Four quadrant Transverse Abdominus Plane (4Q-TAP) block with plain and liposomal bupivacaine vs. Thoracic Epidural Analgesia (TEA) in patient's undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) on an enhanced recovery pathway: a single-blinded, randomized, non-inferiority study.

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Table of Contents

1. **STUDY SYNOPSIS**
2. **STUDY OBJECTIVES**
3. **BACKGROUND**
    A. Postoperative pain after CRS-HIPEC surgery
    B. Thoracic Epidural Analgesia for CRS-HIPEC and side effects
    C. Transverses Abdominus Plane (TAP) Blocks
    D. Liposomal bupivacaine (Exparel)
    E. Rationale for the study
4. **METHODS and STUDY DESIGN**
    A. Setting and Population
        i. Inclusion Criteria
        ii. Exclusion Criteria
    B. Protocol
    C. Measurements
    D. Statistical Analysis
        i. Sample Size Considerations
    E. References

1. STUDY SYNOPSIS

Four quadrant TAP (4Q-TAP) block with plain and liposomal bupivacaine vs. Thoracic Epidural Analgesia (TEA) in patient's undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) on an enhanced recovery pathway: a single-blinded, randomized, non-inferiority study.	
Objectives	To evaluate the impact of 4 quadrants TAP blocks (4Q-TAP) versus Thoracic Epidural Analgesia (routine care) on the quality of recovery and other clinically relevant outcomes after CRS-HIPEC surgery. To study the incidence of adverse events associated with (4Q-TAP) blocks versus Thoracic Epidural Analgesia (routine care) after CRS-HIPEC surgery.
Aims	a. **Primary Aim:** To compare the efficacy of 4 quadrants TAP blocks (4Q-TAP) versus Thoracic Epidural Analgesia (routine care) on the quality of recovery 48 hours after CRS-HIPEC surgery. b. **Secondary Aim 1:** To compare the efficacy of 4 quadrants TAP blocks (4Q-TAP) versus Thoracic Epidural Analgesia (routine of care) on postoperative pain 48 hours after CRS-HIPEC surgery. c. **Secondary Aim 2:** To compare the total opioid consumption between patients with 4 quadrants TAP blocks (4Q-TAP) versus Thoracic Epidural Analgesia (routine care) intraoperatively and up to 48 hours after CRS-HIPEC surgery. d. **Secondary Aim 3:** To compare the length of stay (LOS) between patients with 4 quadrants TAP blocks (4Q-TAP) versus Thoracic Epidural Analgesia (routine care) after CRS-HIPEC surgery. e. **Secondary Aim 4.** To compare the incidence of adverse events (i.e. postoperative hypotension, failed block) related to 4 quadrants TAP blocks (4Q-TAP) versus Thoracic Epidural Analgesia (routine care) 48 hours after CRS-HIPEC surgery. f. **Secondary Aim 5.** To compare the incidence of opioid-related adverse (i.e. respiratory depression, pruritus, sedation, delirium) events related to 4 quadrants TAP blocks (4Q-TAP) versus Thoracic Epidural Analgesia (routine care) 48 hours after CRS-HIPEC surgery. g. **Secondary Aim 6.** To compare the incidence postoperative complications and morbidity in patients receiving 4 quadrants TAP blocks (4Q-TAP) versus Thoracic Epidural Analgesia (routine care) 48 hours after CRS-HIPEC surgery.
Study Design	This is a randomized controlled trial designed to test efficacy of 4Q-TAP against TEA (routine of care) on quality of recovery 48 hours after CRS-HIPEC surgery. All patients will be enrolled at MD Anderson Cancer Center.
Number of Patients	160 patients randomized to the 2 study arms (80 patients per arm)
Sites	MD Anderson Cancer Center

Duration of Study	It is expected that this will take up to 36 months.
Duration of Patient Participation	Patients who consented to participate in the study will remain in the study until last planned outcome is collected on postoperative day 30. Patient will have the opportunity to withdraw from the study at any time.
Primary Endpoint Definition	Quality of recovery (QoR) 48 hours after CRS-HIPEC surgery.
Secondary Endpoints	• Postoperative pain 48 hours • The total opioid consumption within 48 hours after surgery • Length of stay • Incidence of adverse events • Incidence of opioid-related adverse events • Postoperative complications and morbidity • QoR on postoperative day 3, 7 10 and 30.
Primary Safety Endpoint	All reported adverse events.
Follow-Up Schedule	The study will be considered complete after all randomized patients have had 30 days of follow-up data collection.
Inclusion Criteria	1. Written informed consent; 2. 18 years old or older; 3. American Society of Anesthesiologists physical status (ASA) 1-3; 4. Scheduled surgery: open elective CRS-HIPEC; 5. Able to complete the QoR 15 questionnaire; 6. Patients scheduled to receive intraoperative chemotherapy;
Exclusion Criteria	1. Contraindications to epidural analgesia due to thrombocytopenia (platelet count: <100,000 cell/dL), coagulopathy (International Normalized Ratio > 1.5, PT>16.5 seconds or aPTT > 35.9 seconds); 2. Bupivacaine or liposomal bupivacaine sensitive or known allergy; 3. Pregnancy or breastfeeding patients; 4. Patients with recent (within 60 days preoperatively) history severe hepatic disease; 5. Patients with recent (within 15 days preoperatively) history deteriorate kidney function (creatinine serum concentrations > 2.5 mg/dL or eGFR < 30 mL/kg/min);
Study Sponsorship: None	
Study Monitoring: MDACC DMSB	

Abbreviations

aPTT	Activated partial thromboplastin time
AE	Adverse Event
ASA	American Society of Anesthesiologist
CFR	Code of Federal Regulations
CRF	Case Report Form
CRS-HIPEC	Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
Hb	Hemoglobin
Hct	Hematocrit
IFU	Instructions for Use
INR	International normalized ratio
IRB	Institutional Review Board
LOS	Length of stay
PACU	Postoperative acute care unit
PT	Prothrombin time
POD	Postoperative Day
SAE	Serious adverse events
TAP	Transverse Abdominus Plane
TEA	Thoracic epidural analgesia
QoR	Quality of Recovery
VNRS	Verbal numeric rating scale
4Q-TAP	Four quadrant TAP block

2. STUDY OBJECTIVES

a. To evaluate impact of 4 quadrants TAP blocks (4Q-TAP) versus Thoracic Epidural Analgesia (routine care) on the quality of recovery and other clinically relevant outcomes after CRS-HIPEC surgery.

b. To study the incidence of adverse events associated with (4Q-TAP) blocks versus Thoracic Epidural Analgesia (routine care) after CRS-HIPEC surgery.

3. STUDY AIMS

a. **Primary Aim:** To compare the efficacy of 4 quadrants TAP blocks (4Q-TAP) versus Thoracic Epidural Analgesia (routine care) on the quality of recovery 48 hours after CRS-HIPEC surgery.

Hypothesis: The quality of recovery with 4 quadrants TAP blocks (4Q-TAP) 48 hs after CRS-HIPEC surgery is not inferior to Thoracic Epidural Analgesia (routine care).

b. **Secondary Aim 1:** To compare the efficacy of 4 quadrants TAP blocks (4Q-TAP) versus Thoracic Epidural Analgesia (routine of care) on

postoperative pain 48 hours after CRS-HIPEC surgery.

Hypothesis: Postoperative pain 48 hours after CRS-HIPEC surgery is not inferior with 4 quadrants TAP blocks (4Q-TAP) than Thoracic Epidural Analgesia (routine care).

c. **Secondary Aim 2:** To compare the total opioid consumption between patients with 4 quadrants TAP blocks (4Q-TAP) versus Thoracic Epidural Analgesia (routine care) intraoperatively and up to 48 hours after CRS-HIPEC surgery.

Hypothesis: Perioperative opioid consumption after CRS-HIPEC surgery is not higher in patients with 4 quadrants TAP blocks (4Q-TAP) than epidural analgesia (routine care).

d. **Secondary Aim 3:** To compare the length of stay (LOS) between patients with 4 quadrants TAP blocks (4Q-TAP) versus Thoracic Epidural Analgesia (routine care) after CRS-HIPEC surgery.

Hypothesis: The LOS after CRS-HIPEC surgery is shorter in patients with 4 quadrants TAP blocks (4Q-TAP) than Thoracic Epidural Analgesia (routine care).

e. **Secondary Aim 4.** To compare the incidence of adverse events (i.e. postoperative hypotension, failed block) related to 4 quadrants TAP blocks (4Q-TAP) versus Thoracic Epidural Analgesia (routine care) 48 hours after CRS-HIPEC surgery.

Hypothesis: The incidence of adverse events (i.e. postoperative hypotension, failed block) related to 4 quadrants TAP blocks (4Q-TAP) is lower than Thoracic Epidural Analgesia (routine care) 48 hours after CRS-HIPEC surgery.

f. **Secondary Aim 5.** To compare the incidence of opioid-related adverse (i.e. respiratory depression, pruritus, sedation, delirium) events related to 4 quadrants TAP blocks (4Q-TAP) versus Thoracic Epidural Analgesia (routine care) 48 hours after CRS-HIPEC surgery.

Hypothesis: The incidence of opioid-related adverse events is lower in patients receiving 4 quadrants TAP blocks (4Q-TAP) versus Thoracic Epidural Analgesia (routine care) 48 hours after CRS-HIPEC surgery.

g. **Secondary Aim 6.** To compare the incidence postoperative complications and morbidity in patients receiving 4 quadrants TAP blocks (4Q-TAP) versus Thoracic Epidural Analgesia (routine care) 48 hours after CRS-HIPEC surgery.

Hypothesis: The incidence of postoperative complications and morbidity is lower in patients receiving 4 quadrants TAP blocks (4Q-TAP) versus Thoracic Epidural Analgesia (routine care) 48 hours after CRS-HIPEC surgery.

h. **Secondary Aim 6.** To compare the quality of recovery on

postoperative days 3, 7, 10 and 30 in patients receiving 4 quadrants TAP blocks (4Q-TAP) versus Thoracic Epidural Analgesia (routine care) 48 hours after CRS-HIPEC surgery.

Hypothesis: The quality of recovery with 4 quadrants TAP blocks (4Q-TAP) after CRS-HIPEC surgery is not inferior to Thoracic Epidural Analgesia (routine care) on postoperative days 3, 7, 10 and 30.

4. BACKGROUND

A. Quality of recovery after CRS-HIPEC surgery

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) is an extensive and complicated surgical procedure that has been shown to provide long-term survival in select groups of patients with peritoneal carcinomatosis.[1-6] The procedure typically entails an extensive cytoreduction, multiple visceral resections and peritonectomies.[7-10] Due to the extensiveness of CRS-HIPEC ***the postoperative quality of recovery of patients*** undergoing this type of surgery ***is poor***. ***Incisional pain, nausea and vomiting, postoperative ileus, fatigue, poor social interaction and sleep deprivation*** are the most common factor that diminishes the quality of recovery after major abdominal surgery. Furthermore, inadequate pain control may lead to poor outcomes. In fact, poor pain control is one of the leading causes of readmission after CRS-HIPEC,[11] and postoperative pain has been shown to significantly impact the quality of life.[12,13]

High requirements of opioids and their side effects (i.e. ileus, delirium, nausea and vomiting and dry mouth) play a significant role in the recovery of a significant portion of the patients undergoing CRS-HIPEC.[10] This was demonstrated in our recently published study of 215 CRS-HIPEC patients, where the median intraoperative and postoperative opioid consumption were 92 and 595 mg of morphine equivalents, respectively.[14] Attaining adequate pain control while minimizing opioid intake and their side effects, is therefore essential to attain better outcomes and ***improve the quality of recovery*** in this patient population. With regard to this, results of previous studies in patients undergoing CRS-HIPEC have demonstrated decreased opioid consumption by the use of thoracic epidural analgesia (TEA) as part of a multimodal analgesia strategy.[10,14] ***Unfortunately, not all patients undergoing CRS-HIPEC are candidates to receive TEA.***

B. Thoracic Epidural Analgesia for CRS-HIPEC and side effects

Thoracic Epidural analgesia is the most commonly used technique to manage postoperative pain during and after CRS-HIPEC surgery. A recent study from our institution demonstrates that more than two-thirds of the patients who undergo HIPEC surgery receive TEA.[14] This analgesia technique entails the placement of a catheter in the epidural space to administer a solution based on the combination of local anesthetics (ropivacaine or bupivacaine) and opioids (fentanyl or hydromorphone). Epidural catheters are almost always placed before patients

are induced to receive general anesthesia to avoid potential damage to neural structures.

In comparison with intravenous opioids, the related benefits to the use of epidural analgesia include ***adequate postoperative pain control and opioid-sparing effects***.[15-17] As a result of these two factors and a reduction in the stress response to surgery, some studies demonstrated that thoracic epidural analgesia for abdominal surgery decreased respiratory, cardiovascular and gastrointestinal complications.[18,19] Unfortunately, recent studies indicate that the ***rate of failure*** for epidural catheter placement is approximately **10%** but it can be ***as high as 30%***.[20-22] Difficult identification of anatomical landmarks as it occurs in obese patients or displacement of the catheters are the most common reasons of epidural failure. Moreover, suboptimal functioning of successfully inserted epidural catheters are commonly observed and widely described in the literature.[21,23] In this clinical scenario, intravenous opioids are given to achieve optimal pain control.

To complicate the matter, ***not all patients*** who are scheduled for CRS-HIPEC surgery ***are candidates to receive epidural analgesia.*** A large retrospective study from our group demonstrated that close to ***25% of the patients*** who had HIPEC surgery at MD Anderson Cancer Center did ***not receive epidural analgesia*** and were treated with large amounts of intravenous opioids. The most common reasons why epidural analgesia is contraindicated in patients undergoing CRS-HIPEC are a reduced number of platelets (thrombocytopenia), anticoagulant therapies or patient refusal. Both clinical conditions are associated with an increased risk of epidural hematomas. A small fraction of patients might also refuse the placement of epidural analgesia because of concerns such as neurological complications or past experience with epidural failures.

Furthermore, intraoperative coagulation derangements and postoperative thrombocytopenia and coagulopathies are also the most common reasons why epidural catheter cannot be removed immediately after surgery because they can also increase the risk of bleeding in the epidural space.[24] A recent study from our group has shown that most of the coagulopathies observed in CRS-HIPEC patients occur within the first 72 hours after surgery, however there are a portion of patients who remain coagulopathic at day 7 postoperatively.[25] It is in this group of patients that the risk of catheter-related infections and epidural abscess is increased if the catheters are not removed.[26]

While epidural analgesia may be considered the ***"gold standard"*** for postoperative pain management after HIPEC,[27] ***adverse events,*** and need for active postoperative management make the use of this analgesia technique undesirable in some cases.[28,29] Perioperative hypotension, urine retention as a result of opioids and motor weakness secondary to epidural local anesthetic administration are noted potential drawbacks that ***might reduce the quality of recovery of patients.*** Respiratory depression is another complication related to the administration of opioids administered into the epidural space particularly in elder patients.

Considering that a large number of patients undergoing CRS-HIPECs are not suitable candidates to receive epidural analgesia, a high failure rate, and a significant portion of patients suffer from epidural-related adverse effects, there is

a need for an alternative less invasive regional analgesia technique that can provide similar analgesia while ***improving their quality of recovery***.

C. Traditional Transverse Abdominus Plane (TAP) Block

The TAP block is a regional analgesia technique that entails the unilateral or bilateral ***administration of a local anesthesia solution (15-20 cc) into the transverse abdominus plane***. This virtual plane lies above the transverse abdominus muscle in the abdominal wall where spinal nerves that supply the abdominal wall run from posterior to the anterior aspect of the abdomen. The traditional TAP block is performed in the lateral abdominal wall between iliac crest and costal margin and only provides effective analgesia to the distal or lower half of the abdomen.[30] ***The benefits of TAP blocks are well documented in randomized control trials and meta-analysis***.[31-35]

4-quadrant TAP block

To enhance the analgesic efficacy of the traditional TAP block, several authors have added a subcostal approach to provide analgesia to the upper half of the abdomen. In a cadaveric study of the four-quadrant TAP block (4QTAP), dermatomes T8-L1 were adequately covered with the solution of local anesthetic. Therefore, it was originally hypothesized that the 4QTAP block may be more beneficial in major abdominal surgery compared to the traditional TAP approach alone.[36] In a prospective study of 124 patients, the surgical incision for abdominal surgery was within the dermatomal limits of the 4QTAP in 70% of patients.[37] In a later study by Niraj et al, the authors demonstrated that 4QTAP with levobupivacaine resulted in similar pain scores and tramadol consumption when compared to epidural analgesia for laparoscopic colorectal surgery.[38 39]

The 4QTAP block may provide some advantages over epidural analgesia as TAP blocks are associated with more stable hemodynamics and less use of vasopressor and intravenous fluids during and after surgery.[40] In addition, 4QTAP blocks are not associated with postoperative urine retention neither the risk of epidural hematoma or infections. Lastly, the use of 4QTAP blocks can reduce the use of resources and personnel because there is no need for frequent monitoring of the epidural catheter and infusions pumps.

With the increased safety of ultrasound guided needle placement and 'real-time' visualization through dynamic scanning, **serious complications are rare** with the 4QTAP block.[37] Needle puncture thru the peritoneum causing bowel or diaphragm perforation is unlikely, but is still a possibility. The abundance of structures in the peritoneal cavity makes the viewing of the needle in plane at all times during needle advancement of utmost importance. Lacerations of the liver have been reported during placement of right-sided TAP blocks.[41] Abdominal wall hematoma, vascular injury, local anesthetic toxicity and are also potential, but rare complications.[34]

D. Liposomal bupivacaine: A long-acting local anesthetic

The longer duration of analgesia (48-72 hours) with the use of liposomal bupivacaine presents advantages over traditional local anesthetics. A number of

studies support the benefits of liposomal bupivacaine for TAP blocks over standard bupivacaine alone.[42] In a randomized prospective trial by Hutchins et al, patients undergoing robotic hysterectomy and received subcostal TAP with liposomal bupivacaine had lower opioid requirements for the first 72 hours after surgery and lower pain scores when compared to bupivacaine hydrochloride.[43] Giving the relative large volume of local anesthetics required for adequate TAP block analgesia, systemic toxicities are a potential complication. However, staying within the reported maximum local anesthetic volumes significantly decreases the risk.

D1. Pharmacokinetics.

Absorption. Following its release from the liposomal bupivacaine particles, the rate of systemic absorption of bupivacaine is dependent upon the total dose of drug administered, the route of administration, and the vascularity of the administration site. At dosing ratios of greater than 2:1, liposomal bupivacaine and bupivacaine may be co-administered through a single injection. At ratios <2:1, substantial displacement of free bupivacaine from the liposomes may result.[44] In a study by Kharitonov, the compatibility of liposomal bupivacaine with epinephrine, corticosteroids, and opioids were not associated with adverse events.[44]

Distribution. After bupivacaine has been released from liposomal bupivacaine and is absorbed systemically, bupivacaine distribution is expected to be the same as for any bupivacaine HCl solution formulation. To some extent, local anesthetics are distributed to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain.

The rate and degree of diffusion are governed by:

1. The degree of plasma protein binding
2. The degree of ionization
3. The degree of lipid solubility

Metabolism. Amide-type local anesthetics such as bupivacaine HCl are metabolized primarily in the liver via conjugation with glucuronic acid. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics. Pipecolylxylidine (PPX) is the (largely inactive) major metabolite of bupivacaine HCl: approximately 5% of bupivacaine HCl is converted to PPX.

Excretion. After bupivacaine has been released from liposomal bupivacaine and is absorbed systemically, bupivacaine excretion is expected to be the same as for other bupivacaine formulations.

Various pharmacokinetic parameters can be significantly altered by:

- The presence of hepatic or renal disease
- Factors affecting urinary pH
- Renal blood flow

The kidney is the main excretory organ for bupivacaine and its metabolite; only 6% of bupivacaine is excreted unchanged in the urine.

Hepatic Impairment. The effects of decreased hepatic function on bupivacaine pharmacokinetics following administration of liposomal bupivacaine were studied in patients with moderate hepatic impairment. Consistent with the hepatic impairment of bupivacaine, mean plasma concentrations were higher in patients with moderate hepatic impairment than in the healthy control volunteers.

Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, these drugs should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations.

Renal Impairment. Bupivacaine is primarily excreted by the kidneys, and the risk of toxic reactions to liposomal bupivacaine may be greater in patients with impaired renal function.

Storage Liposomal bupivacaine vials should be stored refrigerated between 2°C to 8°C (36°F to 46°F). Liposomal bupivacaine may be held at a controlled room temperature of 20°C to 25°C (68°F to 77°F) for up to 30 days in sealed, intact (unopened) vials. Vials should not be re-refrigerated. As a convenience to the pharmacist, each vial label includes space to record the date when the vial has been removed from refrigeration.

Liposomal bupivacaine should not be frozen or exposed to high temperatures (greater than 40°C or 104°F) for an extended period. Liposomal bupivacaine should not be administered if it is suspected of having been frozen or exposed to high temperatures.

E. Rationale for Study.

Quality of recovery after surgery is a patient-related outcome that integrates postoperative psychosocial and physiologic parameters as perceived by patients. While TEA is the standard of care in patients undergoing CRS-HIPEC surgery, it cannot be offered to a large number of patients, and it is associated with adverse events in those treated with the technique. Therefore, 4Q-TAP block is an attractive and safe analgesic technique to be offered to patients undergoing CRS-HIPEC surgery. However, it is unknown if a 4Q-TAP block with the use of plain and liposomal bupivacaine combination is equally effective in providing the same or better quality of recovery than TEA in patients undergoing CRS-HIPEC surgery.

4Q-TAP blocks with plain and liposomal bupivacaine combination are currently used in our institution in patients undergoing major abdominal surgery, therefore the results of our study could be extrapolated to a larger number of patients. Unpublished results from a retrospective analysis of a group (n=15) of patients who had CRS-HIPEC surgery with 4Q-TAP blocks with liposomal bupivacaine in our institution suggests that the quality of analgesia provided by this technique is similar to that achieved with epidural analgesia. Furthermore, we observed no major complications related to the technique.

We hypothesize that patients who undergo CRS-HIPEC surgery with 4Q-TAP block will have a non-inferior postoperative quality of recovery (QoR) compared to those treated with epidural analgesia.

5. Methods and Study Design

This is a randomized controlled trial designed to test efficacy of 4Q-TAP against TEA (routine of care) on quality of recovery 48 hours after CRS-HIPEC surgery. All patients will be enrolled at MD Anderson Cancer Center.

A. Setting and Population

Inclusion criteria:

1. Written informed consent;
2. 18 years old or older;
3. American Society of Anesthesiologists physical status (ASA) 1-3;
4. Scheduled surgery: open elective CRS-HIPEC;
5. Able to complete the QoR 15 questionnaire;
6. Patients scheduled to receive intraoperative chemotherapy;

Exclusion criteria:

1. Contraindications to epidural analgesia due to thrombocytopenia (platelet count: <100,000 cell/dL), coagulopathy (International Normalized Ratio > 1.5, PT>16.5 seconds or aPTT > 35.9 seconds);
2. Bupivacaine or liposomal bupivacaine sensitive or known allergy;
3. Pregnancy or breastfeeding patients;
4. Patients with recent (within 60 days preoperatively) history severe hepatic disease (defined as liver injury with encephalopathy plus impaired synthetic liver function (i.e. > 1.5))
5. Patients with recent (within 15 days preoperatively) history deteriorate kidney function (creatinine serum concentrations > 2.5 mg/dL or eGFR < 30 mL/kg/min);

B. Withdrawal of Patients

Patients may withdraw from the study at any time, with or without reason and without prejudice to further treatment. In all cases of withdrawal, the reason(s) for withdrawal (if given) will be recorded upon study termination.

In addition, the investigator may withdraw the patient due to any of the following situations:

- adverse event
- any other reason determined by the investigator to be in the best interest of the patient.

Patients withdrawn due to an adverse event should be followed until the event has been resolved or is stable, if at all possible.

B. Interventions

Patients will be randomized 1:1 on the morning of surgery to one of the following 2 interventions:

TEAgroup: Patients in this group will be treated as standard of care. An epidural catheter will be placed before induction of anesthesia by an anesthesiologist. The catheter will be placed between the thoracic vertebral spaces 8 and 12 according to routine care. A bolus or infusion of local anesthetic solution with or without the addition opioids will be given before surgical incision according to anesthesia provider's clinical judgment. If deemed appropriate, a pre-incision epidural bolus of hydromorphone (300-800 micrograms) may be administered according to the anesthesia provider's clinical judgment.

4Q-TAP block group: Patients in this group will have an ultrasound guided 4Q-TAP block. A maximum of 80 cc of a solution consisting of 30 mg of bupivacaine HCl in 10 cc of PFNS and 65 mg of liposomal bupivacaine in 10 cc of PFNS will be injected before surgical incision in each of the four quadrants.

C. Protocol and procedures

Patients will be screened from surgical and preoperative anesthesia clinic schedules and visits. The study team including the PI, Co-PIs or collaborators will approach patients for consenting only after confirmation of inclusion and exclusion criteria. After consenting, ***patients will be free to withdraw from study at any time***.

After enrolling to the study and prior randomization, all data pertinent to the study and the QoR 15 will be obtained by the research personnel involved in the study. After randomization, all patients will have surgery under general anesthesia according routine care. All patients will receive intra- and postoperative multimodal analgesia according to the standard of care and judgment of the attending anesthesiologists. Before surgery, p.o. celecoxib, tramadol extended release and/or pregabalin will be administered according to clinical judgment. Intraoperative infusions of propofol, dexmedetomidine and ketamine will be permitted per standard of care. Intravenous infusion of lidocaine will not be permitted at any time. Intravenous fentanyl, sufentanil or hydromorphone will be administered according to clinical judgment of the attending anesthesiologist. Prophylactic antibiotics will be given per surgical routine care. Medications for prophylaxis of nausea and vomiting (dexamethasone 8-10 mg, ondasentron 4-8 mg and/or aprepitant 80-125 mg) will be given according to the judgment of the attending anesthesiologists.

Upon arrival to the postoperative anesthesia care unit or intensive care unit, postoperative analgesia will consist of the administration of boluses of hydromorphone or fentanyl to achieve a pain score < 4 (on a 0-10 NRS). If needed, patients will receive intravenous patient-controlled analgesia with hydromorphone or fentanyl. Once patients can tolerate p.o. medications, they will transition to oral

analgesics according to standard of care. Patients in the epidural group will have the catheter removed per routine care.

Patients will be encouraged out of bed mobilization per standard of care. Foley catheter will be removed 48 hours after surgery if clinically indicated.

D. Data collection and measurements

Preoperaive data: Demographic data to be obtained includes height (cm), weight (kg), age (yr), gender, (ASA) physical status, and self-declared ethnicity. Patients will be questioned for social history (tobacco) and medical history to calculate Charlson comorbidity index score. QoR 15 will be obtained before surgery. Pain meds (type, dose and frequency)

The following **intraoperative data** will be obtained from electronic medical records: surgery and anesthesia time, surgery type and extent of resection, intraoperative chemotherapy (type and dose), highest temperature, intraoperative anesthetic and opioid consumption. Blood loss, fluid therapy and urinary output will also be collected at the end of surgical procedure.

The following **postoperative data** will be obtained from electronic medical records: Postoperative opioid consumption, breakthrough pain medication requirements and oxygen requirements in PACU and in nursing floor (first 48 hours postoperatively). QoR score and pain scores will be obtained on postoperative day 1, 2, 3, 5, 7, 10(±1) and 30(±2) days if the patient is still admitted to the hospital. Nausea and vomiting, requirement of antiemetics, pruritus, requirement of antihistaminic medications and requirement of naloxone in PACU and first and second postoperative morning after surgery will be collected. Ambulation time, flatus and bowel movements (first time), constipation, length of stay will be obtained. Incentive spirometry will be measured on postoperative day 1 and 2. Postoperative complications (Clavien-Dindo scale during hospital admission) and perioperative morbidity scores (POMS day 7) will be obtained from medical records and 30 days after surgery. Preoperative and postoperative routine laboratory data results will also be collected from electronic medical records.

Duration of Patient Participation

Patients that consent to the optional MDASI questionnaires will participate until the POMS data has been completed on postoperative day 30.

E. Outcomes definitions

Quality of Recovery will be measured using the QoR-15 scale. The QoR scale is a validated scoring system that allows for the quantification of a patient's early postoperative health status.

Pain Intensity at rest and cough will be measure using a VNRS (0 = no pain - 10 = worst pain ever). Data will be reported as time-weighted pain scores from discharge from the PACU until 48 hours after the end of surgery.

Opioid Consumption will be reported as morphine equivalents required during the 48 hours after the end of surgery.

Length of stay will be calculated from day of surgery to date of hospital discharge.

Adverse Event Definition

An adverse event is any symptom, sign, illness, or experience which develops or worsens during the course of the study, whether or not the event is considered related to study drug. **Adverse events (AEs) related to the study interventions** will be recorded within the first 48 hours after the end of surgery. AEs related to the study will include postoperative hypotension needed pharmacological intervention including fluid resuscitation or temporary holding or discontinuation of epidural infusions, failed block (defined as patchy block or unilateral block needing pharmacological interventions or catheter removal), epidural space infection or abscess and epidural hemathoma.

Serious Adverse Event

A serious adverse event is defined as any adverse medical experience that results in any of the following outcomes:

- death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- requires medical or surgical intervention to prevent permanent impairment or damage.

Opioid-related adverse (i.e. respiratory depression, pruritus, sedation, delirium) within the first 48 hours after the end of surgery.

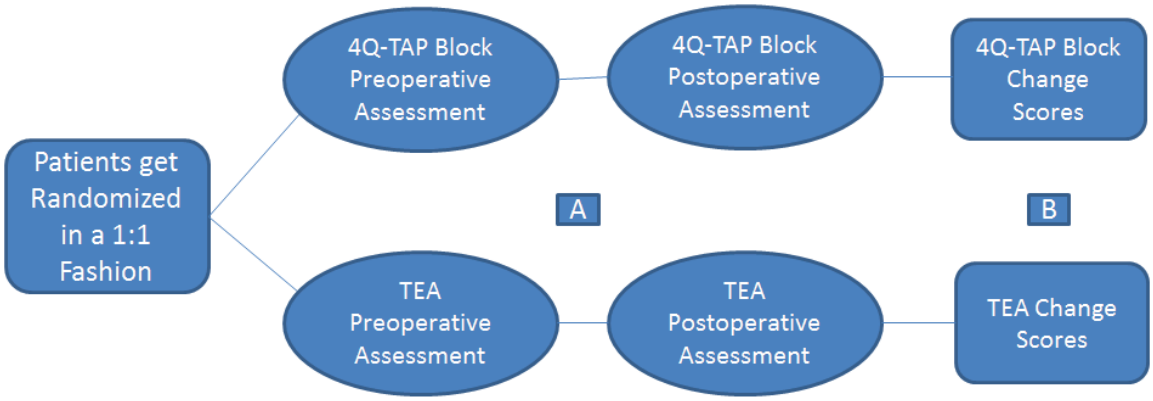
Postoperative complications will be recorded using Clavien-Dindo scale and POMS.

Statistical Considerations

The primary objective of evaluating the impact of 4 quadrants TAP blocks (4Q-TAP) versus Thoracic Epidural Analgesia (TEA - routine care) on the quality of recovery (QoR) will be conducted using total scores on each patient acquired from the QoR-15. The QoR-15, as previously mentioned, is a validated instrument with well-studied psychometric properties used to measure postoperative quality of recovery. The QoR-15 consists of 15 items. All 15 items follow a Likert scale ranging from 0 to 10 (where “0” refers to none of the time [poor] and “10” refers to all of the time [excellent]). A patient’s total score is the sum score across all 15

items (note: the last 5 items are reverse scored). The lowest score a patient can receive is "0" and the highest score is "150"; where higher total scores indicate better quality of recovery. To evaluate the trial changes in QoR-15 total scores will be computed for each treatment arm. The changes will be compared between patients receiving 4Q-TAP Block and patients receiving TEA. Figure 1 illustrates the trial's development over time. Once a patient is randomized and the preoperative QoR-15 is administered, which takes approximately 2.4 minutes to complete, patients will be provided postoperative QoR-15 approximately 26 hours after surgery (Figure 1: [A]; Stark et al). Within patient changes from baseline will be computed for each treatment arm. These changes will be compared between treatment arms (Figure 1: [B]).

Figure 1: Trial Schema



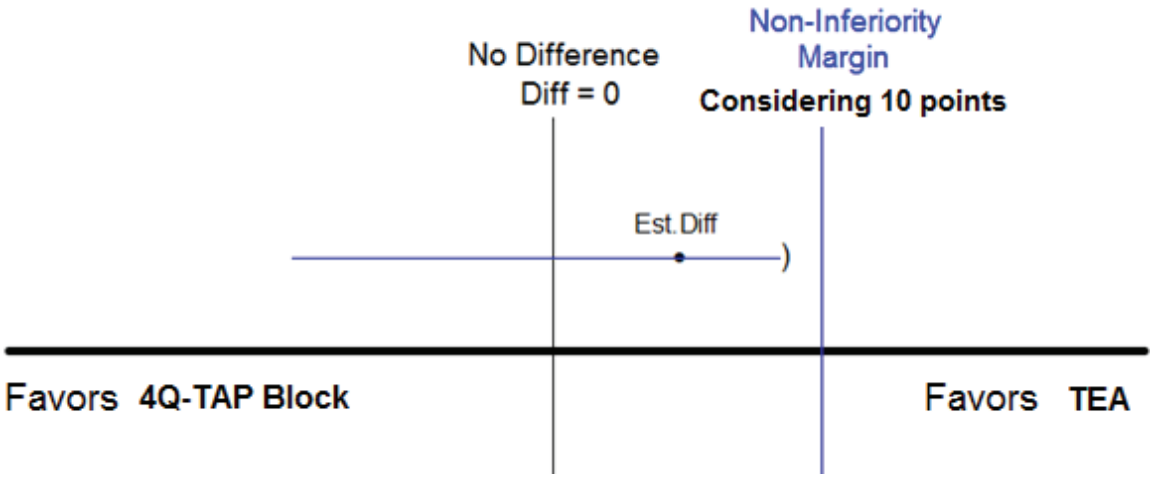
This randomized trial will be used to determine if 4Q-TAP Block is non-inferior to TEA based on postoperative changes in QoR-15 using a non-inferiority margin of 10 units. According to Stark et al., the reported mean change in QoR-15 before and after surgery is -22 (95%CI: -26 to -18) based on 127 adults. This information allowed us to assume of a common standard deviation of 23 units for the change in QoR-15's total score pertaining to each treatment arm, which was ultimately used to derive the study's sample size.

The following hypothesis test will be used to evaluate the trial:

H_0: $\mu_{4Q\text{-}TAP\ Block} - \mu_{TEA} \geq 10.0$
H_a: $\mu_{4Q\text{-}TAP\ Block} - \mu_{TEA} = 0$ (rejecting H_0 implies non-inferiority)

We will use a one-sided t-test test with a significance level of 0.05 and power of 80%. A non-inferiority margin of 10 was considered by assuming an average change in QoR-15 of -25 units in the TEA arm and that the average change in QoR-15 for the 4Q-TAP Block treatment arm would be no greater than -35.

Figure 2: Non-inferiority assessment



These specifications require an approximate sample size of 140 patients as indicated in Table 1. Moreover, an interim analysis will be conducted at after 70 patients are randomized using stopping boundaries provided by the method of Pock and Simon. At the interim, the trial will stop early if $p < 0.006$ for efficacy and $p > 0.367$ for futility (East v6).

Table 1: Estimated sample size given projected study parameters

Expected QoR-15 Avg. Change * for Epidural group	**Non-inferiority Margin**	**Power**	**Alpha (1-sided)**	**Approx Sample Size**
-25	10	80%	5%	140

*Avg. Change before and after surgery; Assumed SD = 23; A non-inferiority margin of 10 implies the Avg. Change for TAP will be -35 [ie. -25 - (-35) = 10]
*Sample size for the difference of two means using a two sample test (East v6).

The data will be evaluated per protocol for patients contributing analyzable data.

Safety

All patients who receive any portion of the intended treatments (TEA or 4Q-TAP) will be included in safety analysis.

Patient demographics, baseline characteristics and medical history will be summarized descriptively by treatment arm. Mean, standard deviation, median, minimum and maximum will be reported for continuous variables. Frequencies and proportions will be reported for categorical variables. An independent samples t-test will be used to evaluate the difference between QoR-15 change scores between treatment arms. Change scores within treatment arms will be summarized using the mean and 95%CIs. Linear regression analysis will be used to assess QoR-15 change scores between treatment arms while adjusting for select covariates of interest.

The association between dichotomous outcomes (dependent variables) and treatment-related factors will be assessed using univariable and multivariable logistic regression. Time-to-event outcomes will be summarized at critical time points using the method of Kaplan-Meier. Kaplan-Meier plots will be used to visualize the time-to-event information. Cox proportional hazards regression will be used to model the time-to-event outcomes using select covariates of interest.

Upon any modifications to the eligibility criteria and with the intention of broadening patient characteristics, for example: by including patients with prior opioid use, we will address this issue by adjusting the treatment effect using a regression model that includes prior opioid use as an indicator variable and assess the relative difference between the unadjusted treatment effect. Moreover, subgroup analyses will be explored even though we anticipate randomization will maintain covariate balance between treatment arms.

Primary Outcome Analysis

Secondary Outcomes Analyses

Safety

Safety will be summarized using the number and proportion of patients reporting any given event and will be tabulated by treatment received according to the worst severity experienced. Separate tables will be constructed for (a) all reported events, (b) procedure related events, (c) serious events. Event rates will be compared between treatment arms by Fisher's exact test.

Data Management – Data Collection and Processing

Study data will be collected and managed using REDCap[16] (Research Electronic Data Capture) electronic data capture tools hosted at MD Anderson. REDCap (www.project-redcap.org) is a secure, web-based application with controlled access designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless downloads to common statistical packages; and 4)

procedures for importing data from external sources.

REDCap (https://redcap.mdanderson.org) is hosted on a secure server by MD Anderson Cancer Center's Department of Research Information Systems & Technology Services. REDCap has undergone a Governance Risk & Compliance Assessment (May 2014) by MD Anderson's Information Security Office and found to be compliant with HIPAA, Texas Administrative Codes 202-203, University of Texas Policy 165, federal regulations outlined in 21 CFR Part 11, and UTMDACC Institutional Policy #ADM0335. Those having access to the data file include the study PI and research team personnel. Users are authenticated against MDACC's Active Directory system. The application is accessed through Secure Socket Layer (SSL). All protected health information (PHI) will be removed from the data when it is exported from REDCap for analysis. All dates for a given patient will be shifted by a randomly generated number between 0 and 160, thus preserving the distance between dates. Dates for each patient will be shifted by a different randomly generated number.

Following publication study data will be archived in REDCap. Since study data may be useful for future research studies performed under separate IRB approved protocols, study data will be archived indefinitely in REDCap. Since REDCap is a secure electronic database with controlled access, and because patient identifiers may be needed to link study data to data from other sources under future IRB approved protocols, patient identifying information will be retained in the archived database.

Investigators are responsible for the accurate completion and timely submission of the data collected during the study. Quality assurance procedures will be established to ensure that complete, accurate and timely data are submitted, that protocol requirements are followed and that complications, adverse events and adverse device effects are correctly reported and investigated, as appropriate. Investigators are to maintain all source documents as required by the protocol, including laboratory results, supporting medical records, and signed Informed Consent forms. The source documents will be used during the regular monitoring visits to verify information from the database against data contained on the completed CRFs.

The Principal Investigator must maintain detailed records on all patients who sign the Informed Consent and begin the pre-procedure evaluation. Data for enrolled patients will be entered directly into the electronic Case Report Forms (eCRFs) in REDCap. For source documents, corrections should be made in a manner that does not obscure or eliminate the original error, by striking through the original data with one line, and initialing and dating the change, along with the reason for the change.

Study exit eCRFs are completed for all enrolled patients, regardless of whether they did or did not complete the Study (e.g., patient discontinuation, study termination).

Monitoring Procedures

Monitoring visits to the clinical sites will be made periodically during the study, to ensure that all aspects of the current, approved protocol/amendment(s) are followed. Original source documents will be reviewed for verification of data in the database. In the event that the original medical records cannot be obtained for a patient that is seen by a non-study physician at a non-study institution, photocopies of the original source documents must be made available for review. It is important that the Investigator and relevant study personnel are available during the monitoring visits and that sufficient time is devoted to the process. Phone contacts and site visits will be conducted to ensure that the protocol is being followed and that any protocol deviations are properly documented. Clinical monitoring will include a verification that Informed Consent was properly obtained for all enrolled study participants, a review of clinical records for accuracy and completeness, resolution of missing or inconsistent results and a review of source documents. The clinical monitor will verify that the CRFs are in agreement with the source documentation and other records. The investigator will make available to the clinical monitor for review all Informed Consent documents, Internet access to completed CRFs, source documentation, original laboratory data and other relevant records for all enrolled patients at the site. It is important that the investigator and other relevant site personnel are available for consultation with the clinical monitors during the monitoring visits and that sufficient time is devoted at the site to the monitoring process.
Additionally, telephone and/or e-mail contact will be conducted on a regular basis with the investigator and the site staff to ensure that the protocol is being followed and to address any issues that may occur during the course of the study.

If a deficiency is noted during an on-site visit (or at any other time during the course of the study), the clinical monitor is required to discuss the situation with the investigator to secure compliance. Monitoring visit will begin after enrollment of first 3 patients.

Data Safety Monitoring Board (DSMB): The monitoring of this trial will be provided by MD Anderson Cancer Center DSMB

Visit Schedule

Table 1, below outlines the required study assessments.

Table 1 Study Event Schedule

	Baseline (within 60 days prior to surgery)	Day of surgical Procedure	First 48 hours after surgery	Procedures until Discharge	Procedures After Discharge
Informed Consent	X[a]				
Inclusion / Exclusion Criteria Assessment	X				
Demographics/ Medical History	X				

Randomization and Intent to Treat		X[b]			
Vital Signs	X[c]	X[c]			
Physical Examination	X				
Laboratory Tests	X[d]				
Data collection	X[e]	X[e]	QoR15, pain scores, opioid consumption,	QoR15, pain scores, opioid consumption, LOS	QoR15, pain scores, opioid consumption,
Adverse Events		X[f]	ORADE, AE, SAE, complications (Clavien-Dindo)		

[a] After confirmation of eligibility and 30 days after surgery.
[b] After confirmation of eligibility and before surgery.
[c] Height, weight, systolic/diastolic blood pressure, heart rate, and respiratory rate (height and weight will only be measured at baseline)
[c] Data will be collected from the patients standard of care lab tests. These typically include creatinine, platelet and white blood cells count, and hemoglobin and hematocrit
[d] Complete blood counts, routine electrolyte determinations and renal function laboratory tests.
collected
[e] ORADE: opioid related adverse effects, AE: adverse events, SAE: serious adverse events, QoR: quality of recovery, LOS: length of stay
[f] During surgery, at PACU discharge and POD1 and 2.

Adverse Events

General

All adverse events (AE) and serious adverse events (SAE) will be monitored from the time of procedure through end of the study.

An AE is defined as any undesirable clinical occurrence in a patient whether or not it is considered to be device related. In addition, the definition of AE applies to any event with an onset post study procedure or to any underlying diseases, present at baseline, that exacerbate in severity post study procedure. Therefore, an underlying disease that was present at the time of enrollment is not reported as an AE, but any increase in the severity of the underlying disease is to be reported as an AE. All reported AEs must be recorded in the database. A description of the event, including the start date, resolution date, action taken, and the outcome should be provided, along with the Investigator's assessment of the relationship between the AE, the study treatment and the study procedure. This protocol will use common terminology criteria for adverse events (CTCAE) version 4.0. For the AEs not characterized in the CTACE, the following definitions for rating severity of AEs will be used:

Mild: Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities;

symptoms would not require medication or a medical evaluation; signs or symptoms are transient.

Moderate: Interferes with the patient's usual activity and/or requires symptomatic treatment.

Severe: Symptom(s) causing severe discomfort and significant impact of the patient's usual activity and requires treatment.

A serious adverse event (SAE) is defined as an event which leads to:

- Death due to any cause
- Life-threatening condition
- Results in persistent or significant disability/incapacity
- Requires in-patient hospitalization or prolonged hospitalization
- Necessitates an intervention to prevent a permanent impairment of a body function or permanent damage to a body structure
- Results in congenital abnormality

All SAE's will be reported.

***Device-Related Adverse Event**:* Not applicable

***Procedure-Related Adverse Event**:* an adverse event is considered to be procedure-related when, in the judgment of the Investigator; it is reasonable to believe that the event is associated with the assigned study procedure. Other products, surgical techniques, or medications required specifically for the procedure are likely to have contributed to the occurrence of the event.

Concomitant Medication-Related Adverse Event: Not applicable

Pre-Existing Condition-Related Adverse Event: an adverse event is considered to be related to a pre-existing condition when, in the judgment of the Investigator, it is reasonable to believe that the event is associated with the patient's pre-existing condition and is not specific to the **STUDY** procedures. Pre-existing conditions that are aggravated or become more severe during or after the procedure should be evaluated on a case-by-case basis to determine if the event may be more appropriately classified as procedure-related.

The Investigator should follow all unresolved serious adverse events until the events are resolved, the patient is lost to follow-up, the patient has withdrawn consent, or the adverse event is otherwise explained.

For purposes of this study, the following events are not considered adverse events, because they are normally expected to occur in conjunction post-surgery, or are associated with customary, standard care of patients undergoing these procedures:

- Early post-operative pain (within 48hours post-index procedure) at the incision site and/or related to position on procedure table

- Post-anesthesia emesis, nausea, or headache (within 24 hours post-index procedure)
- Chest pain without associated ECG changes
- Hematocrit decrease from baseline not associated with hemodynamic changes, remaining above 30% and not requiring transfusion
- Electrolyte imbalance without clinical sequalea following endoscopic procedure, even if requiring correction
- Low grade temperature increase (≤38.3°C/≤101°F)
- Sinus bradycardia/tachycardia that does not require treatment or intervention
- Systolic or diastolic blood pressure changes that do not require treatment or intervention
- Any pre-planned surgical procedures

This listing of events is intended to provide guidance to the investigational sites for purposes of adverse event reporting. The Investigator at the investigational site should utilize his/her own clinical judgment in evaluating adverse experiences, and may decide that the above events should be reported as adverse events.

Reporting of Serious and Non-Serious Adverse Events

Serious Adverse Events, regardless of attribution, will be reported per MDACC's standard practice and requirements, and per sponsor guidelines.

Device Failures and Malfunctions. Not applicable

Ethical Considerations

Institutional Review Board/Ethics Committee

A copy of the protocol, proposed Informed Consent form, other written patient information and any proposed advertising material must be submitted to the IRB/IEC for written approval.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent significant protocol amendments and significant changes to the Informed Consent form.

The Investigator will be responsible for obtaining annual IRB/IEC approval and renewal throughout the duration of the study.

Informed Consent Form

The written Informed Consent documents should be prepared in the language(s) of the potential patient population.

The reviewing IRB/IEC must first approve the Informed Consent forms that are used. The Informed Consent forms that are used should be in accordance with the current guidelines as outlined by the Good Clinical Practices (GCP) guidelines, Declaration of Helsinki and the International Conference on Harmonization (ICH).

Prior to participation in the clinical Study, each patient must give written Informed Consent after the context of the study has been fully explained to the patient in language that is easily understood by the patient. The patients must also be given the opportunity to ask questions and have those questions answered to their satisfaction.

Written Informed Consent must be recorded appropriately by means of the patient's, or their legal representative's dated signature. The patient will receive a copy of the Informed Consent form.

Amending the Protocol

All significant protocol changes that may affect the following must be submitted and approved by the IRB before initiating the change:

- validity of the data or information resulting from the completion of the approved protocol;
- relationship of the likely patient risk to benefit relied upon to approve the protocol;
- scientific soundness of the investigational plan, or;
- rights, safety, or welfare of the human patients involved in the investigation.

Emergency Actions

The Investigator must give notice of any emergency deviations and justification for the deviation to the IRB/IEC as quickly as possible after the episode, in any event no later than 24 hours after the emergency.

Protocol Deviations

A protocol deviation is defined as an event where the Clinical Investigator or site personnel did not conduct the study according to the protocol.
Investigators will adhere to procedures for reporting study deviations to their IRB in accordance with their specific IRB reporting policies and procedures.
Deviations will be submitted annually per MDA policy.

Coverage of Expenses

The treated patients will not be reimbursed or compensated for participating in the Study.

Confidentiality

Confidentiality of patients will be maintained throughout the study. A unique identification code will be assigned to each patient participating in this Study. Any data that may be published in abstracts, scientific journals, or presented at medical meetings will reference a unique patient code and will not reveal the patient's identity.

All laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patient identity is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study.

Information gathered for this study will not be reused or disclosed to any other person or entity, or for other research. Once the research has been completed, identifiers will be retained for as long as is required by law and by institutional regulations, and at that point will be destroyed.

Source Documentation

The Principal Investigator must maintain detailed source documents on all study patients who are enrolled in the study or who undergo screening. Source documents include patient medical records, hospital charts, clinic charts, Investigator's patient study files, as well as the results of diagnostic tests (e.g., laboratory tests).

The following minimum information should be recorded in the patient's medical records:

- The date the patient entered the study and the patient number
- The study protocol number
- The date that informed consent was obtained
- Evidence that the patient meets Study eligibility requirements (e.g., medical history, Study procedures and/or evaluations)
- The dates of all Study related patient visits
- Evidence that required procedures and/or evaluations were completed
- Use of any concurrent medications
- All lab reports taken for this study
- Occurrence and status of any Adverse Events
- The date the patient exited the Study, and a notation as to whether the patient completed the Study or was discontinued, including the reason for discontinuation.

Record Retention

The Investigator will maintain all essential study documents and source documentation, in original format, that support the data collected on the study patients in compliance with the ICH/GCP guidelines.

Following publication study data will be archived in REDCap. Since study data may be useful for future research studies performed under separate IRB approved protocols, study data will be archived indefinitely in REDCap. Since REDCap is a secure electronic database with controlled access, and because patient identifiers may be needed to link study data to data from other sources under future IRB approved protocols, patient identifying information will be retained in the archived database.

Publication Policy

All manuscripts associated with the data collected on this study are not to be submitted for publication without the written consent of the MD Anderson Principal Investigator.

Role of Investigator

The Investigator has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the Food and Drug Administration (FDA). In this study, Investigator will have certain direct responsibilities and will delegate other responsibilities to Consultants. Together, the investigators will ensure adherence to general duties including any regulations applicable to a post-market, Physician Preference Study.

Definitions

For those AEs not listed on CTACE 4.0, the following severity rating will apply:

Mild:	Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs or symptoms are transient.
Moderate:	Interferes with the patient's usual activity and/or requires symptomatic treatment.
Severe:	Symptom(s) causing severe discomfort and significant impact of the patient's usual activity and requires treatment.

ALLERGIC REACTION: A state of abnormal and individual hypersensitivity acquired through exposure to a particular allergen.

APPROVAL (IN RELATION TO INSTITUTIONAL REVIEW BOARDS (IRBs): The affirmative decision of the IRB that the clinical investigation has been reviewed and may be conducted at the institutional site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

CO-INVESTIGATOR / SUB-INVESTIGATOR: Any individual member of the clinical investigation team designated and supervised by the Investigator at an investigational site who performs critical investigation-related procedures and/or makes important investigation-related observations. See also Investigator.

CONFIDENTIALITY: Prevention of disclosure, to other than authorized individuals, of proprietary information or of a patient's identity / Protected Health Information (PHI) in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

CASE REPORT FORM (CRF): A document designed to record all of the protocol-required information on each patient.

INFORMED CONSENT: A process by which a patient voluntarily confirms in writing his or her willingness to participate in a particular investigation, after having been informed of all aspects of the investigation that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated Informed Consent form.
INVESTIGATOR: The person responsible for the conduct of the clinical investigation at an investigational site. If an investigation is conducted by a team of individuals at an investigational site, the Investigator is the responsible leader of the team and may be called the Principal Investigator. See also Co-Investigator.

PAIN SCALE: The 11-point Pain Intensity Numeric Rating Scale (NRS) is a pain assessment method using a numerically based scale allowing the patient to indicate the intensity of pain that he/she experiences. The scale begins at 0 for “no pain” and has a maximum of 10 for “pain as bad as it could be.” (Appendix A)

SERIOUS ADVERSE EVENT (SAE): Any untoward medical occurrence that results in death, is life threatening, requires patient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity.

PATIENT: An individual who participates in a clinical investigation.

UNANTICIPATED ADVERSE DEVICE EFFECTS (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death *caused by, or associated with the study device,* if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the

Investigational Plan or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

Investigator Responsibilities

The investigator is responsible for ensuring that this study is conducted according to this protocol and that signed Informed Consent is obtained from each patient prior to their inclusion in this study.
It is the investigator's responsibility to ensure that all staff assisting with this Study have the appropriate qualifications and are fully instructed on the Study procedures and RPN patient confidentiality.
The investigator is responsible for ensuring that the conduct of the Study conforms to the IRB/EC requirements and provides all necessary communication with the IRB/EC including, but not limited to, annual Study reports and required adverse event notifications.

Investigator Records

Case Report Forms

The standardized Case Report Forms (CRFs) will be used to collect complete and accurate records of the clinical data from the Study according to the Good Clinical Practice (GCP) requirements. The investigator is responsible for collecting and accurately recording the data generated for this Study.

Screening Log

Investigators will maintain a screening log that will record the date of informed consent, the date of screening, the enrollment status (enrolled/excluded) and the reason for exclusion for all screen failures.

Investigator Reports

Final Study Report

A summary of the final report will be prepared and provided to each Principal Investigator for submission to their respective IRB/EC after completion of the Study.

Serious Adverse Events (SAEs)

The investigators will report by CRF any SAEs including serious, and/or potentially device- or procedure-related adverse events as soon as possible, within 24 hours of the investigator becoming aware of the event, to the IRB/C as per the committee's reporting requirements.

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