pain Society Patient Outcome Questionnaire (APS-POQ-R)
Primary Endpoint:	Difference in MMEs consumed in 24-hour period between the prospective cohort who received the ESPB and historical controls.
Secondary Endpoints:	1. Difference in hospital LOS between cohorts, as determined by time from enrollment to hospital discharge. Enrollment for the ESPB cohort will be from the time of the intervention. Enrollment for the standard of care cohort will be from the time of administration of the first analgesic in the ED under the care of a treating physician (ie, not in the waiting room). 2. In the ESPB cohort, difference in pain level as measured by NRS at pre-ESPB and 30 minutes post block. 3. In the ESPB cohort, scores on APS-POQ-R administered at 24 hours after the ESPB *(see Appendix)*
Study Population:	Patients with a GI malignancy presenting with intractable abdominal pain. To any of 4 EDs, (1) Hospital of the University of Pennsylvania (HUP), (2) Penn Presbyterian Medical Center (PPMC), (3) Pennsylvania Hospital (PAH), and (4) HUP Cedar (Cedar) Exclusion criteria: pregnant, incarcerated, admissions for serial abdominal examinations, small bowel obstruction, sepsis, altered mental status, hemodynamic instability. Sample size: • Prospective ESPB cohort: n=25 • Historical controls: n = 25
Phase:	N/A

Description of Sites/Facilities	(1) Hospital of the University of Pennsylvania (2) Penn Presbyterian Medical Center (3) Pennsylvania Hospital (4) HUP Cedar
Enrolling Sites:	EDs of the aforementioned sites. Currently, emergency physicians who are capable of performing the ESPB see patients at all 4 sites.
Description of Study Intervention:	Participants will receive an ESPB, a nerve block performed by injecting anesthetic between a single spinal transverse process and the erector spinae muscle complex (Forero et al). Anesthetic reaches the dorsal nerve root ganglia but also diffuses anteriorly to the paravertebral space which contains the thoracic sympathetic ganglia (Chin et al). Visceral afferent fibers transmit pain signals arising from the stomach to midway through the sigmoid colon utilizing the same anatomical conduit as sympathetic efferent fibers (Moore et al). While physically associated, they travel in the reverse direction of the sympathetic efferents and are functionally distinct. From the abdominal viscera to spinal cord, visceral afferents transmit pain signals first through the peri-aortic autonomic plexuses and prevertebral ganglia, then along the splanchnic nerves to reach the sympathetic trunk, where they travel via the white rami communicantes to reach the spinal nerves of T5 to L2, before finally being conducted centrally. Thus, anesthetizing the thoracolumbar spinal nerves and sympathetic chain, via an ESPB performed between the levels of T5 and L2, should block abdominal visceral pain signaling, and may provide significant analgesia for patients with abdominal pain from GI malignancy. The ESPB is considered a part of standard of care treatment in the ED and thus patients are eligible to receive it regardless of enrollment in the study. Participants will be consented to assess their pain levels immediately before, 30 minutes after, and 24 hours after the ESPB is administered; and to take the APS-POQ-R survey at 24 hours after the ESPB is administered.
Study Duration:	12 months

Participant Duration:	24 hours. Patients who receive the ESPB will receive a final assessment at 24 hours after administration of the ESPB via the APS-POQ-R.
Resources Necessary for Human Research Protection:	This study is being conducted by the Division of Ultrasound within the Department of Emergency Medicine. The Principal Investigator (PI) is an ultrasound faculty member and the Director of Ultrasound Research. Other research staff include a biostatistician, the ultrasound division's clinical research coordinator (CRC), and the research assistants (RAs) within the Emergency Medicine Academic Associates program. Prior to the initiation of enrollment, the PI will meet with the Academic Associates team to discuss recruitment including establishing an EPIC Haiku notification system, as well as inclusion and exclusion criteria. The CRC is trained on data storage in REDCap. All resources required to complete this controlled trial are provided by the Department of Emergency Medicine and the Division of Ultrasound, including the RAs, the CRC, and the biostatistician. Progress of the trial will be discussed at least every other week at the research meetings within the Division of Ultrasound.

1.2 Key Roles and Study Governance

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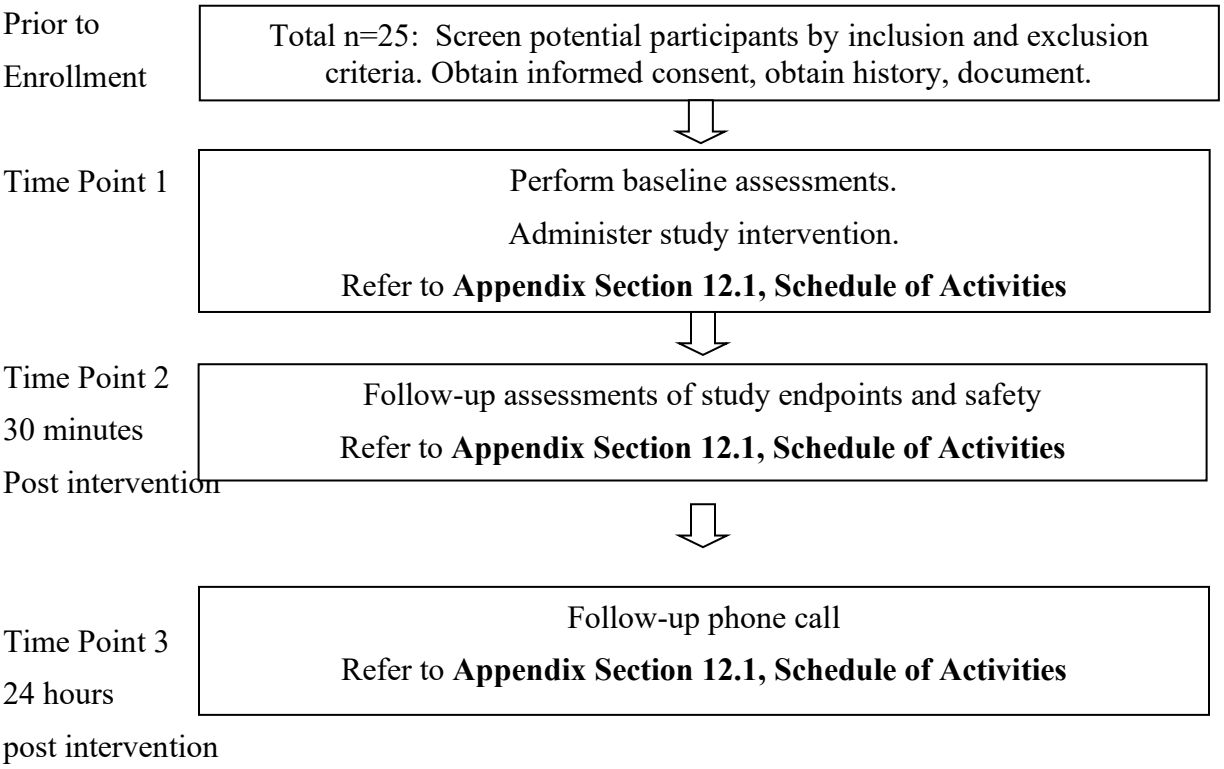
1.3 Schema


Prior to Enrollment
Total n=25: Screen potential participants by inclusion and exclusion criteria. Obtain informed consent, obtain history, document.
Time Point 1
Perform baseline assessments.
Administer study intervention.
Refer to Appendix Section 12.1, Schedule of Activities
Time Point 2
30 minutes
Post intervention
Follow-up assessments of study endpoints and safety
Refer to Appendix Section 12.1, Schedule of Activities
Time Point 3
24 hours
post intervention
Follow-up phone call
Refer to Appendix Section 12.1, Schedule of Activities

2 INTRODUCTION AND RATIONALE

2.1 Study Rationale

In 2024 there were greater than 2 million new cases of cancer in the United States, more than any year prior (Siegel et al). The incidence of new GI malignancies also broke previous records, with more than 350,000 new cases in 2024 (Siegel et al). Over 4 million patients with cancer seek care in EDs for oncologic emergencies annually, with breakthrough pain commonly requiring management with higher-dose opioids and hospital admission (Gould Rothberg et al). Among these patients, those with GI malignancies are the second most prevalent group, and patients' primary presenting complaint is abdominal pain (Siregar et al). The high levels of poorly controlled background pain from which patients with GI malignancy suffer arise from a variety of sources, including local tumor invasion of organs, the omentum, retroperitoneal tissues, and neural tissue (Mercadante et al) (van den Beuken-van Everdingen et al). As tumor burden progresses so do patients' pain and their use of opioids for pain control (Whitney et al). Meanwhile, oncologic treatments, including neurotoxic chemotherapeutics, radiation, and palliative or curative surgical procedures can paradoxically worsen pain (Mercadante et al). Opioids have been the mainstay of treating cancer pain since their recommendation by the World Health Organization (WHO) in 1996 as part of the "analgesic ladder," and most patients with GI malignancy manage their background pain with high-dose home opiate regimens (> 90 mg equivalent dose of oral morphine daily) (Bennett et al) (World Health Organization). Despite this, nearly 90% of patients with GI malignancy experience at least one severe breakthrough pain episode, which is a sudden increase in pain intensity that often leaves patients unable to perform even basic activities of daily living such as walking (Caraceni et al). Therefore, there is a critical need for more effective analgesia for this growing population of patients with GI malignancy presenting to an ED with breakthrough pain.

Breakthrough abdominal pain from GI malignancy is usually treated with high-dose opioids, which have significant short- and long-term side effects. Symptoms of acute opioid overdose include nausea, vomiting, delirium, and hypoxia, and can occur even at normal doses (Wei et al). This, in turn, increases ED presentations, complicates hospital courses, and contributes to longer hospital stays (Oderda et al). Patients with GI malignancies who are on prolonged high-dose home opioid regimens face an increased risk of adverse outcomes related to chronic opioid use. For example, physiologic dependence on and tolerance to opioids forces GI malignancy patients to use increasing doses of opioids to achieve the same or lesser levels of analgesia, which then lowers the threshold for acute overdose (Benyamin et al). Chronic opioid use also precipitates opiate-induced hyperalgesia, a paradoxical phenomenon in which opioid metabolites lead to worsening pain (Benyamin et al). Elevated opioid use among cancer patients, even after accounting for prognosis, is associated with more frequent hospitalizations and an earlier risk of death (Doshi et al). Patients with cancer pain are therefore more susceptible to the adverse effects of opioids, which continue to be the mainstay of treatment for breakthrough cancer pain (Mercadante et al). Additionally, hospitalized patients with cancer pain feel that opioids give

them little control over their level of analgesia, cause them to have trouble sleeping most of their nights in the hospital, and are addictive (Eyigor et al). Unlike the United States, the European Society for Medical Oncology supports the use of regional anesthesia as an adjunct for the treatment of cancer pain, especially for its opioid-sparing effects (Fallon et al). As the number of cancer patients continues to grow yearly, there is a vital need to address non-opioid analgesia for these patients.

The abdominal viscera, from the stomach to midway through the sigmoid colon, derives its sensory innervation from afferent fibers that travel with, but are distinct from, the sympathetic nerve fibers from the 5th thoracic (T5) to the 2nd lumbar (L2) spinal levels (Moore et al). These fibers converge at the celiac plexus, located near the celiac artery and the aorta. From there, they bifurcate into the paravertebral sympathetic chain and subsequently ascend to the spinal cord and integrate into the central nervous system (Lohse et al). The celiac plexus block is an invasive procedure performed by an interventional anesthesiologist or palliative care specialist to lyse the celiac plexus and has been shown to reduce pain and opiate use in patients suffering from GI malignancy (Ashlock et al). While there are multiple methods to perform a celiac plexus block, it involves a steep needle trajectory either posteriorly through the retroperitoneum or anteriorly through the abdominal wall close to or even through the abdominal aorta (Nagels et al). Due to its technical complexity, the availability of the celiac plexus block for patients with acute abdominal pain from GI malignancy is limited, and it carries a risk of serious complications. These complications include GI bleeding from viscus perforation (Pello et al), pneumothorax (Rathmell et al), paraplegia (De Conno et al), aortic dissection, and death (Kaplan et al). Conversely, the ESPB is a novel ultrasound-guided regional anesthesia (UGRA) technique that has gained popularity in emergency medicine due to its effective analgesic properties and low complication rates (Abdelhamid et al). During this procedure, anesthetic injected deep to the erector spinae muscle complex at the thoracic spine level diffuses anteriorly to reach the paravertebral sympathetic chain. Consequently, the ESPB effectively targets the same neural pathways as the celiac plexus block without the same risks of complications and demonstrates promise as a simpler and safer alternative to the celiac plexus block (Abdelhamid et al). However, as yet there are no large, well-designed trials assessing the efficacy of the ESPB for managing abdominal pain associated with GI malignancies in an ED setting. Therefore, this presents a unique opportunity for a rigorously designed trial to investigate the efficacy of the ESPB in managing abdominal pain associated with GI malignancies.

UGRA has become established as an effective adjunct to acute pain management in the ED. Both the American College of Emergency Physicians and the American Academy of Emergency Medicine endorse its integration into multimodal analgesia in the ED (American Academy of Emergency Medicine) (American College of Emergency Physicians). Despite its novelty, the ESPB has already gained traction in emergency care owing to its safety and efficacy (Abdelhamid et al). The ESPB's straightforward needle trajectory requires no redirection and passes through back muscles, avoiding vital structures. For visceral structures, the ESPB is a

potent analgesic: it surpasses ketorolac for renal colic and matches epidural anesthesia for acute pancreatitis (Aydin et al) (Shapkin et al). The thoracic paravertebral sympathetic chain, which innervates the kidneys and pancreas, also innervates the rest of the GI tract. Therefore, in this cohort study we plan to explore the ESPB as a potential tool for managing acute abdominal pain from GI malignancy.

2.2 Background

While there have not been any previously published large-scale trials on the use of the ESPB for treating abdominal pain from GI malignancy, there have been some published cases, including our own (Gawel et al). Ashworth et al utilized an ESPB to resolve intractable abdominal pain for a patient in the ED with colon cancer with metastasis to the liver (Ashworth et al). Similarly, Gopinath and colleagues performed an ESPB on a patient in the ED with intractable abdominal pain from cholangiocarcinoma, who did not require analgesics for 18 hours after blockade (Gopinath et al). In the EASIER trial, a randomized controlled trial exploring the use of the ESPB for treating intractable abdominal pain from hepatic, liver, and biliary sources, David et al performed the ESPB on two patients with cholangiocarcinoma (David et al). Of all patients in the EASIER trial who received the ESPB, the average improvement in pain relief was nearly 90% from baseline, and all patients who received the ESPB reported high satisfaction with the procedure. Bugada et al performed the ESPB on a patient with colon cancer with metastases to the vertebra and retroperitoneal tissues, who subsequently did not require rescue analgesics for three days (Bugada et al). In our publication, we demonstrated that the ESPB successfully treated intractable abdominal pain for patients with hepatic, biliary, and pancreatic cancer (Gawel et al). Two patients with pancreatic cancer opted to be discharged home instead of being admitted for pain control. We have also utilized the ESPB to treat intractable abdominal pain from gastritis and gastroparesis (Gawel et al), acute cholecystitis, acute pancreatitis, and for patients in opiate withdrawal (Gawel et al). All of our patients have reported great satisfaction with the ESPB. There have been no documented adverse effects of the ESPB in the included trials and in our experience. The strength of the prior research and of our experience has been that the ESPB has shown benefit in treating abdominal pain from a variety of sources, but the results are mostly confined to case reports and to our anecdotal experience. In the case reports listed above, all patients consumed fewer opiates after receiving the ESPB. In the EASIER trial, patients who were randomized to the ESPB required a lower dosage of opioids compared to those who were in the standard of care group. Similarly, Hacıbeyoğlu et al demonstrated that patients undergoing hepatectomy who were randomized to receive an ESPB demonstrated significantly lower opioid use than those who were managed with patient-controlled analgesia (Hacıbeyoğlu et al). Additionally, Dubilet et al demonstrated that patients who received a pre-operative ESPB for oncologic surgery used fewer opioids than those who received traditional postoperative analgesia (Dubilet et al). In our practice, all patients who received an ESPB for abdominal pain from GI malignancy were already on home opioid regimens. Both patients with pancreatic cancer who received the ESPB did not receive any more analgesics in the ED. The patients with hepatic cancer, biliary cancer, gastritis, pancreatitis, and acute cholecystitis did not request analgesics for

at least 14 hours after receiving the ESPB. Two of the patients with abdominal pain, vomiting, and diarrhea who were in opiate withdrawal also did not request any symptomatic relief for three hours after receiving the ESPB and stayed for placement in rehab. One of the patients in opiate withdrawal did not request any opiate analgesics at all during his 9-hour stay in the ED.

A meta-analysis of 11 studies by Pepper et al demonstrated that patients who received a single ESPB postoperatively for noncardiac surgery demonstrated reductions in pain and opioid use even up to 24 hours after injection, compared to those who were managed without one (Pepper et al). Similarly, Rambhia et al demonstrated that patients who received a single genicular block had improvements in pain scores and opioid use even at 48 hours post knee surgery (Rambhia et al). A meta-analysis of 16 studies of patients who received a single ESPB after lumbar surgery compared to those who were managed with standard of care also demonstrated a reduction in pain and decrease in opioid use at 48 hours in those who received the ESPB compared to standard of care (Cao et al). Multiple studies have demonstrated that patients who receive UGRA in the ED are more satisfied with their care (Tekin et al) (Nejati et al). Other studies have demonstrated improved functional outcomes in patients who are managed with UGRA, such as mobility after hip surgery for patients receiving a pericapsular nerve group (PENG) block (Kimachi et al). Therefore, even a single ESPB could significantly reduce pain for prolonged periods, improve functional status, and increase satisfaction when used to treat abdominal pain from GI malignancy.

Inpatient opioid use, even at physiologic doses, is known to lead to adverse events and to increase hospital LOS and even mortality (Wei et al). Conversely, by reducing opiate use and their associated complications, UGRA can reduce hospital LOS. Vaughan et al conducted a retrospective examination which revealed that patients who received an ESPB for open cardiac surgery used fewer opioids postoperatively and had a shorter hospital LOS compared to those who did not (Vaughan et al). Similarly, Amoroso et al also demonstrated reduced opioid use and hospital LOS for patients who received an ESPB after lumbar surgery (Amoroso et al). In a prospective cohort trial, Kolodychuk et al demonstrated that hip fracture patients who received a single fascia iliaca plane block in the ED had a shorter hospital LOS compared to those who did not (Kolodychuk et al). In our own practice, the use of the ESPB for abdominal pain from GI malignancy has precluded hospital admission for two patients. Therefore, the ESPB may prevent admission or reduce hospital LOS for patients with GI malignancy.

This project is the first proposed project for specifically treating abdominal pain from GI malignancy with UGRA, and thus for taking one step closer towards replacing opioids as a treatment for breakthrough cancer pain in the ED. The current treatment paradigm as it pertains to abdominal pain from GI malignancy is to utilize intravenous opioids for breakthrough pain control. However, this approach is unsatisfactory because it leaves patients subject to subpar pain relief and to the undesirable effects of opioids, including dependence, tolerance, delirium, hypoxia, increased hospital LOS, and increased mortality rates. The proposed research is

innovative, in our opinion, because it will establish UGRA as a new modality for treating abdominal pain from GI malignancy, not only in the ED but also in other inpatient settings.

The PI, Michael Shalaby, has an extensive background in UGRA in the ED. He has authored over 35 publications on regional anesthesia, with more accepted and in press and others submitted and under review. Dr Shalaby currently serves as the editor-in-chief of the first textbook on emergency regional anesthesia, titled *Regional Anesthesia for the Emergency Physician*, which is in progress and will be published by Taylor and Francis, an esteemed publishing house. In addition to the clinical practice of UGRA, Dr. Shalaby has been teaching it to residents, fellows, and attending physicians since he was a 2nd year emergency medicine resident. In his ultrasound fellowship year alone, Dr Shalaby completed over 100 ultrasound-guided nerve blocks, and he has achieved proficiency and published in regional anesthesia of all areas of the human body that have been performed in the ED setting. Dr. Shalaby leads a year-long didactic curriculum on regional anesthesia for the emergency medicine residency, and he is leading a multi-state "Regional Anesthesia Day" with the Department of Anatomy at the Perelman School of Medicine which will employ fresh cadavers to teach regional anesthesia to medical students, residents, and attending physicians. Specific to the ESPB, Dr Shalaby has published three articles, and two more articles are currently under review. Dr. Shalaby has performed over 40 ESPB's. Dr. Shalaby published a large retrospective cohort study in the *Annals of Emergency Medicine* which demonstrated that nearly 300 ultrasound-guided nerve blocks performed in his community ED (Dr. Shalaby had been faculty at Mount Sinai Medical Center Miami Beach) at that time resulted in no adverse events. Dr. Shalaby authored another review article on the prevention and management of local anesthetic systemic toxicity (LAST). Dr. Shalaby's bibliography can be accessed at https://www.ncbi.nlm.nih.gov/myncbi/michael.shalaby.1/bibliography/public/.

The ESPB is already offered as part of usual care for abdominal pain from GI malignancy in the ED within UPHS. Patients can receive the ESPB for their abdominal pain outside the scope of this trial. In the ED, patients provide written consent before receiving any form of UGRA as part of their care, including the ESPB. Thus, in this trial we will specifically consent patients to document data on their length of stay, 24-hour opiate consumption, and pain / functionality levels (*see Primary and Secondary Endpoints in Section 1.1 above*). However, any patient who receives the ESPB as part of their analgesic regimen for abdominal pain from GI malignancy in the ED, but who does not consent to partake in this study, will not be included in the primary or secondary analysis. Furthermore, they will not be included as part of the historical control group either. For authorization of the use of data for the historical control group, please see the separate "Request for Waiver of HIPAA Authorization" form submitted through HSERA.

2.2.1 Pharmacokinetics, Pharmacodynamics and Toxicology

N/A

2.2.2 Assessment for Potential Study Products Drug-Drug, Drug-Device, Device-Device Interactions

N/A

2.2.3 Clinical Adverse Event Profile

N/A

2.2.4 Dosing Rationale

N/A

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

We anticipate no immediate or long-term risks of patient participation in this study. We will not collect the following sensitive data: social security number (SSN), home address, or bank information. The CRC or academic associates will collect the following data:

- Pain level on NRS immediately before the ESPB.
- Pain level on NRS 30 minutes after the ESPB.
- APS-POQ-R at 24 hours after the ESPB.
- Total length of stay (ED + hospital)
- Opioid use while in the ED / hospital

If patients choose not to participate in this study, they will still be offered the ESPB for their pain.

2.3.2 Known Potential Benefits

Patients with GI malignancy often have significant background abdominal pain. By the time they present to the ED, they are in significant pain which requires admission, sometimes with patient-controlled analgesia. Previous anecdotal experience for patients with GI malignancy who receive an ESPB has demonstrated that they achieve significant pain control with even a single nerve block.

2.3.3 Assessment of Potential Risks and Benefits

There are few potential risks of this project. Patients will only be approached by members of the study team, their data will be recorded and stored via REDCap, and best clinical practices will be maintained. For patients who are discharged home from the ED, the CRC will obtain a method of

follow-up at 24 hours which the patient consents to provide. At no time will patients be coerced to provide protected health information (PHI) or answers to assessments to which they are not comfortable. Prior to participation, patients will sign informed consent which will outline the risks and benefits of participating in the study, the assessments which will be performed, and the method of follow-up which will be used at 24 hours. Patients will be given enough time to read and comprehend the informed consent form and ask their provider any questions about participation. Patients will also be made aware that they may withdraw from the study at any time.

3 STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Reduction in Opiate Use To determine whether patients with GI malignancy receiving an ESPB for intractable abdominal pain consume less opioids (measured in MMEs) in a 24 hour period compared to standard of care analgesia.	Difference in MMEs consumed in 24 hour period between the prospective cohort and historical controls	Since we will not be able to interview historic controls about their pain levels, we will use opiate consumption as a marker of efficacy of the ESPB in relieving abdominal pain.
Secondary		
LOS To determine whether patients who receive an ESPB have shorter hospital LOS compared to standard of care analgesia.	Difference in hospital LOS between the prospective cohort and historical controls, as determined by time from enrollment to hospital discharge. LOS for the ESPB cohort will defined as time of the block to hospital discharge whereas the standard of care historical control group will be from the time of administration of the first analgesic in the ED under the care of a treating physician (ie, not in the waiting room).	This endpoint will evaluate whether treatment with the ESPB can shorten ED LOS compared to standard of care analgesia.
Pain Within the cohort receiving the ESPB, to determine whether there was a change in pain level as measured by the NRS pre/post block.	In the ESPB cohort, difference in pain level as measured by NRS at pre-ESPB and 30 minutes post block	This endpoint will evaluate whether the ESPB provides a clinically meaningful reduction in pain pre/post block.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Exploratory		
Functionality and satisfaction Within cohort receiving the ESPB, to determine level of patient satisfaction and functionality as measured by the Revised American Pain Society Patient Outcome Questionnaire (APS-POQ-R)	In the ESPB cohort, scores on APS-POQ-R administered at 24 hours after the ESPB *(see Appendix)*	This endpoint will evaluate whether patients will have improved satisfaction with treatment when receiving the ESBP using a modified version of the APS-POQ

4 STUDY PLAN

4.1 Study Design

This is a prospective trial of patients with breakthrough abdominal pain from GI malignancy presenting to the ED for which a prospectively collected cohort of patients will receive the ESPB for pain control and compared to a matched group of historical controls who received current ED standard of care (ie, opioid analgesia) for their abdominal pain who were treated in the ED at the same time frame as the prospective cohort was recruited.

The matched group of historical controls will equal the interventional group in number (n=25) and we will match as closely as possible based on oncological diagnosis (eg, an equal number of patients with liver cancer, and an equal number with pancreatic cancer). Patients who received the ESPB but who were not enrolled to participate in the study will be excluded from the historical control group for analysis.

The data on the historical cohorts will be obtained after study recruitment is completed. At that time, the prospectively collected data on all 25 patients will be separated by ICD-10 diagnosis code of their pre-existing oncologic diagnosis (or new diagnosis obtained during the same ED visit during which they were recruited to participate in this study) and a 10-year age range and gender (eg, 1 prospectively enrolled patient who is a 45 year old female with liver cancer will be matched with 1 retrospective patient who is a female aged 35-55 with liver cancer). With the assistance of the HUP Data Analytics Team, the charts of 25 patients with matching oncological ICD-10 diagnosis codes, age, and gender who were seen and treated at any of the 4 ED sites during the study period (the beginning and end of which will be defined by the day the first patient was recruited patient and 24 hours after the last patient was recruited, respectively) will be randomly selected. A “Request for Waiver of HIPAA Authorization” form has been submitted through HSERA to retrospectively collect the following data for the historical controls: ICD-10 diagnosis code, LOS, opiate consumption (in MME) over 24 hours starting from the first dose of analgesic administered while roomed in the ED. Prospectively and retrospectively collected patient data will be stored in REDCap. The CRC is a trained REDCap user and will collect and store all documents and information relevant to the study, including protocols, adverse events, informed consent, and the abstraction of prospective and retrospective patient data.

Our hypotheses are: 1) patients who receive the ESPB will consume less opioids and 2) therefore have a shorter hospital LOS and/or increase discharges from the ED compared to the historical standard of care group; 3) within the ESPB cohort, the ESPB will significantly reduce participants’ abdominal pain, improve their functionality, and improve satisfaction from before receiving the ESPB to after (at 30 minuets and 24 hours). For the ESPB cohort, patients with either previously diagnosed or newly diagnosed GI malignancy who present to one of four primary ED sites within UPHS will be eligible for inclusion. After receiving a computed tomography (CT) scan of the abdomen / pelvis as part of their normal care performed in the ED, which demonstrates a malignant cause of abdominal pain, and who

otherwise meet inclusion criteria (see section 5.1), they will be approached by a member of the study team (physician, academic associate, or CRC) to participate in the study. Additional exclusion criteria will include: 1) patients receiving a research CT as part of this study, and 2) patients admitted for serial abdominal examinations due to unknown surgical planning (ie, potentially ruptured viscous, small bowel obstruction, biliary colic) until the time that a definite surgical plan is known, if they are still in the ED. Furthermore, an EPIC Haiku notification will be created to notify the research team when potential participants arrive in the ED. Participants will be offered an ESPB for pain control after being consented by the performing RA, who will ask patients to rate their pain on a 0-10 NRS. The ESPB will be performed with the ideal body weight-based dose of ropivacaine 0.2%, mixed with 4 mg dexamethasone immediately prior to administration in the ED, by the treating physician. If a participant's body mass index (BMI) is under 25 kg/m^2, their actual body weight will be used for dosing. Participants will be placed on the cardiopulmonary monitor prior to blockade for at least 30 minutes while remaining in the ED, and thereafter should their clinical condition or diagnosis require it. 30 minutes after blockade, the RA will ask participants to rate their pain on the NRS. 24 hours after blockade participants will be contacted by the CRC, who will administer the modified APS-POQ-R *(see Appendix)* (Gordon et al). The patient's encrypted medical record number (MRN) and NRS and APS-POQ-R responses will be recorded by the CRC, who will store all data in REDCap.

An interim analysis will be performed after 10 patients are recruited to participate, to assess progress towards the study's primary and secondary endpoints. (See section 9.4.6 Planned Interim Analyses). For the historical standard of care comparator group, these patients are patients with GI malignancy and abdominal pain who will be treated at any of the 4 ED sites within UPHS during the time period of recruitment of the prospective cohort, but who do not receive the ESPB and who are not enrolled to participate in the study prospectively. These patients will have been treated with standard of care analgesia (ie, opioids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and others). We will randomly match 25 patients from the historical standard of care group based on ICD-10 code for GI malignancy (eg, matching an equal number of historical standard of care patients with the same or similar oncologic diagnoses as those who are prospectively recruited), gender, and age. Data for patients in the "standard of care cohort" will be collected with the assistance of the HUP Data Analytics Team. Abstracted data from patients in the standard of care cohort will consist of the same data points as that of study participants, including diagnosis, age, gender, ED / hospital LOS, opioid consumption in MMEs. Standard of care group patients will not be contacted and their information will be kept confidential, stored, and password-protected on REDCap.

4.2 Scientific Rationale for Study Design

This study is a first step in determining the efficacy of whether an ESPB can provide superior analgesia (both greater relief of pain and longer acting) for patients suffering from GI malignancy pain as compared to a matched historical group of patients receiving current standard of care (opioid analgesia). For cancer pain management, opioids have been the analgesic mainstay since the WHO began supporting their use in this patient population starting in 1996. Yet opioids do not provide adequate baseline analgesia for up to 25% of cancer patients. Opioids are also associated with a plethora of adverse effects including delirium (especially in the elderly), nausea/vomiting, hypotension, constipation, respiratory depression, dependence, and tachyphylaxis. Moreover, breakthrough pain is common despite opioid therapy and represents an acute driver of ED presentation. A survey study on patients with abdominal cancer pain revealed that even among patients with optimized background pain regimens, episodes of breakthrough pain occurred frequently (88%) (Mercadante et al). All together, there is a critical need for novel, safer, more efficacious, and better tolerated oncologic pain management strategies. In terms of abdominal visceral cancer pain, emergency regional anesthesia has the potential to provide long-acting, potent analgesia. This cohort study design was chosen as this was the next step in proving efficacy before moving to a more rigorous study design such as an RCT.

4.3 Justification for Dose

N/A

4.4 End of Study Definition

Participants are considered to have completed the study if they have completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Appendix Section 12.1.

For the ESPB cohort, a participant will have completed this study at 24 hours after the intervention, when the CRC or performing physician will contact the patient and administer the APS-POQ-R at 24 hours, even if the patient decides to go home *(see Appendix)*. Adverse events will be treated, but will not prolong the study duration for participants. Since there is no active participation of the standard of care cohort, study end, is when data has been extracted from the EMR and deidentified.

5 STUDY POPULATION

5.1 Inclusion Criteria

1. Patients age ≥ 18 years old with GI malignancy presenting to a Penn Medicine ED with intractable abdominal pain.
2. Same-day or recent CT scan of the abdomen / pelvis which demonstrates that the patient's abdominal pain can be reasonably attributed to a malignant source.

5.2 Exclusion Criteria

1. Allergy to ropivacaine or history of local anesthetic systemic toxicity.
2. Pregnancy
3. Incarcerated
4. Patients being admitted for serial abdominal examinations to determine their surgical course.
5. Altered mental status or inability for patient to consent for the procedure
6. Hemodynamic instability
7. Previously enrolled in the study

Rationale for selected inclusion/exclusion criteria:

1. CT scan: oncologic processes quickly evolve so care must be taken not to miss a new potentially surgical cause of abdominal pain
2. Patients being admitted for serial abdominal examinations to determine their surgical course: An ESPB may mask a developing surgical pathology. Patients with a known surgical course (either definitely going to get surgery or definitely not) will still be included.
3. Pregnant patients have decreased levels of alpha-1 glycoprotein which places them at inherently increased risk for LAST.
4. Incarcerated: incarcerated patients will be more difficult to contact for the 24-hour APS-POQ-R if they are discharged before then.
5. Pediatric patients: GI malignancy is rare in pediatric patients. Furthermore, most pediatric oncology patients receive their care CHOP, and will not be encountered in the EDs within UPHS.

5.3 Lifestyle Considerations

N/A

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the case series but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory

authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.5 Strategies for Recruitment and Retention

General strategies for the ESPB cohort:

- Target sample size: 25 patients in ESPB cohort, 25 patients in the historical standard of care group.
- Anticipated accrual rate: 100%
- Anticipated number of sites and participants to be enrolled: 4 clinical sites (EDs of HUP, PPMC, PAH, or HUP Cedar)
- Source of participants: ED patients
- Recruitment venues: ED
- How potential participants will be identified and approached: Participants in the ESPB cohort will be identified via chart screening by either participating physicians or research assistants. For the retrospective standard of care cohort, review of EMR for patients with GI malignancy presenting to one of the site EDs and treated with standard analgesia.
- Justification for exclusion of pregnant patients: pregnant patients have naturally lower levels of alpa-1 glycoprotein, which leaves them more susceptible to developing LAST (Shalaby et al).
- Justification for exclusion of prisoners: prisoners may not be available for follow-up, so they will be excluded.
- Justification for exclusion of pediatric patients: rarity of condition in pediatric patients, who also receive their care at CHOP.

Patients with GI malignancy presenting to the ED at HUP, PPMC, PAH, and HUP Cedar with abdominal pain will be screened by a member of study team to determine eligibility based on inclusion and exclusion criteria described in sections 5.1 and 5.2. If patient is eligible, a member of study team (physician or RA) will approach the patient to obtain informed consent for the ESPB.

Although not directly targeted, mentally disabled persons, economically or educationally disadvantaged persons, and/or employees or students of the University of Pennsylvania will not be denied enrollment and any special protections and/or additional safeguards will be undertaken in order to protect the rights and welfare of these subjects from coercion or undue influence as appropriate.

6 STUDY INTERVENTION

6.1 Study Intervention(s) Administration

6.1.1 Study Intervention Description

The study intervention consists of questions about pain levels which the participants will report on NRS before and 30 minutes after receiving the ESPB, the APS-POQ-R which will be administered to participants at 24 hours after the ESPB, of data collected prospectively on participants' LOS and opioid consumption in MME, and of retrospective data on a matched group of historical controls' LOS and opioid consumption.

6.1.2 Dosing and Administration

N/A

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and accountability

N/A

6.2.2 Formulation, Appearance, Packaging, and Labeling

N/A

6.2.3 Product Storage and Stability

N/A

6.2.4 Preparation

N/A

6.3 Measures to Minimize Bias: Randomization and Blinding

This study is not blinded. The treating physician, the participant, and all members of the study team will be aware that the injectate consisted of ropivacaine 0.2% and dexamethasone. Given the exploratory nature of this study, blinding is not desirable.

6.4 Study Intervention Compliance

Protocol adherence will require that participants rate their pain on a NRS immediately before and 30 minutes after receiving the ESPB, and to provide survey responses to the APS-POQ-R at 24 hours after receiving the ESPB.

6.5 Concomitant Therapy

N/A

6.5.1 Rescue Medicine

N/A

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

The intervention in this study is the recording of participants' pain levels on the NRS, their overall symptoms on the APS-POQ-R, their opioid consumption while in the hospital, and their LOS. Patients who do not wish to provide this information will be excluded.

7.2 Participant Discontinuation/Withdrawal from the Study

Participants may voluntarily withdraw from participation in the study at any time upon request.

7.3 Lost To Follow-Up

Participants who do not provide responses to the APS-POQ-R at 24 hours will be considered lost to follow-up.

8 STUDY ASSESSMENT AND PROCEDURES

8.1 Efficacy Assessments

Patients with GI malignancy presenting to any of the ED sites within UPHS with abdominal pain will be screened by a member of study team to determine eligibility based on inclusion and exclusion criteria described in sections 5.1 and 5.2. For the ESPB cohort, if the patient is eligible, the RA will obtain informed consent. Recruitment, consent discussion, and all procedures will be performed in a private setting. An EPIC Haiku notification will also be created in which patients with a diagnosis of GI malignancy will alert the notification system upon arrival to the ED. The Academic Associates program in the Department of Emergency Medicine consists of post-graduate RAs who are available in the ED at HUP and PPMC from 7 AM to 10 PM daily, 7 days a week. Patients will not be recruited outside these hours. The PI will lead a training session with the Academic Associates prior to initiation of patient recruitment to establish the process of recruitment and of notifying the PI and other physicians when an eligible patient has been identified. Although the Academic Associates only staff HUP and PPMC, this project will still recruit patients from PAH and HUP Cedar, since physicians who are able to participate in this proposal staff the latter two ED sites as well.

As discussed in section 6, the ESPB cohort will receive a single ESPB with ideal body weight (or actual body weight, if BMI <25) ropivacaine 0.2% with dexamethasone 4 mg for abdominal pain in patients with GI malignancy. Prior to the block, patients will be placed on the cardiopulmonary monitor and will remain monitored for at least 30 minutes after the intervention.

The primary endpoint and determination of efficacy will be the total MMEs consumed of the participants enrolled prospectively in the ESPB cohort compared to the retrospective group of patients with GI malignancy who were also treated in the ED during the same study period, but who were not enrolled and instead were managed with standard of care (excluding patients who may have received the ESPB as part of their care). After the enrollment period concludes in the ESPB cohort, when all participants have been enrolled prospectively, the CRC will gather data from EMR on each participants' MME. An average MME will be compared to the average of the standard of care cohort.

The secondary endpoints include pain levels and LOS. An exploratory analysis will measure functionality and patient satisfaction based on the APS-POQ-R questionnaire. Prior to the procedure, pain level measured on the NRS will be recorded by the RA. The ESPB will be performed under clean conditions and with ultrasound guidance. The injection site will be between the transverse process and the erector spinae muscle group at the appropriate thoracic vertebra, on either side. A guide for appropriate injection site based on organ involvement will be available to all physicians who partake in the study *(see appendix)*. A mixture of ropivacaine 0.2% and dexamethasone 4 mg will be injected within this fascial plane. None of the imaging acquired during this procedure will be provided to the patient. At 30 minutes after injection the RA will ask patients to rate their pain on the NRS. At 24 hours after blockade the CRC will

contact the patient to administer the modified APS-POQ-R questionnaire, which will determine their levels of functionality during the 24 hours after receiving the block and assess their satisfaction with the procedure. Lastly, at the conclusion of the study period the CRC will also gather data from the EMR on each participant's LOS. The HUP Data Analytics team will gather datapoints for the retrospective standard of care group. Hospital LOS (in hours) in the ESPB cohort will be compared to the LOS of the retrospective standard of care group.

Additional analgesia will be available to study participants in the ESPB cohort throughout participation, and at no time will be withheld from participants, in keeping with the current standard of care. This includes any analgesic available within the ED, including opioids, NSAIDs, acetaminophen, and others. Administration of standard of care analgesia will not have a confounding effect on the primary or secondary endpoints:

- Primary endpoint: Difference in MME use between the ESPB cohort and usual care cohort.
- Secondary endpoints:

  Pain reduction 30 minutes after ESPB: if participants do not meaningfully achieve analgesia after the ESPB, standard of care analgesia will be available, even before the 30-minute reassessment time point. For each participant, all analgesic medications will be documented and will be noted for any participants who receive repeat analgesics prior to the 30-minute reassessment period. However, we opted to reassess pain levels at 30 minutes because anecdotally we have noted that patients who receive the ESPB for abdominal pain have achieved analgesia within 30 minutes.

8.2 Safety and Other Assessments

Patients will be placed on the cardiorespiratory monitor before the intervention and will remain on it during the procedure and for at least 30 minutes after the intervention (thereafter depending on their clinical diagnosis and requirements). Cardiopulmonary monitoring allows physicians to detect signs of LAST early, such as tachy- or bradyarrhythmias and desaturation (Shalaby M et al). Other methods to enhance safety of ultrasound-guided regional anesthesia, as recommended by the American Society of Regional Anesthesia, include the use of real-time ultrasound guidance, ideal body-weight dosing (unless BMI <25, in which actual body weight dosing will be used), aspiration prior to the initiation of injection, and injection in 5-10 ml aliquots followed by a pause and a repeat aspiration prior to continued injection (Neal et al).

The CRC will follow up with patients via phone call 24 hours after the procedure to determine the presence of complications.

In the informed consent, participants will be provided with the PI's institutional email address and contact information to report any complications or concerns which may arise after discharge. To help guide participants' understanding of complications of the ESPB, these will be listed and

explained, and will include shortness of breath (in the case of undetected or missed pneumothorax), neuropathy, and cellulitis at the injection site. The study team will not independently contact patients to assess for these risks.

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of Adverse Events (AE)

An adverse event (AE) is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related. Intercurrent illnesses or injuries should be regarded as adverse events.

A pre-existing condition should be recorded as an adverse event if the frequency, intensity or the character of the condition changes.

8.3.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Events (SAE)

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that, in the view of either the investigator or the sponsor, is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.
- required intervention to prevent permanent impairment or damage (for devices only)

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

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 the ESPB 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 considered.

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

8.3.3.3 Expectedness

The PI, Dr. Michael Shalaby, 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 ESPB.

8.3.4 Time Period and Frequency for Event Assessment and Follow-Up

Safety will be assessed by monitoring and recording potential adverse effects using Common Terminology Criteria for Adverse Events (CTCAE) at each study visit. Participants will be

monitored by medical histories, continuous cardiorespiratory monitoring during and after the procedure. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, life-threatening, and death, corresponding to Grades 1-5, will be used whenever possible.

At each contact with the subject, the investigator will seek information on adverse events by non-directive questioning and, as appropriate, by examination. Adverse events may also be detected when they are volunteered by the subject during the screening process, through physical examination, or other assessments. Information on all adverse events will be recorded in the source documentation. To the extent possible, adverse events will be recorded as a diagnosis and symptoms used to make the diagnosis recorded within the diagnosis event.

As much as possible, each adverse event or follow-up information will be evaluated to determine:

1. Severity grade (CTCAE Grade 1-5)
2. Duration (start and end dates)
3. Relationship to the study treatment or process – [Reasonable possibility that AE is related: No (unrelated/ not suspected) or Yes (a suspected adverse reaction)]. If yes (suspected) - is the event possibly, probably or definitely related to the investigational treatment?
4. Expectedness to study treatment or process – [Unexpected – if the event severity and/or frequency is not described in the investigator brochure (if applicable) or protocol].
5. Action taken with respect to study or investigational treatment or process (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
6. Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
7. Whether the event is serious

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

8.3.5 Adverse Event Reporting

Reporting Period

Adverse events will be reported from the time of informed consent until study completion.

Investigator Reporting: Notifying the Study Sponsor

Every SAE, regardless of suspected causality (e.g., relationship to study product(s) or study procedure(s) or disease progression) must be reported to the sponsor within **24 hours** of learning of its occurrence.

Recurrent episodes, complications, or progression of the initial SAE must be reported to the Sponsor as a follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE considered completely unrelated to a previously reported one should be reported separately as a new event.

Send the SAE report to the PI.

New information regarding the SAE will be reported as it becomes available and in the same manner that the initial SAE (i.e. SAE form). The investigator must follow the event to resolution or until the event is deemed and documented irreversible, whichever is longer.

Investigator Reporting: Local Reporting Requirements

The investigator will report AEs and SAEs to the IRB/EC of record and other local regulatory groups per the local requirements.

8.3.6 Serious Adverse Event Reporting

The study clinician will immediately report to the PI any serious adverse event, whether or not considered the ESPB related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the ESPB 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 ESPB and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

New information regarding the SAE will be reported as it becomes available and in the same manner that the initial SAE (i.e. SAE form). 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.

8.3.7 Reporting Events to Participants

Participants who experience adverse events or serious adverse events will be immediately informed and consented for treatment. The only delayed adverse event which we expect to be a possibility is injection site infection, which participants will be educated on both verbally and in the informed consent form prior to consenting to partake in the study.

8.3.8 Events of Special Interest

N/A

8.3.9 Reporting of Pregnancy

Given that pregnant patients will be excluded from this study, all potential pre-menopausal female participants will be screened with a urine or serum hCG pregnancy test.

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 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

Unanticipated problems (UPs) such as:

- Post-marketing withdrawal of a drug, device, or biologic used in a research protocol due to safety concerns.
- FDA ban of a drug, device, or biologic used in a research protocol due to safety concerns.
- Complaint of a participant when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team
- Breach of confidentiality
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study

- Premature closure of a study (e.g., due safety, lack of efficacy, feasibility, financial reasons, etc.)

should be reported by the investigator to the 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 as any other SAE.
- Any other UP will be reported to the IRB and to the DCC within 48 hours 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 48 hours of the IRB's receipt of the report of the problem from the investigator.

8.4.3 Reporting Unanticipated Problems To Participants

N/A

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

Primary endpoints:

- H_0: Mean/median morphine equivalents in 24 hours in the ESPB group = Mean/median morphine equivalents in 24 hours in the standard of care cohort.

  H_1: Mean/median morphine equivalents in 24 hours in the ESPB group ≠ Mean/median morphine equivalents in 24 hours in the usual care cohort.

Secondary endpoints:

- H_0: Mean/median hospital LOS in the ESPB group = Mean/median hospital LOS in the usual care cohort.
- H_1: Mean/median hospital length of stay in the ESPB group ≠ Mean/median hospital length of stay in the usual care cohort.
- H_0: Mean pain difference pre/post ESPB=0.
- H_1: Mean pain difference pre/post ESPB≠0.

9.2 Sample Size Determination

Sample size determination will be based on the primary endpoint, mean difference in MME between the ESPB cohort and the historical cohort who received standard of care. The sample size was based on the EASIER trial (Ref P), for which the median MMEs at 24 hours was 13 (IQR:11, 19) and 22 (IQR:17, 32), for ESPB and IV opioids respectively. Assuming the mean difference in MMEs between the ESPB and usual care cohort will be at least 9-10, with a standard deviation between 10-12, sample sizes between 17-25 for each cohort will achieve 80% power to detect a difference in MMEs between ESPB, with alpha set at 0.05 using a two-sided two-sample unequal-variance t-test. Although we will only need 25 in the usual care cohort, since it is retrospective data and easily obtainable, we will increase this sample size to between 50-100, which will provide us with a more heterogeneous sample and also reduce the error.

9.3 Populations for Analyses

There will be 2 groups: 1) A prospective cohort of participants with GI malignancy during the 12 month period compared to 2) a retrospective group of patients with GI malignancy who did not receive the ESPB and who instead were treated at our EDs with standard of care during the same period of time. Data from the first cohort will be collected prospectively, whereas the second cohort will be retrospective obtained by EMR review.

9.4 Statistical Analyses

9.4.1 General Approach

Prior to analysis, all primary and secondary outcome measures will be summarized with descriptive statistics (mean ± standard deviation (SD) or median and IQR), their distributions examined, tested for normality and transformed as needed. Additionally all demographics will be summarized using mean ± SD, for continuous variables and frequencies and percentages for categorical variables.

Results from statistical testing for continuous variables, will be presented with p-values and 95% confidence intervals for tests using means or medians and IQR if a non-parametric test is used. For categorical variables, the chi-square or Fisher's exact test will be performed to examine

whether treatment arms differ with regard to demographics and other baseline variables. Similarly, for side effects, descriptive statistics and Fisher's exact tests will be performed for possible differences between the treatment arms. Regardless of type statistical test, all will be two-sided.

9.4.2 Analysis of the Primary Efficacy Endpoint(s)

The primary efficacy endpoint is difference in opioid consumption at 24 hours between the ESPB and standard of care cohorts. Opioid consumption will be measured in MMEs and is an interval/ratio variable. To assess differences in MMEs between cohorts, either a 2-sample t-test (normally distributed) or a Wilcoxon rank-sum test (positively skewed) will be performed. Results will be presented as means ± 95% confidence intervals for each cohort, if normally distributed or medians with interquartile range (IQR) if study samples are positively skewed.

9.4.3 Analysis of the Secondary Endpoint(s)

One secondary endpoint is difference in hospital LOS between cohorts. This endpoint, measured in hours, is an interval/ratio variable. To assess differences in LOS between cohorts we will perform similar analyses as for the primary endpoint of MMEs.

The secondary endpoint of change in pain level in the ESPB will be measured using the NRS (0-10) which is an ordinal variable. To assess differences in NRS pre/post block in the ESPB cohort, a paired t-test (normally distributed) or a Wilcoxon signed rank test will be performed.

The final secondary endpoint is score on the modified APS-POQ-R. For the APS-POQ-R each of 15 questions are based on an ordinal scale from 0-10. Functionality score on the APS-POQ-R is a continuous variable based on 14 questions (does not include satisfaction) with a range of scores from 0-140, higher scores indicating worse outcomes. Results for this endpoint are descriptive and will be presented as means ± SD, or median and IQR if distribution of scores positively skewed.

9.4.4 Safety Analyses

Safety endpoints are not primary endpoints for analysis for this proposal, but will be documented in REDCap for each participant. Adverse events and serious adverse events will be documented for each participant.

9.4.5 Baseline Descriptive Statistics

Baseline and demographic characteristics will be summarized using descriptive statistics (mean ± SD or median and IQR) for continuous variables such as age, NRS, total opioids consumed

(MMEs), hospital LOS and frequencies and percentages for categorical variables such as race/ethnicity, insurance, gender.

9.4.6 Planned Interim Analyses

An interim analysis will be conducted after the enrollment and completion of data collection for the first 10 patients receiving the nerve block intervention. The primary objectives of this interim analysis are to review preliminary data on study endpoints and to determine whether continuing the study is justified based on the observed data.

Objectives of Interim Analysis:

- **Efficacy and Endpoint Assessment:** The interim analysis will include descriptive statistics to examine preliminary data on the primary and secondary endpoints, including:
  - Length of hospital stay
  - Post-procedure opioid consumption
  - Pain scores and patient satisfaction levels at 24 hours
- **Safety Oversight:**
  - Since the ESPB is part of routine standard of care, a DSMB will not be created to provide oversight of safety.
  - However, if any safety concerns arise, such as an unexpected pattern of adverse events, the methodology will either be modified with a halt in recruitment until the IRB approves, or if necessary the study will be halted.
  - Based on the findings, potential protocol modifications or additional monitoring measures may be recommended and implemented with IRB approval.
- **Confidentiality, Data Integrity, and Best Clinical Practices**
  - All analyses will be conducted in accordance with data confidentiality protocols.
  - The PI will ensure adherence to best clinical practices, including storage of signed informed consent forms and patient data on Penn Vault.
  - The interim analysis report will be shared only with designated study oversight personnel and IRB, and will not be used to make definitive conclusions until the full study is completed, unless early termination is otherwise deemed necessary.

The PI and study statistician will review the interim analysis report.

9.4.7 Sub-Group Analyses

None

9.4.8 Tabulation of Individual Participant Data

Individual patient data will be listed by endpoint of total MMEs at 24 hours, hospital LOS, (both cohorts). For the ESPB cohort, NRS at baseline and 30 minutes post ESPB, as well as APS-POQ-R at 24 hours.

9.4.9 Exploratory Analyses

None.

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

Prior to receiving the ESPB, participants will sign the standard procedure consent form available at all ED sites. However, their consent for this particular study will entail permission to record their responses to NRS pain scale and the APS-POQ-R, and to document their LOS and opioid consumption while in the hospital.

The following consent materials are submitted with this protocol: Informed Consent Form.

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 will be Institutional Review Board (IRB)-approved and the participant will be 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 by the Sponsor or the PI at any site 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 investigator. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- 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).

In terminating the study, the Sponsor and the PI will assure that adequate consideration is given to the protection of the subjects' interests.

10.1.3 Confidentiality and Privacy

Participant confidentiality and privacy are 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.

The study monitor, representatives of the Institutional Review Board (IRB), or regulatory agencies 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 entered and stored on REDCap. 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 will be secured and password protected. At the end of the study, all study databases will be de-identified and archived on REDCap.

Throughout participant recruitment, intervention, and during the study period, we will maintain patient privacy. Patients will be approached to participate in the study while they are in their room in the ED, and not while they are in the waiting room or otherwise in a public area of the ED, so as to maintain their privacy and keep their protected health information private. Furthermore, all interventions will be performed when the patients are in their room, and again not in a space in the ED in which other patients are present. Prior to discussing recruitment and participation, if patients are not alone in the room (ie, with their family or other loved ones) they will be asked if they would like to discuss participation privately. The CRC will use a hospital-provided phone to contact patients at follow-up at 24 hours, and their names and phone numbers will not be stored in the hospital phone and patients will not be contacted from the private phone lines of any member of the team. The patient will only interact with the investigator while in their assigned room in the ED.

10.1.4 Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored on REDCap. After the study is completed, the de-identified, archived data will be on REDCap, for use by other researchers. Permission to store data on REDCap will be included in the informed consent.

When the study is completed, access to study data and/or samples will be provided through REDCap.

10.1.5 Safety Oversight

Since this trial is not a trial to determine the safety and efficacy of a novel intervention, a DSMB will not be established for safety oversight. Rather, this trial is to determine if an intervention which is already offered as standard of care in the ED (the ESPB) results in improved outcomes for participants who receive it, compared to patients who do not.

10.1.6 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).

Centralized monitoring of this study will be completed by the Division of Ultrasound in the Department of Emergency Medicine, including a biostatistician, five faculty members, five fellows, and a research coordinator. The monitoring will occur once every two months and will consist of a random review of the data for verification of endpoint and safety.

Independent audits may be conducted by the Office of Clinical Research at UPHS to ensure monitoring practices are performed consistently across all participating sites.

10.1.7 Quality Assurance and Quality Control

All monitoring and audits are to be performed according to ICH GCP E6(R2).

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

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 site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated, and specimens are collected, 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 the sponsor, and inspection by local and regulatory authorities.

10.1.8 Data Handling and Record Keeping

10.1.8.1 Data Collection and Management Responsibilities

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

All source documents should be completed in REDCap and follow ALCOAC standards (Attributable, Legible, Contemporaneous, Original, Accurate, and Complete).

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into PennCRMS (Velow) a 21 CFR Part 11-compliant data capture system provided by the Perelman School of Medicine (PSoM). The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Clinical and laboratory data will be entered into a Penn CRMS, 21 CFR Part 11-compliant electronic data capture system (EDC) that includes individual user account level password protection. This EDC (Velos version 9) supports programmable data entry validation rules and edit checks to identify data entry errors.

10.1.8.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the phrenic nerve block. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.9 Protocol Deviations

The PI and the study team should document all scenarios where the protocol is not followed and provide, in particular:

- Who deviated from the protocol
- What was the deviation
- When did the deviation occur
- How did the deviation happen
- What is the impact of the deviation
- A root cause analysis of why the deviation occurred

If the assessment results in a determination that any of the following are potentially affected, the deviation would be considered of significant impact:

- having the potential to adversely affect subject safety; OR

- increases risks to participants; OR
- adversely affects the integrity of the data; OR
- violates the rights and welfare of participants, OR
- affects the subject's willingness to participate in research.
- there is a potential for an overall impact on the research that should be shared with the IRB for consideration and development of next best steps to address it

Publication and Data Sharing 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.

10.1.10 Conflict of Interest Policy

10.2 Protocol Amendment History

Version	Date	Description of Change	Brief Rationale

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12 APPENDIX

12.1 Schedule of Activities (SoA)